publiziert bei: AWMF online
Portal der wissenschaftlichen Medizin

S3-Leitlinie
Epidemiologie, Diagnostik, Therapie und Nachsorge des Blasenekstrophie-Epispadie Komplex (BEEK)

Registernummer: 043-058
Version 1.0 – Stand Mai 2024

Evidenztabellen

DGU Deutsche Gesellschaft für Urologie e.V.

Das dieser Veröffentlichung zugrundeliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss unter dem Förderkennzeichen 01VSF21009 gefördert.

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1. Informationen zum Leitlinienreport

1.1 Herausgeber & Federführung

Herausgeber dieses Evidenztabellendokumentes ist die Deutsche Gesellschaft für Urologie e. V. (DGU). Der DGU oblag die Federführung und Erstellung der Leitlinie.

1.2 Finanzierung der Leitlinie

Das dieser Veröffentlichung zugrundeliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss unter dem Förderkennzeichen 01VSF21009 gefördert. Die Mandatsträger*innen der Leitliniengruppe arbeiteten ehrenamtlich ohne Honorar. Die wissenschaftliche und organisatorische Unterstützung erfolgte durch das Team UroEvidence der DGU-Geschäftsstelle Berlin.

1.3 Kontakt

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1.4 Zitierweise des Dokumentes

Deutsche Gesellschaft für Urologie e. V. (Hrsg.): S3-Leitlinie Epidemiologie, Diagnostik, Therapie und Nachsorge des Blasenekstrophie-Epispadie Komplex (BEEK), Evidenztabellen 1.0, 2024, AWMF-Registernummer: 043-058, https://register.awmf.org/de/leitlinien/detail/043-058 (abgerufen am: TT.MM.JJJJ).

1.5 Weitere Dokumente zur Leitlinie

Bei diesem Dokument handelt es sich um den Leitlinienreport der S3-Leitlinie Epidemiologie, Diagnostik, Therapie und Nachsorge des Blasenekstrophie-Epispadie Komplex (BEEK), welche über folgende Seite zugänglich ist:

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF): http://www.awmf.org/leitlinien/aktuelle-leitlinien.html

Der Leitlinienreport ist die methodische Grundlage zu folgenden Dokumenten:

- Kurzfassung der Leitlinie
- Langfassung der Leitlinie
- Methodenreport

Zu dieser Leitlinie existiert zudem eine Patient*innenleitlinie in laienverständlicher Sprache, welche ebenfalls kostenfrei auf der AWMF-Seite zur Verfügung steht.

1.6 Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Bedeutung
3D-US	3-Dimensionaler Ultraschall
AG	Arbeitsgruppe
aPR	adjustierte Prävalenzrate (*adjusted Prevalence Ratio*)
BE	Blasenekstrophie
BEEK/BEEC	Blasenekstrophie-Epispadie Komplex *(Bladder-Exstrophy-Epispadias Complex)*
BMI	*Body Mass Index*
BNC	Blasenhalsverschluss *(Bladder Neck Closure)*
BNR	Blasenhalsrekonstruktion *(Bladder Neck Reconstruction)*
BNS	Blasenhalschirurgie *(Bladder Neck Surgery)*
BUR	Bilaterale Ureterreimplantation
CBE	Klassische Blasenekstrophie *(Classic Bladder Exstrophy)*
CI	Konfidenzintervall *(Confidence Interval)*
CIC	Saubere intermittierende Katheterisierung *(Clean Intermittent Catheterization)*
CNV	Kopienzahlvarianten (*Copy Number Variations*)
CPRE	Komplette primäre Rekonstruktion der Blasenekstrophy *(Complete Primary Repair of Bladder Exstrophy)*
CPRE-BUR	Vollständige primäre Reparatur der Blasenekstrophie und beidseitige Reimplantation des Ureters *(Complete Primary Repair of Bladder Exstrophy and Bilateral Ureteral Reimplantation)*
CT	Computertomografie
CUD	Kontinente Harnableitung *(Continent Urinary Diversion)*
DGU	Deutsche Gesellschaft für Urologie e. V.
EEC	Ekstrophie-Epispadie Komplex *(Exstrophy-Epispadias Complex)*
eGFR	geschätzte glomeruläre Filtrationsrate *(estimated Glomerular Filtration Rate)*
FSFI	Weiblicher Sexualfunktionsindex *(Female Sexual Function Index)*
h	Stunde *(hour)*
HAD	Menschliche azelluläre Haut *(Human Acellular Dermis)*
HCG	Menschliches Choriongonadotropin *(Humanes Choriongonadotropin)*
IgE	Immunoglobulin E
IIEF	Internationaler Index der Erektilen Funktion

IL	Interleukin
IPS-ABNR	Innervationserhaltende Sphinkterplastik in Verbindung mit anatomischer Blasenhalsrekonstruktion *(Innervation Preserving Sphincteroplasty along with Anatomical Bladder Neck Reconstruction)*
IQR	Interquartilbereich *(Interquartile Range)*
IS/IP	interischial/interpubisch
LoE	Evidenzlevel *(Level of Evidence)*
mo	Monat
MRI/MRT	Magnetresonanztomographie *(Magnetic Resonance Imaging)*
MSHQ	Fragebogen zur sexuellen Gesundheit von Männern *(Male Sexual Health Questionnaire)*
MSHQ-EjD-SF	Kurzform des Fragebogens zur sexuellen Gesundheit von Männern zur Beurteilung von Ejakulationsstörung *(Male Sexual Health Questionnaire Short Form for assessing Ejaculatory Dysfunction)*
MSRE	Mehraktige Rekonstruktionstechnik *(Modern-Staged Repair)*
NOS	*Newcastle Ottawa Quality Assessment Scale*
OEIS	Omphalozele, Ekstrophie, Imperforate Anus und Spinale Defekte
OR	Odds Ratio
Parm	Prostata-Androgen-reguliertes muzinähnliches Protein 1 (*Prostate androgen-regulated mucin-like protein 1*)
PDA	Periduralanästhesie
POD	Postoperativer Tag *(Postoperative Day)*
PPS	Penis-Wahrnehmungswert *(Penile Perception Score)*
PR	Prävalenzratio (*Prevalence Ratio*)
RCT	Randomisierte kontrollierte Studie *(Randomized Controlled Trial)*
RoB	Risko für Bias *(Risk of Bias)*
RR	Relatives Risiko
SD	Standardabweichung *(Standard Deviation)*
SHIM	Bestandsaufnahme der sexuellen Gesundheit für Männer *(Sexual Health Inventory for Men)*
SNP	Einzelnukleotid-Polymorphismus (*Single Nucleotide Polymorphism*)
SRBE-BUR	Mehraktige Reparatur der Blasenekstrophie mit bilateraler Ureter-Reimplantation *(Staged Repair of Bladder Exstrophy with Bilateral Ureteral Re-implantation)*
SUPER	Enukleationsresektion suburothelialer Polypen *(Sub-Urothelial Polyp Enucleation Resection)*

UAAC	Urotheliale Auto-Augmentationszystoplastik *(Urothelial Auto-Augmentation Cystoplasty)*
US	Ultraschall
UUE	Ureter-Harnröhren-Transplantation *(Ureteric-Urethral Engraftment)*
USA	Vereinigte Staaten von Amerika *(United States of America)*
VUR	Vesikoureteraler Reflux
wks	weeks
y	year
YDL	*Young-Dees-Leadbetter*

2. Schema der Evidenzklassifikation

Es erfolgte eine Einordnung bezüglich des Evidenzlevels aller eingeschlossenen Referenzen nach den Evidenzleveln des Oxford Centre for Evidence-Based Medicine 2011 [1]. Auf eine Abwertung des Evidenzlevels aufgrund der Studienqualität, Ungenauigkeit, einem indirekten Bezug auf die Schlüsselfrage, sehr kleiner absoluter Effektstärke oder bei inkonsistenten Studien wurde verzichtet. Für eine bessere Einordnung der Evidenz wurde neben den methodischen Bemerkungen in den Evidenztabellen, eine nummerische Bewertung des Risikos für Bias ausgewiesen. Hierbei gilt: Umso kleiner die Zahl, umso höher das Risiko für Bias.

Tabelle 2: Schema der Evidenzgraduierung nach Oxford 2011 (deutsche Übersetzung durch UroEvidence), (OCEBM Levels of Evidence Working Group 2011)

Frage	Schritt 1 **Evidenzgrad 1***	Schritt 2 **Evidenzgrad 2***	Schritt 3 **Evidenzgrad 3***	Schritt 4 **Evidenzgrad 4***	Schritt 5 **Evidenzgrad 5***
Wie häufig ist das Problem?	Lokale und aktuelle Stichproben-erhebung (oder Volkszählung)	Systematischer Review von Erhebungen, die eine Anpassung an die örtlichen Gegebenheiten ermöglichen**	Lokale nicht-zufällige Stichprobe**	Fallserien**	Nicht anwendbar
Ist der Diagnose- oder Überwachungs-test genau? (Diagnose)	Systematischer Review von Querschnitts-studien, welche durchweg den Referenz-standard anwendeten und verblindet durchgeführt wurden	Individuelle Querschnitts-studien, welche durchweg den Referenz-standard anwendeten und verblindet durchgeführt wurden	Nicht-konsekutive Studien oder Studien ohne konsequent angewandten Referenz-standard**	Fallserien oder schlechte und nicht-unabhängige Referenz-standards	Beweis-führung aufgrund von Mechanismen
Was passiert, wenn wir keine Therapie anbieten/ hinzufügen? (Prognose)	Systematischer Review von frühzeitig beginnenden Kohorten-studien	Frühzeitig beginnende Kohortenstudie	Kohortenstudie oder Kontrollarm eines RCTs	Fallserien oder Fall-Kontroll-Studien oder prognostische Kohorten-studien von schlechter Qualität**	Nicht anwendbar
Hilft diese Intervention?	Systematischer Review von	RCT oder Beobachtungs-studie mit	Nicht-randomisierte kontrollierte	Fallserien, Fall-Kontroll-Studien oder	Beweis-führung

Frage	Schritt 1 **Evidenzgrad 1***	Schritt 2 **Evidenzgrad 2***	Schritt 3 **Evidenzgrad 3***	Schritt 4 **Evidenzgrad 4***	Schritt 5 **Evidenzgrad 5***
(Nutzen einer Behandlung)	RCTs oder "N-of-1"-Studien	dramatischen Effekt	Kohorten- oder Nach-beobachtungs-studie	historisch kontrollierte Studien**	aufgrund von Mechanismen
Was sind <u>häufige</u> Nachteile der Behandlung?	Systematischer Review von RCTs oder genesteten Fall-Kontroll-Studien, "N-of-1"-Studie mit Patient aus Zielpopulation oder Beobachtungs-studie mit dramatischen Effekt	Individuelle RCTs oder (ausnahms-weise) Beobachtungs-studien mit dramatischen Effekten	Nicht-randomisierte kontrollierte Kohorten- oder Nach-beobachtungs-Studie mit ausreichend großer Stichprobe und ausreichend langer Nach-beobachtung	Fallserien, Fall-Kontroll-Studien oder historisch kontrollierte Studien**	Beweis-führung aufgrund von Mechanismen
Was sind <u>seltene</u> Nachteile der Behandlung?	Systematischer Review von RCTs oder "N-of-1"-Studien	RCTs oder (ausnahms-weise) Beobachtungs-studien mit dramatischen Effekten			
Ist ein frühes Erkennen lohnenswert? (Screening)	Systematischer Review von RCTs	RCT	Nicht-randomisierte kontrollierte Kohorten- oder Nach-beobachtungs-studie	Fallserien, Fall-Kontroll-Studien oder historisch kontrollierte Studien**	Beweis-führung aufgrund von Mechanismen

* Evidenzgrad kann aufgrund der Studienqualität, Ungenauigkeit, einem indirekten Bezug auf die Schlüsselfrage, sehr kleiner absoluter Effektstärke oder bei inkonsistenten Studien herabgesetzt oder bei großer oder sehr großer Effektgröße heraufgesetzt werden

** Systematische Reviews sind im Allgemeinen einer Einzelstudie gegenüber zu bevorzugen.

Übersetzung angelehnt an [2]

3. AG Epidemiologie

Schlüsselfrage Ist eine genetische Untersuchung gerechtfertigt?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Kontrollgrup pe**	**Gene**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Pitsava, 2021 [3]	Case-control study 1997-2911 USA	Exome sequencing of child–parent trios with bladder exstrophy	n=26 children with bladder eystrophy with or without epispadia (buccal) Male: 18/26	n=52 mother/father of the children (buccal)	Exome sequencing	• loss-of-function variants in TUBE1 (n=2) • rare missense (n=4) or nonsense variants (n=1) in WNT3, CRKL, MYH9, or LZTR1 • rare compound heterozygous loss-of-function variants in PLCH2 and CLEC4M • rare inherited missense or loss-of-function variants in additional genes applying autosomal recessive (three genes) • two genes identified may implicate disruption in cell migration (TUBE1) and adhesion (TSPAN4) processes, mechanisms proposed for bladder exstrophy **17 de novo missense variants in 13 children**: p.T351A, p.R441C, p.T653I, p.V132M,	Our study identified variants in several genes that may potentially contribute to bladder exstrophy. Our results underscore the potential role of genetic factors in the pathogenesis of BE and provide important clues for future investigations.	control group family-based Dr. Finnell was formerly in a leadership position with TeratOmic Consulting LLC, a now dissolved consulting firm. This work was also supported through Centers for Disease Control and Prevention (CDC) cooperative agreements under PA #96043, PA #02081, FOA #DD09-001, FOA #DD13-003, and NOFO #DD18-001 to the Centers for Birth Defects Research and Prevention participating in	4 RoB: 7/9

						p.R327H, p.E525X, p.W141fs, p.R96X, p.L225F, p.G767R, p.R2922Q, p.Y171C, p.M3124T, p.L74R, p.P847L, p.E295X, p.A373T, p.L283V, p.G279C, p.S633F **3 de novo loss-of-function variants** AKR1C2, PRRX1, PPM1D (one per child) **X-linked recessive inheritance models** p.P178A, p.R260S, p.S97P, p.S58P, p.A735T, p.A27T, p.L35V, c.1137 + 1G > A, p.A563T, p.S65R, p.T129A, p.S892A, p.S1359P		the National Birth Defects Prevention Study (NBDPS) and/or the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), and the Iowa Center for Birth Defects Research and Prevention U01 DD001035 and U01 DD001223 (PAR). The University of Washington Center for Mendelian Genomics (UW-CMG) was funded by NHGRI and NHLBI grants UM1 HG006493 and U24 HG008956.	
Rieke, 2020 [4]	Case-control study	We resequenced SLC20A1 in 690 individuals with BEEC including 84 individuals with cloacal exstrophy.	n=690 BEEC • bladder exstrophy (n=564) • cloacal exstrophy (n=84) Male: 440/690	parents	SLC20A1	identified two additional monoallelic de novo variants: • phosphate transport was not compromised, suggesting that it is not a disease mechanism • there was a tendency for lower levels of cleaved caspase-3, perhaps implicating	Our results suggest SLC20A1 is involved in urinary tract and urorectal development and implicate SLC20A1 as a disease-gene for BEEC.	control group family-based, less information about the recruitment process, number of analyzed family trios unclear The authors declare that the research was	4 RoB: 5/9

						apoptosis pathways in the disease		conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding: reported in detail in the paper	
Chen, 2020 [5]	Case-control study USA	To investigate the presence and the functional impact of ALX4 variants in patients with genitourinary defects.	n=52 ALX4 Sanger-sequenced individuals (blood) • epispadias (n=11) • classic bladder exstrophy (n=30) • cloacal exstrophy (n=11) n= 7500 clinical exome-sequencing data	parents (salvia)	ALX4	**BEEC** • 1/52: p.L373F heterozygous variant • p.L373F did not alter transcriptional activity in HeLa and HEK293 cells	Variant p.L373F (predicted pathogenic by only MutationTaster) did not affect ALX4 function in vitro.	control group family-based, less information about the recruitment process, no information about the control group No information about conflict of interest. National Institute of Digestive Diseases and Kidney, Grant/Award Number: K12DK0083014	4 RoB: 5/9
Sharma, 2019 [6]	Case-control study	We aim to examine whether aberrant DNA methylation patterns are potentially associated with classic bladder	n=10 classic bladder exstrophy (peripheral blood samples) Additionally:	n=10 age and gender matched healthy controls (peripheral blood samples)	Methylome	**Classic bladder exstrophy tissues** • 10 statistically significant CpGs (adjusted p -value < 5%) with at least 25% increase or	In comparison to other bladder anomalies, classic bladder eystrophy tissue methylation profiles differ from those of adenocarcinoma,	information about the recruitment process and the patient characteristics,	4 RoB: 6/9

		exstrophy of the urinary bladder.	• 3 tissue samples of the urinary bladder (with adenocarcinoma, with primary adenocarcinoma, without adenocarcinoma) • 4 healthy tissue • 4 urothelial carcinoma samples • 2 urachal carcinoma samples			decrease of DNA methylation • none of these CpG sites have been previously linked to bladder related phenotypes or pathways **ISL1 and PLAGL1** no statistically significant differences in methylation status at these loci between patients and control samples Using unsupervised cluster analysis, we could show that healthy tissues together with cancer tissues group separately from classic bladder exstrophy samples.	adenocarcinoma with classic bladder exstrophy, urothelial carcinoma and urachal carcinoma. In this preliminary study, we did not provide any strong evidence of major DNA methylation alterations which would be suggestive for strong underlying epigenetic mechanism.	The authors declare no conflict of interests. This work was funded by a grant of the German Research Foundation (Deutsche Forschungsgemeinschaft, RE 1723/1-3).	
Arkani, 2018 [7]	Case-control study 2006 Sweden	Evaluation of the ISL1 gene in the pathogenesis of bladder exstrophy in a Swedish cohort	n=125 patient with BEEC (blood, skin)	n= 1000 Swedish genomes n=714 non-Finnish DNA samples (358 placenta tissue and 356 peripheral blood)	ISL1 gene	• Array-CGH analysis did not reveal any deletions or duplications in the 5q11.2 region harboring the ISL1 gene.	we did not detect any known or likely pathogenic variants in the ISL1 gene in 125 Swedish BEEC patients, indicating that variation in the ISL1 gene is not a common genetic mechanism of BEEC development in the Swedish population	representative-ness of the BEEC cases unclear, comparability of cases and controls not described The authors declare no conflict of interest. Funding: reported in detail in the paper	4 RoB: 5/9

Lundin, 2019 [8]	Case-control study	The aim of this study was to search for the 22q11.2 microduplication in an unpublished cohort of Swedish BEEC patients and to further investigate the 22q11.2 region in cases without the microduplication as well as to functionally evaluate identified candidate variants.	n=422 BEEC patients	n=1219 controls (DNA samples from placentas, blood donors)	22q11.2 microduplication	**BEEC development associated with the 22q11.2 duplication** BEEC: 2.61% controls: 0.08% OR = 32.6 (95% CI = 4.2–253.3; p = 8.7 × 10−4)	In conclusion, the 22q11.2 duplication is more common among patients with intellectual disability and various congenital defects compared to normal controls (0.32%; p = 1.3 × 10−5) and even more common among BEEC patients (2.61%: p <0.00001).	Pooled data (cases and controls) from different cohorts, comparability of cases and controls not described, no information on recruitement period and countries The authors declare no conflict of interest. Funding: reported in detail in the paper	4 RoB: 3/9
Sharma, 2018 [9]	Cross-sectional study	We aimed to determine the molecular and functional consequences of ISL1 variants and estimate the dependence of ISL1 protein on other predicted candidates.	human bladder exstrophy-epispadias complex		ISL1 • rs9291768 • rs6874700 • c.137C > G (p.Ala46Gly)	• all rsIDs showed a GWAVA score less than 0.5, which indicates that the variants are non-functional and they are likely to be associated with the disease conditions • nearest transcript start sites were 4288 and 6467 bp rs6874700 and rs9291768: This also indicates that these non-coding variants are potentially disease-associated • ISL1 protein specific N-terminal LIM domain (which harbors the variant	We investigated whether the most significantly associated variants rs9291768 and rs6874700 might constitute potential targets of the lncRNA (NONHSAT249106), residing in their close vicinity. However, the results of our analysis do not support this hypothesis. Interestingly, our analysis suggests that the ISL1 variant c.137C >	number of cases and case recruitement not clearly described, no statistical analysis performed The authors declare no conflicts of interest. This work was funded by a grant of the German Research Foundation (Deutsche Forschungsgem	4 RoB: 2/8

						c.137C > G), limits its transcriptional ability, and might interfere with ISL1-estrogen receptor interactions.	G, results in decreased protein stability. In addition, by integrating multiple parameters, we provide novel insights about the involvement of ISL1 in the etiology of BEEC.	einschaft, RE 1723/1-3).	
Zhang, 2017 [10]	Case-control study Australia, German, Italy, Spain, Sweden, United Kingdom, USA	This study sought to further explore the genetics in a larger set of patients following-up on the most promising genomic regions previously reported.	n=268 classic bladder exstrophy patients n=92 classic bladder case-parent trios	n= 1,354 ethnically matched controls	ISL1	**rs6874700** Cases vs. controls RR 1.80 (95% CI 1.44–2.25) Case-parent trios RR 1.61 (95% CI 1.07–2.41) Cases, Controls, Case-parent trios RR 1.75 (95% 1.44–2.13) p=2.2 × 10−08	Our present association study in classic bladder exstrophy patients together with functional studies in mouse embryos and zebrafish larvae suggest ISL1 as a regulator of urinary tract development.	less information about the recruitment process The authors declare no competing financial interests. Funding: reported in detail in the paper *only significant results shown*	4 RoB: 8/9
Zhang, 2017 [11]	Case-control study Europe	We analyzed its sequence in 200 classic bladder exstrophy patients.	n=200 isolated classic bladder exstrophy patients (blood and salvia)	n=1,006 alleles	ISL1	• only five patients to be heterozygous (C/T) for rs35665267, a single nucleotide polymorphism (SNP), deposited in the SNP database (dbSNP Build 147) with a frequency for the rare T-allele among Europeans (n=1,006 alleles) of 0.0159	Although we identified two enhancer variants in five classic bladder exstrophy patients, their clinical significance seems unlikely, implying that sequence variants in the ISL1 LF-SINE	less information about case and control recruitement, comparability of cases and controls not described supported by a grant from the German Research	4 RoB: 4/9

						• observed frequency in classic bladder exstrophy patients was 0.0125, and hence not significantly different	enhancer are not frequently associated with classic bladder exstrophy.	Foundation (Deutsche Forschungsgemeinschaft,DFG; grantnumber RE1723/1–1).	
Raman, 2016 [12]	Case-control study 2000-2010 India	We aimed to establish a correlation between MTHFR gene 677 polymorphism and BEEC.	n=50 BEEC patients • classical bladder exstrophy (n=42) • cloacal exstrophy (n=2) • epispadias (n=4) Male: 44/50 Median age: 9.5 y (4-15 y)	n=age- and sex matched healthy school children Male: 42/50 Median age: 10 y (5-11 y)	MTHFR gene	**MTHFR polymorphism** <u>Bladder exstrophy</u> Homozygous normal (CC): 36/42 (85%) Heterozygous genotype (CT): 6/42 (15%) <u>Epispadias</u> Homozygous normal (CC): 3/4 (75%) Heterozygous genotype (CT): 1/4 (25%) <u>Cloacal exstrophy</u> Homozygous normal (CC): 0 Heterozygous genotype (CT): 2/2 (100%) <u>Variant</u> Homozygous normal (CC): 1/2 (50%) Heterozygous genotype (CT): 1/2 (50%) <u>Controls</u> Homozygous normal (CC): 46/50 (92%) Heterozygous genotype (CT): 4/50 (8%)	C677T MTHFR polymorphism has a strong association with severe variety (cloacal exstrophies) of BEEC occurrence.	consecutive or obviously representative series of cases unclear There are no conflicts of interest. Financial support and sponsorship: Nil.	4 RoB: 8/9
Kolarova, 2016 [13]	Cross-sectional study	PLAGL1 Epimutation and Bladder Exstrophy: Coincidence or Concurrent Etiology?	n=23 BEEC patients • epispadias (n=1) • classic bladder		PLAGL1	• No significant differences in the DNA methylation of the not imprinted and imprinted CpG were observed	Considering that it is highly unlikely to detect a PLAGL1 epimutation among 23 individuals given	patient recruitement not clearly described, small sample size, no statistical	4 RoB: 4/8

			exstrophy (n=10) • cloacal exstrophy (n=12) Male: 12/23 Median age: 10 (2-17 y)			depending on subtype of BEEC • 1 patient with classic bladder exstrophy: hypomethylation of the imprinted PLAGL1 locus in chromosome 6q24 • verified this hypomethylation by MS-MLPA and showed further the methylation loss to be caused most likely by a mosaic epimutation	the low incidence of this alteration in the population, our observations further support a link between BEEC and imprinting disorders	analysis performed The authors have no conflict of interest to declare. Funding: reported in detail in the paper	
von Lowtzow, 2016 [14]	Case-control study Bosnia, Central Europa Croatia, Italy, Portogal, Spain, Turkey	The aim of the present study was to detect further BEEC-associated CNVs by performing a state-of-the-art genome-wide single nucleotide polymorphism-array based analysis in 169 BEEC patients.	n=169 BEEC patients (Blood or saliva) • Epispadias (n=17) • Classic bladder exstrophy (n=126) • cloacal exstrophy (n=26) Male: 109/169	n=1307 population-based controls n=125 parents of the present BEEC patients (Blood or saliva)	CNV	**CNVs found in regions not previously associated with BEEC** • 4q26 (n=1 epispadias) • 5q22.2 (n=1 bladder exstrophy) • 13q33.1-q33.2 (n=1 bladder exstrophy) • Xq11.1-q13.1 (n=1 bladder exstrophy) • 22q11.1a (n=1 bladder exstrophy) • Xp22.31 (n=2 bladder exstrophy) **CNVs in regions previously associated with BEEC** • 1p36.33 (n=3; 2 bladder exstrophy, 1 epispadias) • 1q41 (n=1 bladder exstrophy) • 9q34.2 (n=1 bladder exstrophy)	Around 98.5 % of cases with BEEC are isolated, and yet many of the described CNVs in this study and by others are inherited from a supposedly healthy parent. This argues either, that non-penetrance is extremely common, or that the CNVs detected are unrelated. Further research is warranted to determine the role of the presently identified CNVs in BEEC etiology. Some of these rare inherited CNVs might at least constitute	case recruitement not clearly described, comparability of cases and controls not described The authors declare that they have no competing interests. HR is supported by grant RE 1723/1-1 from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). MMN received support from the Alfried Krupp von Bohlen und	4 RoB: 5/9

						• 19q13.42 (n=1 bladder exstrophy)	modifiers or contributors in a multifactorial mode of inheritance.	Halbach-Stiftung, and is a member of the DFG-funded Excellence Cluster Immunosensa-tion.	
Baranowska Körberg, 2015 [15]	Case-control study 2006 Sweden	The aim of this study was to explore the mutation spectrum of the WNT gene family network in an extensive Swedish BEEC patient material using next generation sequencing technology and to evaluate the identified candidate genes in the zebrafish model.	n=95 BEEC patients • bladder exstrophy patients without the 22q11 duplication (n=20)	n=376 placenta sample controls	WNT	13 variants were identified as potentially disease causing: • WNT3 • WNT6 • WNT7A • WNT8B • WNT10A • WNT11 • WNT16 • FZD5 • LRP1 • LRP10 **WNT3** no statistically significant difference was detected between patients and controls (Chi square 2857, P-value 0.091, permutated P-value (10,000) = 0.1547) Our study suggests that the function of the WNT3 p.Cys91Arg variant was altered, since RNA overexpression of mutant Wnt3 RNA does not result in embryonic lethality as seen with wild-type WNT3 mRNA.	In aggregate our data support the involvement of WNT-pathway genes in BEEC and suggest that WNT3 in itself is a rare cause of BEEC.	case recruitement not clearly described, no information about the control group, comparability of cases and controls not described The authors have declared that no competing interests exist. Funding: reported in detail in the paper	4 RoB: 2/8

						rs9890413 no statistically significant association was detected (Chi square 0.407, P-value 0.5233, permutated P-value (10,000) = 0.7847)			
Draaken, 2015 [16]	Case-control study	The aim of the present study was to identify susceptibility loci for classic bladder exstrophy.	n=110 classic bladder exstrophy patients	n=1177 controls (European)	5q11.1	**ISL-1** In this region, 138 single nucleotide polymorphisms reached genome-wide significance. **rs6874700** most significant marker, rs6874700, showed a P value of 6.27 x 10−11 **rs9291768** RR: 2.18 [95% CI 1.75–2.71] showing the lowest P value (p = 2.13 x 10−12)	The present study identified the first genome-wide significant locus for classic bladder exstrophy at chromosomal region 5q11.1, and provides strong evidence for the hypothesis that ISL1 is the responsible candidate gene in this region.	case recruitement not clearly described, representative-ness of the BEEC cases uncleary, comparability of cases and controls not described The authors have declared that no competing interests exist. Funding: reported in detail in the paper	4 RoB: 4/9
Draaken, 2014 [17]	Case-control study	The aims of the present study were to estimate the frequency of the 22q11.21 duplication in classic bladder exstrophy patients compared with healthy controls by screening the largest	n=244 BEEC patients • n=217 classic bladder exstrophy patients	n=665 healthy controls	22q11.2 microdupli cation	**New duplications of variable size** classic bladder exstrophy: 4/217 controls: 0/665 **Pooling of previous and presented data** Classic bladder exstrophy: 8/305 controls: 1/1218 OR: 31.86 (95% CI 4.24-1407.97)	Our data suggest that duplication of 22q11.21 increases classic bladder exstrophy risk and implicate a phenocritical region in disease formation.	case recruitement not clearly described, pooling of cases with previous publicated datas, comparability of cases and controls not described	4 RoB: 4/9

		classic bladder exstrophy sample to date.						Funding and conflict of interest: reported in detail in the paper	
Ramaeker, 2014 [18]	Case reports	Bladder Exstrophy–Epispadias Complex and Triple-X Syndrome: Incidental Finding or Causality?	n=2 cases Case 1: fetus (47,XXX) with bladder exstrophy with absence of the anterior bladder wall and protrusion of the posterior bladder wall Case 2: 34 y (triple-X syndrome) and classic bladder exstrophy		Triple-X Syndrome	The presence of fetal bladder exstrophy and triple-X syndrome together can be an incidental finding.	This suggests that a presumed dosage effect leads to gene overexpression of proteins involved in bladder development.	Patient recruitement not clearly described, descriptive description of all known cases (no interventions and results reported) The array-based analysis of Case 2 was supported by a grant from the German Research Foundation (DFG; RE 1723/1-1).	4 RoB: 9/10
Reutter, 2014 [19]	Case-control study Central European	We report the first study which utilizes genome-wide association methods to analyze a cohort comprising patients presenting the most common BEEC form, classic bladder exstrophy, to identify common variation associated with risk for isolated classic bladder exstrophy.	n=218 cases (blood and salvia)	n=865 controls n=78 trios in total (blood and salvia)	• WNT3 • WNT9b	• discovery sample identified amarker near SALL1, showing genome-wide significant association with classic bladder exstrophy (not further support for this finding) • identify an association with classic bladder exstrophy across our study samples (discovery: P 5 8.88 3 1025; followup: P	Our suggestive findings support the hypothesis that larger samples are warranted to identify association of common variation with classic bladder exstrophy.	patient recruitement not clearly described, no information about the control group, comparability of cases and controls not described The authors have declared that no competing interests exist.	4 RoB: 5/9

						5 0.0025; combined: 1.09 3 1026) in a highly conserved 32 kb intergenic region containing regulatory elements between WNT3 and WNT9B • not able to replicate our findings for the WNT3-WNT9B locus (P=0.51)		Funding: reported in detail in the paper	
Darling, 2013 [20]	Case-control study Australia, Bangladesh, Canada, China, India, Spain, USA	The aim of this new study is to identify TAP63 promoter sequence variations, which may contribute to up-regulation of TAP63 isoforms in patients with BEEC.	n=112 BEEC patients (109 buccal, 3 bladder tissue)	normal population frequency data	TAP63	• No novel sequence variation or mutation was uncovered • Two known SNPs were identified • allele frequency analysis was not statistically significant	Our data do not associate genetic variation within the TAP63 promoter region with an increased risk of BEEC. Our data so far suggests that only ΔNP63 promoter aberration is involved in BEEC pathogenesis.	patient recruitement not clearly described, no information about the control group, comparability of cases and controls not described No information about conflict of interest. Funding: reported in detail in the paper	4 RoB: 3/9
Draaken, 2013 [21]	Case-control study Central European	The aim of the present study was to identify causative de novo microaberrations characterized by loss or gain of genomic material (i.e., CNV), which may contribute to the BEEC at a genome-wide level.	n=110 BEEC patients without 22q11.2 microduplication (blood and salvia) • epispadias (n=8) • classic bladder	n=91 both parents n=15 only one parent n=4 no parent (blood and salvia)	19p13.12	• 1 patient: de novo 0.9 Mb microduplication involving chromosomal region 19p13.12 • Sanger sequencing of the complete cohort did not reveal any pathogenic alterations affecting	Our study showed classic bladder exstrophy to be associated with a 0.9 Mb 19p13.12 duplication. WISH analysis of the genes encompassed by the duplication revealed WIZ as a	patient recruitement not clearly described, family-based controls, not all parents participated in the control group	4 RoB: 5/9

			exstrophy (n=95) • exstrophy of the cloaca (n=7)			the coding region of WIZ.	plausible candidate to be involved in the development of the urogenital system. Our mutation screening study, however, could not confirm that mutations affecting human WIZ are a frequent cause of BEEC.	No information about conflict of interest. Funding: reported in detail in the paper	
Qi, 2013 [22]	Case-control study Germany, USA	We conducted a candidate gene association study to further investigate the role of p63 in human BEEC.	n=154 Caucasian patients with nonsyndromic BEEC (blood) • epispadias (n=16) • classic bladder exstrophy (n=130) • exstrophy of the cloaca (n=8) Male-female-ratio: 99:55	their unaffected parents (blood)	• p63	• rs17447782: OR 0.55; p=0.04 • rs1913720: OR 0.71; p=0.04 • rs6790167: OR 1.4; p=0.04 • rs9865857: OR 0.68; p=0.02 • rs1543969: OR 0.69; p= 0.04 • rs4687100: OR 0.65; p=0.02 • After correction for multiple comparisons, none of the single nucleotide polymorphisms was significant.	The altered transmission of p63 variants in nonsyndromic BEEC patients may be suggestive of its involvement in the disease etiology.	patient recruitement not clearly described, control group family-based *only significant results shown* The authors have no conflicts of interest to declare. Funding: reported in detail in the paper	4 RoB: 6/9
Wilkins, 2012 [23]	Case-control study Australia, Bangladesh, India, Canada, China, Spain	We hypothesised that TP63 is involved in human BEEC pathogenesis	n=163 BEEC patients (foreskin)	n=285 ethnicity-matched controls	• TP63	• Sequencing of the DeltaNp63 promoter showed 7 single nucleotide • polymorphisms and 4 insertion/deletion polymorphisms. • insertion/deletion polymorphisms were	We found promoter sequence variants that were statistically associated with the disease and the sequence variant	less information about recruitement of cases and controls, comparability of cases and controls not described	4 RoB: 6/9

						associated with an increased risk of BEEC • 12-base-pair deletion was associated with an increased risk with only Caucasian patients (p = 0.0052 OR= 18.33) • 4-base-pair insertion was only associated with non-Caucasian patients (p = 0.0259 OR = 4.583) • We found a consistent and statistically significant reduction in transcriptional efficiencies of the promoter sequences containing insertion/deletion polymorphisms in luciferase assays	location varied between Caucasian and non-Caucasian patients. This is particularly important as Caucasian populations have a higher risk of BEEC. These findings provide an explanation of BECC and a base for further study of TP63 related genes in this disease.	(except ethnicity) The authors have declared that no competing interests exist. Funding: reported in detail in the paper	
Wittler, 2012 [24]	Case-control study European descent	Since the spatio-temporal localization of Parm1 corresponded to tissues which are affected in human epispadias, we sequenced PARM1 in 24 affected patients.	n=24 patients with epispadias Male: 14/24	parents	Parm1	• only two heterozygous variants • PARM1 gene analysis revealed no alterations in the coding region of any of the investigated patients	These findings suggest that PARM1 does not play amajor role in the development of human epispadias.	patient recruitement not clearly described, family-based controls, not all parents participated in the control group, less information about the control group The authors have no conflicts of interest to declare.	4 RoB: 3/9

								Funding: reported in detail in the paper	
Qi, 2011 [25]	Case-control study	This study provides the first expression profile of urogenital genes during bladder development and points to the high probability candidate genes for BEEC.	n=3 exstrophy bladder samples (bladder tissue) race- and gender matched: two female pairs, one male pair, all Caucasian younger than 3 y	n=3 normal bladder (bladder tissue)	Genome-wide expression profiling	• identified 162 genes differentially expressed in both embryonic and postnatal human samples • found 30% of the candidate genes to be directly associated with desmosome structure/ function or cytoskeletal assembly, pointing to desmosomal and/or cytoskeletal deregulation as an etiologic factor for BEEC	Further findings indicate that p63, PERP, SYNPO2 and the Wnt pathway may also contribute to BEEC etiology.	case recruitement not clearly described, small sample size, No information about conflict of interest. Funding: reported in detail in the paper	4 RoB: 7/9
Reutter, 2011 [26]	Cohort study *(for the comparison)* 2003-2008: Europe (Austria, France, Germany, Italy, Spain, Switzerland, and The Netherlands) 2001-2005: North America	To identify genetic and non-genetic risk factors contributing to the severity of the BEEC.	n=441 patients with BEEC • Epispadias (n=43) • classic bladder exstrophy (n=366) • cloacal exstrophy (n=31) Europe: 274 North America: 167 Males: 305/441	EUROCAT survey	• Down syndrome • Ventricular septal defect • Cleft lip with or without cleft palate	**Down syndrom** BEEC cohort: 3/441 (0.68 %) EUROCAT survey: 13 317/11 943 497 (0.11 %) Prevalence ratio: 6.10 (95% CI 2.08; 17.77) p=0.014 **Ventricular septal defect** BEEC cohort: 5/438 (1.14 %) EUROCAT survey: 29 691/11 712 426 (0.25 %) Prevalence ratio: 4.47 (95% CI 1.91; 10.36) p=0.006	Further research is needed to clarify whether the prevalence of Down syndrome is genuinely increased in the BEEC population.	different recruitement frames (e.g. time, countries, settings), an adequately matched control cohort cannot be generated from the EUROCAT sample The authors declare no conflicts of interest This project has been partially supported	4 RoB: 6/9

						Cleft lip with or without cleft palate BEEC cohort: 3/438 (1.14 %) EUROCAT survey: 10 470/12 288 732 (0.09 %) Prevalence ratio: 7.98 (95% CI 2.72; 23.25) • p=0.007		through NIH grants (R01 DE016886 from the NIDCD/NIH; M01-RR00052 from the NCRR/NIH) and a CMN grant (CMNSB06).	
Vlangos, 2011 [27]	Case-control study USA	The goal of this study was to identify genetic aberrations in 13 patients with Omphalocele–exstrophy of the bladder-imperforate anus-spinal defects/cloacal exstrophy using a combination of candidate gene analysis and microarray studies.	n=13 patients with Omphalocele–exstrophy of the bladder-imperforate anus-spinal defects • patients with bladder exstrophy (n=11) (blood or buccal samples)	n=100 control samples	CNV	• DNA gains and/or losses were detected in four patient samples tested, and a total of 11 different changes were identified. • 10 of the changes were unique • 1 occurred in 3 of the seven 7 tested. • Recurrent change is a duplication mapping to chromosome 17q21.31 covering bases 41,521,621–41,647,903 **Copy Number Variation Identified by SNP Array** <u>Patient #1</u> • 7p15.1 (Gain) • 17q21.31–q21.32 (Gain) <u>Patient #2</u> • 5q21.1 (Gain) • 11p15.1 (Gain) • 17q21.31–q21.32 (Gain) • 22q11.1 (Gain) • Xp22.31 (Loss)	We conclude that Omphalocele–exstrophy of the bladder-imperforate anus-spinal defects a complex disorder from an etiological perspective, likely involving a combination of genetic and environmental predispositions. Based on our data, Omphalocele–exstrophy of the bladder-imperforate anus-spinal defects complex is unlikely to be caused by a recurrent chromosomal aberration.	no information about the control group, comparability of cases and controls not described supported by the Department of Pediatrics Amendt-Heller award for newborn research and a Rackham faculty research grant to CEK. CNV was supported by a postdoctoral fellowship from the Center for Genetics in Health and Medicine at the University of Michigan.	4 LoE: 2/9

						Patient #9 • 17p13.2 (Gain) • 18q12.1 (Gain) • 4p15.31 (Loss) • 6q21 (Loss) Patient #11 • 7p21.3 (Loss) • 17q21.31–q21.32 (Gain)			
Ching, 2010 [28]	Case-control study Central Europe, Marocco, Panama	We compared p63 expression in cDNA samples derived from bladder tissues and lymphocytes of 15 BEEC newborns against control samples by semiquantitative PCR and quantitative real-time PCR.	n=15 BEEC newborns (bladder tissues and lymphocytes) n=22 BEEC patients • classic bladder exstrophy (n=18) • exstrophy of the cloaca (n=4)	control samples	p63	• Tissue-specific expression of a novel and already known mRNA isoforms were established • Reproducible dysregulation of variable p63 isoforms was observed in 11/15 indicating altered gene expression • No obvious p63 gene mutations were identified in any of the patients	Our findings strongly suggest that p63 is not only involved in embryonic formation of the urogenital and ventrocaudal anatomy but is also highly dysregulated in human BEEC bladder tissue. Since p63 has been shown to self-regulate its expression through a balance of its isoforms, the dysregulation observed may contribute to the formation of BEEC.	case and control recruitement not clearly described, comparability of cases and controls not described Conflict of interest and fundig: reported in detail in the paper.	4 RoB: 4/9
Draaken, 2010 [29]	Cross-sectional study	The Cyr61 gene exhibited the highest response to FLU in rat fetal testis, and we suggested it a promising candidate gene for epispadias in humans, because	n=20 patients with BEEC • epispadias (n=11) • classic bladder exstrophy (n=8) (blood)		CYR61 gene	• Examination of all CYR61 exons and their adjacent splice sites failed to reveal any mutation in the CYR61 genes from our patient samples. • 16 variants that • were detected are all common SNPs	Our mutation screening study, however, could not confirm that mutations affecting the CYR61 gene are a frequent cause of epispadias or	patient recruitement not clearly described, small sample size, no statistical analysis performed	4 RoB: 3/8

		its protein product promotes proliferation, migration, and adhesion of endothelial cells and fibroblasts	Male: 12/20				classic bladder exstrophy, although rare mutations might be detectable in larger patient samples	No information about conflict of interest. Funding: reported in detail in the paper	
Reutter, 2010 [30]	Case-control study Iran	In the present study, genome-wide linkage analysis was performed in a recently reported consanguineous Iranian multiplex family with an affected sibling pair: a female with epispadias and a male with classic exstrophy of the bladder	siblings • female: epispadias • male: classic bladder exstrophy	parents and 2 further siblings	genome-wide linkage	**7 loci with LOD scores >1.6** • 1p33 • 4q31.21-22 • 9q22.33 • 12q13.13-2 • 13q12.12-13 • 18q23 • 19q13.31-41 • Haplotype analysis showed that the affected individuals were homozygous identical by descent for all seven regions. • Two of these regions overlapped with further findings: 4q31.21-22, and 19q13.31-41	These results suggest that chromosomal regions 4q31.21-22 and 19q13.31-41 are likely to harbor genes for an autosomal recessive form of BEEC.	case and control recruitement not clearly described, family-based control group No information about conflict of interest. Supported by German Federal Ministry of Education and Research (Bundesministe-rium für Bildung und Forschung)	4 RoB: 6/9
Ludwig, 2009 [31]	Case-control study Germany, Spain	To our knowledge, the present study represents the first approach to identify susceptibility genes involved in the etiology of the BEEC by using a genome-wide linkage scan.	n=2 classic bladder exstrophy (blood)	Two pedigrees First Family: five-generation family with nine subjects Second: five-generation family where 10 individuals could be tested	genome-wide linkage	Evidence for possible risk/modifying loci on chromosomes (LOD scores >1.50): • 2p22.1–p21 • 2p25.2–p25.1 • 4q23–q32.3 • 7q21.3–q33 • 7q34–q36.1, 14q31.1–q32.2 • 19q13.33–q13.43 was obtained	This study was the first positional approach to identify chromosomal candidate regions causally related to bladder exstrophy-epispadias complex. Our results suggest the presence of susceptibility	case and control recruitement not clearly described, family-based control group No information about conflict of interest. Funding: reported in detail in the paper	4 RoB: 6/9

							genes in the regions identified. These regions need to be confirmed in future studies.		
Reutter, 2009 [32]	Retrospective case reports 1999-2009	We suggest that exstrophy–epispadias complex represents a rare but inherent part in the spectrum of Down syndrome-associated midline defects.	n=6 cases • bladder exstrophy (n=5) • cloacal exstrophy (n=1)		trisomy 21	• Six cases of the co-occurrence of exstrophy–epispadias complex and Down syndrome have now been reported. The increased prevalence of Down syndrome among exstrophy–epispadias complex patients suggests that exstrophy–epispadias complex is a rare but inherent part of Down syndrome-associated midline defects.	*Results correspond with the conclusion*	descriptive description of all known cases (no interventions and results reported) supported by a research grant from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF).	4 RoB: 10/20
Hipp, 2008 [33]	Case-control study	To compare the genetic profiles of 'healthy' bladder smooth muscle cells and exstrophic smooth muscle cells to identify genes that are over- and under-expressed in exstrophic smooth muscle cells, thus providing a molecular evaluation of the quality and therapeutic potential of	n=3 newborn children (bladder tissue) Age: 1 day Male: 2/3	'healthy' bladder smooth muscle cells	genetic profiles	**Exstrophic smooth muscle cells** • 961 genes that are over-expressed • 432 genes that are under-expressed Analysis of these signatures identified an over-expression of inflammatory genes and an under-expression of developmental genes.	Our data is in concordance with previous studies and histological data showing that exstrophic smooth muscle cells are developmentally immature relative to healthy bladder smooth muscle. The clinical implication of the exstrophic smooth muscle cells genetic signature is that it provides a list of targets that can	patient recruitement not clearly described, no information about the control group, comparability of cases and controls not described The authors declare no conflicts of interest This work was supported, in	4 RoB: 3/9

		exstrophic smooth muscle cells tissue.					be (i) manipulated ex vivo and/or in vivo to induce differentiation (the completion of development) and (ii) used as biomarkers to explain the variability of the clinical symptoms after surgical closure.	part, by a grant from the Crown Foundation and Basic Research Program of the Korean Science & Engineering Foundation (KOSEF) # R01-2003-000-10438-0.	
Reutter, 2007 [34]	Case reports Morocco/The Netherlands	We aimed to investigate a possible genetic basis of BEEC in a consanguineous kindred of Moroccan origin with three members showing the same phenotypic expression of BEEC.	n=3 males with nonsyndromic classic bladder exstrophy (two were cousins)		chromosomal aberrations and micro-aberrations	• Chromosome banding revealed normal karyotypes • By array-CGH, one of 8000 clones was aberrant in both affected cousins: clone from 1p21.1 contained the AMY1B, AMY2B, AMY2A genes	The aberration detected by array-CGH in both affected cousins is a known copy-number variant and most likely unrelated to the exstrophy of the bladderphenotype. Nevertheless, in this family the nonsyndromic exstrophy of the bladder could be a monogenic disorder inherited in an autosomal-recessive or X-linked fashion.	recruitement time not reported, no statistical analysis performed The authors state that there is no conflict of interest. This work was supported by the Doktor Robert Pfleger-Stiftung.	4 RoB: 18/20
Reutter, 2006 [35]	Case-control study German	We considered the suppressor of variegation, enhancer of zeste and Trithorax (SET) gene, located at chromosome 9q34, to be a good	n=33 BEEC patients	n=50 healthy Caucasian	zeste and Trithorax (SET) gene	SET analysis did not reveal either a mutation or the presence of four single-nucleotide polymorphisms (dbSNP124) already	The data obtained in this study most likely exclude the SET gene as a possible genetic cause of BEEC.	less information about case and control recruitement, comparability of cases and controls not described	4 RoB: 4/9

		candidate, as the protein encoded is involved in the regulation of cell proliferation and differentiation.				described in the database.		No information about conflict of interest and funding.	
Boyadjiev, 2004 [36]	Cross-sectional study USA	To identify genetic and nongenetic factors contributing to the risk of bladder exstrophy epispadias complex.	n=163 families with bladder exstrophy epispadias complex n=440 DNA samples • n=2 chromosomal abnormalities, 46XY, t(8;9)(p11.2; q13) and 47XYY		HLXB9	• present in samples from normal controls and are unlikely to confer increased susceptibility to BEEC • mutations of HLXB9 are not a common cause of BEEC, although changes in more distant regulatory regions or within introns of this gene cannot be excluded.	Molecular analysis of the HLXB9 gene, which causes Currarino syndrome, did not detect mutations in the blood or bladder DNA of 10 patients with bladder or cloacal exstrophy.	No random sample or whole population data, biased sampling frame: invitation via institutionally database and internet support group, no recruitment period described, small sample size, less response rate (232/815), self-reported information to drugs, alcohol and smoking The authors declare no conflict of interest. Source of funding: Johns Hopkins – GCRC.	4 RoB: 3/8

Schlüsselfrage Welche Risikofaktoren können die Entstehung eines BEEK begünstigen?								
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Risikofaktor(en)**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Down-Syndrom & Angeborene Fehlbildungen								
Reutter, 2011 [26]	Cohort study *(for the comparison)* 2003-2008: Europe (Austria, France, Germany, Italy, Spain, Switzerland, and The Netherlands) 2001-2005: North America	To identify genetic and non-genetic risk factors contributing to the severity of the BEEC.	n=441 patients with BEEC • Epispadias (n=43) • classic bladder exstrophy (n=366) • cloacal exstrophy (n=31) Europe: 274 North America: 167 Males: 305/441	• Down syndrome • Ventricular septal defect • Cleft lip with or without cleft palate	**Down syndrom** BEEC cohort: 3/441 (0.68 %) EUROCAT survey: 13 317/11 943 497 (0.11 %) Prevalence ratio: 6.10 (95% CI 2.08; 17.77) p=0.014 **Ventricular septal defect** BEEC cohort: 5/438 (1.14 %) EUROCAT survey: 29 691/11 712 426 (0.25 %) Prevalence ratio: 4.47 (95% CI 1.91; 10.36) p=0.006 **Cleft lip with or without cleft palate** BEEC cohort: 3/438 (1.14 %) EUROCAT survey: 10 470/12 288 732 (0.09 %) Prevalence ratio: 7.98 (95% CI 2.72; 23.25) p=0.007	Further research is needed to clarify whether the prevalence of Down syndrome is genuinely increased in the BEEC population.	different recruitement frames (e.g. time, countries, settings), an adequately matched control cohort cannot be generated from the EUROCAT sample The authors declare no conflicts of interest This project has been partially supported through NIH grants (R01 DE016886 from the NIDCD/NIH; M01-RR00052 from the NCRR/NIH) and a CMN grant (CMNSB06).	4 RoB: 6/9
Reutter, 2009 [32]	Retrospective case reports 1999-2009	We suggest that exstrophy–epispadias complex represents a rare but inherent	n=6 cases • bladder exstrophy (n=5)	Co-occurrence down-syndrome	Six cases of the co-occurrence of exstrophy–epispadias complex and Down syndrome have now been	*Results correspond with the conclusion*	descriptive description of all known cases (no interventions and results reported)	4 RoB: 10/20

		part in the spectrum of Down syndrome-associated midline defects.	• cloacal exstrophy (n=1)		reported. The increased prevalence of Down syndrome among exstrophy–epispadias complex patients suggests that exstrophy–epispadias complex is a rare but inherent part of Down syndrome-associated midline defects.		supported by a research grant from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF).	
Elterliche Risikofaktoren								
Wang, 2021 [37]	Cross-sectional study 2009-2013 China	This study aimed to survey the overall situation of birth defects among citizens of Hangzhou, China, and the risk factors of different birth defect types.	n=4349 perinatal infants with bith defects n=41 bladder exstrophy patients Average maternal age: 28.61±4.7 y Average gestational age: 232.05±49.66 days	Demographic characteristics: • Mother's age • Gravidity • Parity • Family monthly income • Education level • Sex Risk factors in early pregnancy: • Fever • Pesticide exposure • Radiation exposure	**Bladder exstrophy** <u>Parity</u> R -0.04 (p=0.008) No significant correlation: • Mother's age • Gravidity • Family monthly income • Education level • Sex <u>Radiation exposure</u> R 0.098 (p<0.001) No significant correlation: • Fever • Pesticide exposure	*no conclusion to risk factors and bladder exstrophy*	unclear if all available data were included in the analysis (data from all available medical institutions in Hangzhou), small bladder exstrophy sample The authors declare that they have no conflict of interest. This study is supported by Research Fund Project of Zhejiang Health and Family Planning Commission (no. 2017KY552) and Study on the Feasibility of Gene Screening and Precise Intervention for Hereditary Deafness in Cord Blood.	4 RoB: 6/8

Reinfeldt Engbert, 2016 [38]	Matched case-control study 1973-2011 Sweden	To describe and assess bladder exstrophy and the potential maternal risk factors, for a time period of four decades, by conducting a nationwide register study of bladder exstrophy in Sweden.	n=720 • bladder exstrophy cases (n=120) • controls (n=600)	• Sex • Maternal age • Parity • Assisted conception • Origin of birth • BMI • Smoking • Comorbidities	**Bladder exstrophy** *Multivariate logistic regression* Maternal age (≥35 years vs. 25-29.9 y) OR 3.6 (95% CI 1.62-7.99) BMI (obesity vs. normal) OR 1.44 (95% CI 0.57-3.63) Smoking at any time OR 0.98 (95% CI0.47-2.05) no significant results for • Parity • Assisted conception • Origin of birth • Comorbidities	Advanced maternal age was the only significant potential maternal risk factor.	The authors have no relevant financial or nonfinancial conflicts of interest to disclose. Financial support was provided through the Regional Agreement on Medical Training and Clinical Research (ALF) between the Stockholm County Council, Karolinska Institutet, the Swedish Society of Medical Research, the Promobilia Foundation, the Swedish Society of Medicine, HRH Crown Princess Lovisa's Memorial Fund, the Samariten Foundation, the Freemasons' Fund for Children's Health, and the Swedish Research Council.	4 RoB: 9/9
Marengo, 2013 [39]	Cross-sectional study USA	Body Mass Index and Birth Defects	n=142 Epispadias cases	• Body Mass Index • Diabetes	**Epispadias** Maternal Body Mass Index Mothers with diabetes • BMI <18.5: aPR 0.7 (95% CI 0.22-1.76) • BMI 18.5–24.9: Reference • BMI 25–29.9: aPR 1.25 (95% CI 0.84-1.86)	Risk for birth defects was substantially increased among some obese mothers (BMI ≥30) (e.g., spina bifida, tetralogy of Fallot, cleft lip with or	patient recruitment not clearly described (e. g. recruitment period), small bladder exstrophy sample, self-reported maternal height, weight and	4 RoB: 3/8

					• BMI 30–34.9: aPR 0.57 (95% CI 0.26-1.2) • BMI 35–39.9: aPR 2.79 (95% CI 1.6-4.61) • BMI ≥40: aPR 1.56 (95% CI 0.62-3.27) Mothers with any diabetes • BMI <18.5: - • BMI 18.5–24.9: Reference • BMI 25–29.9: aPR 2.11 (95% CI 0.42-14.61) • BMI 30–34.9: aPR 0.68 (95% CI 0.03-6.8) • BMI 35–39.9: - • BMI ≥40: aPR 1.18 (95% CI 0.06-11.91)	without cleft palate, hypospadias, and epispadias).	diabetes status, less information about study subjects No information about conflict of interest. This project was supported in part by the CDCfunded Texas Center for Birth Defects Research and Prevention (#U01DD000494) through a cooperative agreement with the Texas Department of State Health Services (DSHS) as well as the Title V office at DSHS.	
Reutter, 2011 [26]	Cross-sectional study 2003-2008: Europe (Austria, France, Germany, Italy, Spain, Switzerland, and The Netherlands) 2001-2005: North America	To identify genetic and non-genetic risk factors contributing to the severity of the BEEC.	n=441 patients with BEEC • Epispadias (n=43) • classic bladder exstrophy (n=366) • cloacal exstrophy (n=31) Europe: 274 North America: 167 Males: 305/441	• Maternal intake of medications and/or drugs of abuse • Maternal exposure to tobacco, alcohol, and soft drinks • Maternal exposure to toxins or medical radiation • Maternal disease • Maternal periconceptiona l folic acid	**Maternal antacid intake** • Epispadias: 11/41 (27 %) • Classic bladder exstrophy: 48/333 (14 %) • Cloacal exstrophy: 8/28 (29 %) p=0.028 (Epispadias vs. bladder vs. cloacal exstrophy) OR: 2.14 (95% CI 0.9-5.08) **Maternal smoking** • Epispadias: 3/43 (7 %) • Classic bladder exstrophy: 47/347 (14 %)	Periconceptional folic acid supplementation appears to prevent the development of the severe phenotype of BEEC.	different recruitement frames (e.g. time, countries, settings), self-reported exposure *only significant results shown* The authors declare no conflicts of interest This project has been partially supported through NIH grants (R01 DE016886 from the NIDCD/NIH;	4 RoB: 5/8

				supplementation • Parental age	• Cloacal exstrophy: 9/29 (31 %) p=0.012 (Epispadias vs. bladder vs. cloacal exstrophy) p=0.009 (Epispadias/bladder vs. cloacal exstrophy) OR: 3.06 (95% CI 1.32-7.09) **Maternal exposure to chemical detergents** • Epispadias: 0/41 (0 %) • Classic bladder exstrophy: 39/345 (11 %) • Cloacal exstrophy: 2/27 (8 %) p=0.04 (Epispadias vs. bladder vs. cloacal exstrophy) OR: 0.71 (95% CI 0.16-3.12) **Maternal medical radiation (multiple x-rays or computer tomography)** • Epispadias: 4/43 (9 %) • Classic bladder exstrophy: 16/343 (14 %) • Cloacal exstrophy: 5/28 (18 %) p=0.013 (Epispadias vs. bladder vs. cloacal exstrophy) p=0.011 (Epispadias/bladder vs. cloacal exstrophy) OR: 3.98 (95% CI 1.37-11.56)		M01-RR00052 from the NCRR/NIH) and a CMN grant (CMNSB06).	

					Maternal age: Mean (SD) • Epispadias: 30.8 (3.5) • Classic bladder exstrophy: 29.8 (5) • Cloacal exstrophy: 27.3 (4.1) p=0.008 (Epispadias vs. bladder vs. cloacal exstrophy) p=0.005 (Epispadias/bladder vs. cloacal exstrophy) OR: 0.89 (95% CI 0.83-0.97) **Paternal age: Mean (SD)** • Epispadias: 34.3 (5) • Classic bladder exstrophy: 32.2 (5.6) • Cloacal exstrophy: 30.3 (5.9) p=0.012 (Epispadias vs. bladder vs. cloacal exstrophy) p=0.045 (Epispadias/bladder vs. cloacal exstrophy) OR: 0.93 (95% CI 0.87-1)			
Siffel, 2011 [40]	Cross-sectional study 1980-2006 Australie, Canada, China, Finland, France, Germany, Hungary, Israel, Italy, Mexico,	In this report we (1) provide an overview of historical aspects, embryology, etiology, clinical characteristics and genetics, epidemiology, prognosis, and treatment of bladder exstrophy, and (2) describe the current epidemiology of	n=564 cases with bladder exstrophy	Maternal age	**Bladder exstrophy** <u>Maternal age</u> • 1.52 per 100,000 births in age group<20 years to 2.69 per 100,000 births in age group ≥40 years • prevalence rates showed a significant (P<0.01) increase in prevalence by maternal age group • highest prevalence rates: 35–39 years (PR=1.76; 95% CI: 1.16–2.67) and ≥40	The higher prevalence among male cases and older mothers, especially among isolated cases are important factors to note for clinicians when assessing risk, and to include in future epidemiologic studies.	no random sample or whole population, biased sampling frame: variation in prevalence is most likely attributable to differences in registration of cases, different recruitment periods between the coutries, less information about study subjects	4 RoB: 5/8

	Netherlands, United Kingdom, Slovak Republic, USA	bladder exstrophy using a large dataset from the International Clearinghouse for Birth Defects Surveillance and Research.			years (PR=1.76; 95% CI: 0.92–3.39).		No information about conflict of interest. Funding is reported in detail in the paper.	
Tinker, 2011 [41]	Case-control study 1997-2005 USA	The aim of our analysis was to examine the association between maternal reports of injuries during early pregnancy and selected major structural birth defects using population-based case–control data.	n=22402 mothers • birth defects (n=16074) • controls (n=6328)	Maternal injuries	**Bladder exstrophy** Proportion of mothers reporting maternal injury during the periconceptional period* 6.4% (3/47) Association between reported maternal periconceptional injury Unadjusted odds ratio: 2.5 [95% CI 0.8, 8.2] ** month prior to pregnancy until the end of the third month of pregnancy*	no conclusion to risk factors and bladder exstrophy	potential for selection bias: participation rate was 69.3% for cases and 66.2% for controls, comparability of cases and controls not clearly described, injuries were self-reported (blinding of interviewer unclear) No information about conflict of interest. This study was funded by the Centers for Disease Control and Prevention.	4 RoB: 4/9
Gambhir, 2008 [42]	Cross-sectional study Algeria, Austria, Croatia, France, Germany, Italy, Netherlands, Poland, Romania,	To identify causative non-genetic and genetic risk factors to the bladder exstrophy epispadias complex.	n=214 families • 9% epispadias (n=19) • 84% classical exstrophy of the bladder (n=180) • cloacal exstrophy (n=15)	• Parental age • Smoking Status • Alcohol exposure • Medication • Miscarriages • periconceptional folic acid supplementation • Radiation • Infections	**Parental age** Mean maternal age Epispadias: 29.7 y Classical exstrophy 30.0 y Cloacal exstrophy: 27.9 y Mean paternal age Epispadias: 33.8 y Classical exstrophy: 32.7 y Cloacal exstrophy: 31.4 y *no significant difference* **Smoking**	Our study corroborates the hypothesis that epispadias, classical exstrophy of the bladder and cloacal exstrophy are causally related, representing a spectrum of the same developmental defect, with a small	no random sample or whole population, biased sampling frame: recruitement through various pediatric urology clinics and self help groups, small sample size, some outcomes are self-reported, response rate and	4 RoB: 3/8

	Serbia, Spain, Switzerland, Turkey, United Kingdom				Epispadias and classic bladder exstrophy: 13% Cloacal exstrophy: 43% p=0.009 **Folic acid supplementation** cloacal exstrophy mothers were more compliant with folic acid supplementation than mothers of the combined group of patients with epispadias/classic bladder exstrophy (p = 0.037) No association with parental age, maternal reproductive history or periconceptional maternal exposure to alcohol, drugs, chemical noxae, radiation or infections was found.	risk of recurrence within families. Embryonic exposure to maternal smoking appears to enforce the severity, whereas periconceptional folic acid supplementation does not seem to alleviate it. There is a disproportional prenatal ultrasound detection rate between severe and mild phenotypes, possibly due to the neglect of imaging of full urinary bladders with focus on neural tube defects.	recruitment period not described S.A.B is partially funded through a Children's Miracle Network Endowed Chair and through grants K23 DE00462, R03 DE016342, and R01 DE016886 from NIDCD/NIH and M01-RR00052 from NCRR/NIH	
Caton, 2007 [43]	Cross-sectional study 1983-1999 USA	We examined epidemiologic trends and risk factors for bladder exstrophy and cloacal exstrophy in a large population-based dataset.	n= 4603747 live births • bladder exstrophy (n=77) • cloacal exstrophy (n=29)	• Conception season • Maternal residence • Plurality • Infant sex • Gestational age • Birth weight • Weight for gestational age • Maternal age • Maternal education • Prenatal care • Primary payor • Total previous live births	**Bladder exstrophy** Conception season Winter (Dec–Feb): Reference Spring (Mar–May): aPR 1.63 (0.74–3.59) Summer (Jun–Aug): aPR 2.46 (1.19–5.10) Fall (Sep–Nov): aPR 1.79 (0.83–3.86)	Factors associated with bladder exstrophy included summer conception, white, non-Hispanic maternal race/ethnicity, and male sex.	small sample size No information about conflict of interest and funding. *only significant results for baldder exstrophy cases shown.*	4 RoB: 7/8
Boyadjiev, 2004	Cross-sectional study	To identify genetic and nongenetic factors	n=232 families with bladder	• Maternal age • Paternal age • Tabacco	**Bladder exstrophy epispadias complex** Maternal age	In addition to race	No random sample or whole population data,	4

[36]	USA	contributing to the risk of bladder exstrophy epispadias complex.	exstrophy epispadias complex • epispadias (n=33) • classic bladder exstrophy (n=180) • cloacal exstophy (n=19)	• Alcohol • Drugs	a trend for older mothers among those in the exstrophy epispadias complex group that was statistically different from the general population data (p<0.001) <u>Paternal age</u> was greater than in the general population (p<0.001) <u>Parity</u> comparing parity with the general population was marginally significant (p= 0.08) No significant effects: • tobacco • alcohol • drugs	and advanced parental age, birth order may be a risk factor for bladder exstrophy epispadias complex.	biased sampling frame: invitation via institutionally database and internet support group, no recruitment period described, small sample size, less response rate (232/815), self-reported information to drugs, alcohol and smoking *the analysis also includes cloacal exstrophy cases* The authors declare no conflict of interest. Source of funding: Johns Hopkins – GCRC.	RoB: 3/8
Yang, 1994 [44]	Cross-sectional study 1980-1987 USA	We present comparative epidemiologic characteristics of five congenital abnormalities that have been suggested to result from midline abnormal developmental disturbances: esophageal atresia with or without tracheoesophageal fistula, imperforate anus with or without fistula,	n= 22 bladder exstrophy cases	Maternal age	<u>Maternal age</u> Results showed no significant trend for bladder exstrophy.	*no conclusion to risk factors and bladder exstrophy*	patient recruitment not clearly described, small sample size, less information about study subjects No information about conflict of interest and funding.	4 RoB: 4/8

		omphalocele, bladder exstrophy, and diaphragmatic hernia. The purpose was to assess the extent of epidemiologic similarities among these five defects.						
Swerdlow, 1988 [45]	Cross-sectional study 1974-1978 United Kingdom	Data from the England and Wales national congenital malformation notification scheme were examined for associations of male genital tract malformations.	n=3963 selected malformations in males epispadias (n=89)	• Maternal parity • Maternal age	**Epispadias** Maternal parity • were not significantly related to parity • relative risk was lower for secondborn than for malformations with maternal age and with parity was firstborn boys (significant) Maternal age <20 y: RR 1.72 (95% CI 0.94-3.15) 20-24 y: RR 1.1 (95% CI 0.67-1.81) 25-29 y: 1.0 30-34 y: RR 0.78 (95% CI 0.4-1.55) ≥35 y: RR 1.31 (1.03-1.67) p<0.001	*no conclusion to risk factors and epispadias*	unclear if the sample is unbiased: voluntary notification by doctors and midwives, small sample sizes No information about conflict of interest and funding.	4 RoB: 6/8
Anonymous, 1987 [46]	Cross-sectional study 1967-1985 Australia, Denmark, French, Italy, Mexiko, Norway, Spaon, Sweden, USA	Epidemiology of bladder exstrophy and epispadias	n=6276038 births • epispadias (n=148) • bladder exstrophy (n=208)	• Maternal age • Parity	**Bladder exstrophy** Parity increased risk at high parity **Epispadias** Parity no increased risk at high parity **Bladder Exstrophy & Epispadias** Maternal age	Both bladder exstrophy and epispadias seem to occur more frequently among infants of teenage mothers than in other age groups. The effect is not strong and barely reaches statistical significance.	no random sample or whole population (partly data from the whole country, partly only from cities/regions), biased sampling frame: different recruitment periods, small sample size No information about conflict of	4 RoB: 5/8

					There is an excess of very young mothers, just reaching statistical significance		interest and funding.	
Ethische Gruppen								
Le, 2019 [47]	Cross-sectional study 1999-2015 USA	This study estimated birth defect prevalence among the less studied non-Hispanic Asian/Pacific Islander and American Indian/Alaska Native populations in Texas relative to non-Hispanic Whites.	n=77 bladder exstrophy patients	Ethnic groups	**Prevalence of bladder exstrophy** • Non-Hispanic White (n=73): 0.32 (0.25–0.40) • Non-Hispanic Asian/Pacific Islander (n=4): 0.16 (0.04–0.40) • Any American Indian/Alaska Native: (n=0): - **Adjusted prevalence ratios of bladder exstrophy** • Non-Hispanic Asian/Pacific Islander (n=4): 0.50 (0.19–1.04) Any American Indian/Alaska Native: (n=0): -	*no conclusion to risk factors and bladder exstrophy*	small sample size, less information about study subjects The authors report no conflict of interest. Funding information: State of Texas; Office of Title V and Family Health, Texas Department of State Health Services	4 RoB: 6/8
Caton, 2007 [43]	Cross-sectional study 1983-1999 USA	We examined epidemiologic trends and risk factors for bladder exstrophy and cloacal exstrophy in a large population-based dataset.	n= 4603747 live births • bladder exstrophy (n=77) • cloacal exstrophy (n=29)	Maternal race/ethnicity	**Bladder exstrophy** Maternal race/ethnicity White non-Hispanic: 3.20 (1.20–8.52) Black non-Hispanic: Reference Hispanic: 1.82 (0.59–5.62) Other: 1.45 (0.28–7.53)	Factors associated with bladder exstrophy included summer conception, white, non-Hispanic maternal race/ethnicity, and male sex.	small sample size No information about conflict of interest and funding. *only significant results for baldder exstrophy cases shown.*	4 RoB: 7/8
Yang, 1994 [44]	Cross-sectional study 1980-1987	We present comparative epidemiologic characteristics of five congenital abnormalities	n= 22 bladder exstrophy cases	Ethnic group	**Bladder exstrophy** Ethnicity White: Prevalence 0.41 (16/22) All other: Prevalence 0.31 (6/22)	*no conclusion to risk factors and bladder exstrophy*	patient recruitment not clearly described, small sample size, less information about study subjects	4 RoB: 4/8

	USA	that have been suggested to result from midline abnormal developmental disturbances: esophageal atresia with or without tracheoesophageal fistula, imperforate anus with or without fistula, omphalocele, bladder exstrophy, and diaphragmatic hernia. The purpose was to assess the extent of epidemiologic similarities among these five defects.			Ratio: 1.43 (95% CI 0.56-3.64) p=0.229		No information about conflict of interest and funding.	
Geschlecht								
Ebert, 2021 [48]	Cross-sectional study 2009-2011 Germany	The purpose of this study is to evaluate the live prevalence of the exstrophy–epispadias complex in Germany, to assess the male-to-female ratio, and to consider the treatment incidence of various age groups with the help of the German insurance documentation, including a representative nationwide population.	n=370 patients with exstrophy-epispadias complex • epispadias (n=126) • exstrophy (n=244)	Sex	**Exstrophy (Q64.1)** <u>Male-to-female ratio</u> • Adult (18 years onwards): 1.322 (range 1.247–1.394) • Children and adolescents (1–17 years): 1.597 (range 1.561 to 1.681) • below 1 year of age: 1.4 (range 1-2)	The male-to-female ratio for exstrophy is 1.4:1 for infants and 1.6:1 for all minors.	no random sample or whole population analysis The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding is reported in detail in the paper.	4 RoB: 7/8

Ko, 2018 [49]	Cross-sectional study 2008-2014 South Korea	The aims of this study were to estimate the recent prevalence of selected birth defects and to analyze the prevalence trends of selected birth defects during the period 2008–2014.	n=23 Epispadias n=19 bladder exstrophy	Sex	**Prevalence per 10000 (95% CI)** <u>Epispadias (Q64.0)</u> • Overall (n=23): 0.07 (0.05–0.11) • Male (n=22): 0.13 (0.08–0.2) • Female (n=1): 0.01 (0–0.04) <u>Bladder exstrophy (Q64.1)</u> • Overall (n=19): 0.06 (0.04–0.09) • Male (n=8): 0.05 (0.02–0.1) • Female (n=11): 0.07 (0.04–0.13)	*no conclusion to risk factors and bladder exstrophy/epispadias*	unclear if all available data were included in the analysis (data from the Korea National Health Insurance Service), small sample size, less information about study subjects The authors declare no conflict of interest. This work was supported by INHA UNIVERSITY Research Grant (2016).	4 RoB: 5/8
Reinfeldt Engbert, 2016 [38]	Matched case-control study 1973-2011 Sweden	To describe and assess bladder exstrophy and the potential maternal risk factors, for a time period of four decades, by conducting a nationwide register study of bladder exstrophy in Sweden.	n=720 • bladder exstrophy cases (n=120) • controls (n=600)	Sex	**Bladder exstrophy** Male-to-female ratio: 1.14:1	Advanced maternal age was the only significant potential maternal risk factor.	The authors have no relevant financial or nonfinancial conflicts of interest to disclose. Financial support was provided through the Regional Agreement on Medical Training and Clinical Research (ALF) between the Stockholm County Council, Karolinska Institutet, the Swedish Society of Medical Research, the Promobilia Foundation, the Swedish Society of	4 RoB: 9/9

							Medicine, HRH Crown Princess Lovisa's Memorial Fund, the Samariten Foundation, the Freemasons' Fund for Children's Health, and the Swedish Research Council.	
Jayachandran 2011 [50]	Cross-sectional study 1985-2008 United Kingdom	We describe the prevalence, associated anomalies, prenatal diagnosis and survival of patients with bladder exstrophy-epispadias complex.	n=43 patients with bladder exstrophy-epispadias complex • bladder exstrophy (n=24) • epispadias (n=13) • cloacal exstophy (n=6)	Sex	**Male-to-female ratio** • Overall: 2.2:1 • bladder exstrophy: 1.6:1 • epispadias: 3.3:1 • cloacal exstophy: 4:1	*no conclusion to risk factors and bladder exstrophy*	small sample size One author supported by a Personal Award Scheme Career Scientist Award from the National Institute of Health Research (Department of Health). NorCAS is funded by the Healthcare Quality Improvement Partnership	4 RoB: 7/8
Reutter, 2011 [26]	Cross-sectional study 2003-2008: Europe (Austria, France, Germany, Italy, Spain, Switzerland, and The Netherlands)	To identify genetic and non-genetic risk factors contributing to the severity of the BEEC.	n=441 patients with BEEC • Epispadias (n=43) • classic bladder exstrophy (n=366) • cloacal exstrophy (n=31) Europe: 274 North America: 167	Sex	**Overall** Males: 305 Female: 135 Male-to-Female ratio: 2.3 p<0.001 **Epispadias** Males: 27 Female: 16 Male-to-Female ratio: 1.7 p=0.127 **Classic bladder exstrophy** Males: 259	Periconceptional folic acid supplementation appears to prevent the development of the severe phenotype of BEEC.	different recruitement frames (e.g. time, countries, settings), self-reported exposure The authors declare no conflicts of interest This project has been partially supported through NIH grants (R01	4 RoB: 5/8

	2001-2005: North America		Males: 305/441		Female: 107 Male-to-Female ratio: 2.4 p<0.001 **Cloacal exstrophy** Males: 19 Female: 12 Male-to-Female ratio: 1.6 p=0.281		DE016886 from the NIDCD/NIH; M01-RR00052 from the NCRR/NIH) and a CMN grant (CMNSB06).	
Siffel, 2011 [40]	Cross-sectional study 1980-2006 Australie, Canada, China, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, United Kingdom, Slovak Republic, USA	In this report we (1) provide an overview of historical aspects, embryology, etiology, clinical characteristics and genetics, epidemiology, prognosis, and treatment of bladder exstrophy, and (2) describe the current epidemiology of bladder exstrophy using a large dataset from the International Clearinghouse for Birth Defects Surveillance and Research.	n=564 cases with bladder exstrophy	Sex	**Bladder exstrophy** <u>Male-to-female ratio</u> • Overall: 1.85:1 (p<0.01) • isolated bladder exstrophy: 2.09:1 • multiple congenital anomalies: 1.26:1 p=0.02	The higher prevalence among male cases and older mothers, especially among isolated cases are important factors to note for clinicians when assessing risk, and to include in future epidemiologic studies.	no random sample or whole population, biased sampling frame: variation in prevalence is most likely attributable to differences in registration of cases, different recruitment periods between the coutries, less information about study subjects No information about conflict of interest. Funding is reported in detail in the paper.	4 RoB: 5/8
Gambhir, 2008 [42]	Cross-sectional study Algeria, Austria, Croatia, France, Germany, Italy, Netherlands, Poland,	To identify causative non-genetic and genetic risk factors to the bladder exstrophy epispadias complex.	n=214 families • 9% epispadias (n=19) • 84% classical exstrophy of the bladder (n=180) • cloacal exstrophy (n= 15)	Sex	**Male-to-female ratio** Epispadias: 1.4 (11/8), Classical exstrophy: 2.8 (132/48) p=0.001 Cloacal exstrophy: 2.0 (10/5)	Our study corroborates the hypothesis that epispadias, classical exstrophy of the bladder and cloacal exstrophy are causally related, representing a spectrum of the same developmental	no random sample or whole population, biased sampling frame: recruitement through various pediatric urology clinics and self help groups, small sample size, some outcomes are self-reported,	4 RoB: 3/8

	Romania, Serbia, Spain, Switzerland, Turkey, United Kingdom					defect, with a small risk of recurrence within families. Embryonic exposure to maternal smoking appears to enforce the severity, whereas periconceptional folic acid supplementation does not seem to alleviate it. There is a disproportional prenatal ultrasound detection rate between severe and mild phenotypes, possibly due to the neglect of imaging of full urinary bladders with focus on neural tube defects.	response rate and recruitment period not described S.A.B is partially funded through a Children's Miracle Network Endowed Chair and through grants K23 DE00462, R03 DE016342, and R01 DE016886 from NIDCD/NIH and M01-RR00052 from NCRR/NIH	
Caton, 2007 [43]	Cross-sectional study 1983-1999 USA	We examined epidemiologic trends and risk factors for bladder exstrophy and cloacal exstrophy in a large population-based dataset.	n= 4603747 live births • bladder exstrophy (n=77) • cloacal exstrophy (n=29)	Sex	**Infant sex** Male: Reference Female: aPR 0.53 (0.33–0.87)	Factors associated with bladder exstrophy included summer conception, white, non-Hispanic maternal race/ethnicity, and male sex.	Small sample size No information about conflict of interest and funding.	4 RoB: 7/8
Boyadjiev, 2004 [36]	Cross-sectional study USA	To identify genetic and nongenetic factors contributing to the risk of bladder exstrophy epispadias complex.	n=232 families with bladder exstrophy epispadias complex • epispadias (n=33) • classic bladder	Sex	**Male-to-Female ratio** Epispadias: 2.2 Bladder exstrophy: 1.8	In addition to race and advanced parental age, birth order may be a risk factor for bladder exstrophy epispadias complex.	No random sample or whole population data, biased sampling frame: invitation via institutionally database and internet support group, no recruitment period	4 RoB: 3/8

			exstrophy (n=180) • cloacal exstophy (n=19)				described, small sample size, less response rate (232/815), self-reported information to drugs, alcohol and smoking The authors declare no conflict of interest. Source of funding: Johns Hopkins – GCRC.	
Martinez-Frias, 2001 [51]	Cross-sectional study 1967-1999 Spain	We present the epidemiological analysis of a group of characteristics in infants with cloacal exstrophy and infants with bladder exstrophy to determine if they constitute two different entities.	n=28773 infants with birth defects • bladder exstrophy (n=46) • cloacal exstrophy (n=11)	Sex	**Sex ratio** Bladder exstrophy Ratio: 1.32 Male: 25/46 Female: 19/46 Intersex/Absence: 2/46	We posit that cloacal exstrophy and bladder exstrophy are two different expressions of a primary polytopic developmental field defect. Cloacal exstrophy, we think, represents the manifestation of an earlier hit indevelopment than bladder exstrophy, which is the milder consequence of a hit that occurs later on in embryogenesis and affects the same primary developmental field.	unclear if all available data were included in the analysis (only hospitals which cooperate with the program), small sample size No information about conflict of interest supported in part by a grant from the ”Fundación Inocente-Inocente'', and by a Grant from Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo of Spain	4 RoB: 6/8
Yang, 1994 [44]	Cross-sectional study	We present comparative epidemiologic characteristics of	n= 22 bladder exstrophy cases	Sex	**Bladder exstrophy** Sex Male: Prevalence 0.32 (9/21)	*no conclusion to risk factors and bladder exstrophy*	patient recruitment not clearly described, small sample size, less	4 RoB: 4/8

	1980-1987 USA	five congenital abnormalities that have been suggested to result from midline abnormal developmental disturbances: esophageal atresia with or without tracheoesophageal fistula, imperforate anus with or without fistula, omphalocele, bladder exstrophy, and diaphragmatic hernia. The purpose was to assess the extent of epidemiologic similarities among these five defects.			Female: Prevalence 0.44 (12/21) Ratio: 0.72 (95% CI 0.30-1.70) p=0.768		information about study subjects No information about conflict of interest and funding.	
Anonymous, 1987 [46]	Cross-sectional study 1967-1985 Australia, Denmark, French, Italy, Mexiko, Norway, Spaon, Sweden, USA	Epidemiology of bladder exstrophy and epispadias	n=6276038 births • epispadias (n=148) • bladder exstrophy (n=208)	Sex	**Bladder exstrophy** Female-to-Male ratio 1:5 (1.1-2) **Epispadias** Female-to-Male ratio 144 male 4 female	Both bladder exstrophy and epispadias seem to occur more frequently among infants of teenage mothers than in other age groups. The effect is not strong and barely reaches statistical significance.	no random sample or whole population (partly data from the whole country, partly only from cities/regions), biased sampling frame: different recruitment periods, small sample size No information about conflict of interest and funding.	4 RoB: 5/8
In vitro Fertilization								
Reutter, 2011	Cross-sectional study	To identify genetic and non-genetic risk factors	n=441 patients with BEEC	Assisted reproduction	• Epispadias: 2/43 (5 %) • Classic bladder exstrophy: 5/353 (1 %)	It was impossible to determine whether assisted	different recruitement frames (e.g. time,	4 RoB:

[26]	2003-2008: Europe (Austria, France, Germany, Italy, Spain, Switzerland, and The Netherlands) 2001-2005: North America	contributing to the severity of the BEEC.	• Epispadias (n=43) • classic bladder exstrophy (n=366) • cloacal exstrophy (n=31) Europe: 274 North America: 167 Males: 305/441		• Cloacal exstrophy: 1/29 (18 %) p=0.183 (Epispadias vs. bladder vs. cloacal exstrophy) p=0.528 (Epispadias/bladder vs. cloacal exstrophy) OR: 1.26 (95% CI 0.62-256)	reproduction per se is a risk factor for the development of BEEC because no valid external data were available for comparison.	countries, settings), self-reported exposure The authors declare no conflicts of interest This project has been partially supported through NIH grants (R01 DE016886 from the NIDCD/NIH; M01-RR00052 from the NCRR/NIH) and a CMN grant (CMNSB06).	5/8
Wood, 2007 [52]	Case series 1997-2004 USA	To expand on a previously published analysis of children fertilized in vitro who demonstrate the cloacal/bladder exstrophy-epispadias complex.	n=8 patients with cloacal/bladder exstrophy-epispadias complex • bladder exstrophy (n=5) • male epispadias (n=1) • cloacal exstophy (n=2) Male: 7/8	in vitro fertilization	**Incidence of in vitro fertilization in cloacal/bladder exstrophy-epispadias complex** Expected: 0.6-1.59% Observed: 4.2-6.7% p=0.0182	The incidence of in vitro fertilization in cloacal/ bladder exstrophy-epispadias complex children appears to be higher than what would be expected if there was no association between in vitro fertilization and cloacal/bladder exstrophy-epispadias complex.	No information about conflict of interest and funding. *the analysis also includes cloacal exstrophy cases*	4 Rob: 16/20
weitere Faktoren								

Tang, 2006 [53]	Cross-sectional study 1996-2000 USA	This study addressed two questions: 1) Is there a significantly higher risk of birth defects in multiple births compared to singletons after adjusting for important covariates? and 2) which types of birth defects are more likely to occur among multiple births compared to singletons?	• bladder exstrophy patients (n=37) • hypospadias and epispadias patients (n=3259)	multiple births	**Bladder exstrophy** Multiple birth: 3/37 Singleton: 34/37 adjusted RR: 2.81 (95% CI 1.67–4.71) **Hypospadias and Epispadias** Multiple birth: 114/3259 Singleton: 3145/3259 adjusted RR: 1.33 (95% CI 1.23–1.45)	Birth defects with the five highest adjusted RRs among multiple births were: anencephalus, biliary atresia, hydrocephalus without spina bifida, pulmonary valve atresia and stenosis, and bladder exstrophy.	small sample size for bladder exstrophy No information about conflict of interest and funding.	4 RoB: 7/8
Swerdlow, 1988 [45]	Cross-sectional study 1974-1978 United Kingdom	Data from the England and Wales national congenital malformation notification scheme were examined for associations of male genital tract malformations.	n=3963 selected malformations in males • epispadias (n=89)	Birth weight	**Epispadias** <u>Birth weight</u> Risk of epispadias showed no significant relation to birth weight.	*no conclusion to risk factors and epispadias*	unclear if the sample is unbiased: voluntary notification by doctors and midwives, small sample sizes No information about conflict of interest and funding.	4 RoB: 6/8

4. AG Diagnostik

Schlüsselfrage Bringt ein zusätzliches MRT einen diagnostischen Zusatzgewinn?									
Referenz	**Studien-charak-terisitika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Weiss, 2020 [54]	Prospective diagnostic study 2000-2018 USA	We hypothesized that there are key features seen on fetal US and fetal MRI that can distinguish between BE and OEIS, and that there are areas of diagnostic concordance and discordance between the two imaging modalities.	n=21 infants with bladder or cloacal exstrophy Median age (prenatal imaging): 25 wks (IQR 23.1-28.5 wks)	Fetal MRI n=19	Fetal US n=17	**Postnatal** • 14/21 diagnosed with BE • 7/21 diagnosed with OEIS **Prenatal** 100% concordance between fUS and fMRI <u>Fetal US</u> • 9/13 patients with BE were correctly diagnosed • 3/3 patients with cloacal exstophy were correctly diagnosed • 4 incorrect classifications: interpreted prenatally to OEIS, were postnatally found to be classic BE	An everting bladder plate with bowel loops posterior to the plate in classic BE may be misdiagnosed as cloacal exstophy. Identification of the location of umbilical cord insertion relative to the abdominal wall defect, with fetal US or fetal MRI, results in the correct differentiation between BE and cloacal exstophy.	No consecutive or random sample, unclear if imaging results were interpreted independently, only 15 patients received both US and MRI There are no conflicts of interest. No information about funding.	3 RoB: high

						<u>Fetal MRI</u> • 10/13 patients with BE were correctly diagnosed • 6/6 patients with cloacal exstophy were correctly diagnosed • 2 incorrect classifications: interpreted prenatally to OEIS, were postnatally found to be classic BE **Sensitivity** fUS: 69% fMRI: 83%			
Goldman, 2013 [55]	Prospective case series Brazil	We reviewed our experience with prenatal MRI of bladder exstrophy to describe our findings and correlate them with postnatal clinical presentation and surgical outcome.	n=3 female patients Mean gestational age: 27.3 wks	Fetal MRI		• MRI defined a lower abdominal mass prolapsing below the umbilical vessels, having the ureters ending on it in an anterior position • cloacal malformation, a cloacal exstrophy and accompanying spinal abnormalities could be excluded • renal system and oligohydramnio	The MRI showed a detailed scenario of the abnormality with advantages over the US evaluation in regard to excluding cloacal anomalies. MRI allowed accurate sexual differentiation and may be indicated after suspected bladder exstrophy on US evaluation.	No detailed information on patient recruitment and patient characteristics, no statistical analysis The authors received no specific funding for this work. The authors declare that they have no conflicts of interest.	4 RoB: 11/20

						s could be well documented			

Schlüsselfrage Ist eine elektive Kaiserschnittentbindung notwendig?								
Referenz	**Studien-charakteristika**	**Studienziel**	**Patientenmerkmale**	**Endpunkt**	**Ergebnisse**	**Schluss-folgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Systematische Übersichtsarbeiten								
Bey, 2021 [56]	Systematic review n=25 studies • 1 single-center study • 3 retrospective multiple-center study • 15 retrospective single-center studies/case series • 6 case reports 1972-2020	The aim of this systematic review of the literature was to pool all the existing data regarding pregnancy and delivery in women with neurogenic bladder or bladder exstrophy who had undergone previous lower urinary tract reconstruction	n=229 women • 98 bladder exstrophy • 58 spinal dysraphism • 14 spinal cord injury • 59 other pathological conditions	Pregnancy and delivery	**Bladder exstrophy** • Premature delivery occurred in 16% (n=46) • in case of heavily reconstructed genitals, duplicated vagina, significant genital prolapse: discuss pros and contras with the patient: spontaneous vaginal delivery or planned c-section may be considered <u>Spontaneous vaginal delivery</u> • unless obstretrical, neurological or anesthesiological contra-indication	Pregnancy and vaginal delivery are possible for women with lower urinary tract reconstruction who have no obstetric or medical contraindications, except for some particular cases of bladder exstrophy.	No detailled risk of bias assessment reported for the included studies The authors declare that they have no conflicts of interest. Funding: no information given	3 RoB: low

					• Delivery planned in an expert center • Urologist informed and present during delivery • Artificial urinary sphincter desactivated, Foley catheter placed in uretra or/and ostomies before delivery or incision <u>C-section:</u> • Systematic planned at 37 weeks of gestation with Urologist • Use of diathermy in case of artificial urinary sphincter • Median laparotomy, no Pfannenstiel, consider high uterine incision vs low transverse • Perform leak test before parietal closure			
Primärstudien								
Quiroz, 2021 [57]	Retrospective case series Median follow-up: 26 y (IQR 1-48 mo)	This work reports on female patients with exstrophy-epispadie complex who	n=37 women with exstrophy-epispadie complex Mean age: 35.5 y (1-48 y)	• Pregnancies • miscarriages • urological, gynecolo-gical and obstetric	**Pregnancies** (n=17) Spontaneous: 88.2% (15/17)	Exstrophy-epispadie complex patients can achieve spontaneous pregnancies but have an increased risk of miscarriage. For	Recruitment process, study population and inclusion criteria were not described in detail	4 RoB: 14/20

	Spain	achieved pregnancies and was followed up at our Functional High-Risk Pregnancy Unit with the aims of establishing the characteristics of pregnancy and determining whether exstrophy-epispadie complex patients are at higher risk of spontaneous abortion and complications.		complications • impaired renal function • newborn characteristics postpartum urogynecological complications	In vitro fertilization: 11.8% (2/17) Live birth: 58.8% (10/17) Spontaneous abortions: 41.2% (7/17) 50% reached term, the shortest gestation time in the preterm group being 33 weeks. **Complications** (overall) Urinary tract infections: 8/17 (46%) Intestinal occlusion: 12% (2/17) Uterocutaneous fistula: 12% (1/17) **Complications** (successful pregnancies) Urinary tract infections: 70% (7/10) Urinary sepsis: 10% (1/10) No intraoperative injuries of the urinary or gastrointestinal system occurred, nor were there any instances of damage to the	this reason, monitoring and control by a specialized and integrated multidisciplinary team is required to minimize complications	None of the authors has conflicts of interest. No subsidy or financial aid was received.	

					structures that made up the urinary diversions **Postpartum complications** Genital prolapses: 62.5% (5/8) Continent diversion and dry in follow-up: 85.7% (7/8) **Newborns** No exstrophy-epispadie complex or any other type of malformation.			
Sinatti, 2021 [58]	Retrospective case series 1990-2019 Median follow-up: 260 mo (IQR 241-328 mo) Belgium	The primary aim of this study is to evaluate long-term sexual outcomes in exstrophy-epispadias complex patients and the secondary endpoint is to assess long-term continence.	n=29 patients with exstrophy-epispadias complex Female: 13.8% (4/29) Male: 86.2% (25/29) Median age: 21 y (20-27)	• Pregnancy and delivery	**Women (n=4)** • two (67%) women who were trying to conceive children succeeded in doing so (100%) • one woman conceiving twice and the other conceiving C-section was recommended	*No conclusion regarding delivery*	The authors report no conflict of interests. This reasearch was funded by Research Fund for Pediatric Urology 'Gianni Eggermont fonds ter bevordering van de kinderurologie'.	4 RoB: 20/20
Canalichio, 2020 [59]	Retrospective case series 2018-2019 Worldwide	The aim of the study was to assess long-term patient-reported sexual, reproductive and continence outcomes.	n=130 women with bladder exstrophy Median age: 30 y (26-41 y)	• Urinary • Reproductive & gynecological outcomes • Sexual	**Pregnancy Outcomes** Miscarriage: 34% (34/100) Therapeutic/elective abortion: 7% (7/100) Preterm vaginal delivery: 3% (3/100)	*No conclusion regarding delivery*	Patient recruitment via social media, anonymus and self-reported outcomes, no statistical analysis	4 RoB: 10/20

					Preterm delivery by cesarean: 19% (19/100) Term vaginal delivery: 2% (2/100) Term delivery by caesarean: 35% (35/100) Cesarean complications: 15.9% (10/63)		The authors report no conflict of interests. Funding: None	
Mallmann, 2019 [60]	Retrospective case series 2004-2018 Germany	We report on a series of 12 cases with classic bladder exstrophy diagnosed prenatally and illustrate the spectrum of prenatal ultrasound findings with comparison to prior published reports on this entity.	n= 12 fetuses with classic bladder exstrophy Male: 8/12 Average maternal age: 30 y Median diagnosis: 24+5 weeks of gestation	• prenatal course • postnatal outcome	**Mode of delivery** 1/12 termination of pregnancy 9/11 caesarean section 2/11 vaginal birth • 11/12 fetuses were live born and received reconstructive surgery. Prenatally diagnosed malformations were confirmed in all children.	*No conclusion regarding delivery*	no statistical analysis The authors declare that they have no conflict of interest. no information about funding	4 RoB: 14/20
Ebert, 2017 [61]	Prospective cohort study 2009-2014 Germany	The aim of this study was to evaluate the sexual function in adult females with exstrophy-epispadias-complex using the German valuated Female Sexual Function Index.	n=21 females • 11 bladder exstophy • 4 cloacal exstrophy • 3 epispadias Age: 26 ± 5.1 y	• Functional outcome • Sexuality and pregnancy • Female Sexual Function Index	**Sexuality and pregnancy** Delivered one baby: 14% (3/21) • one female reported 3 pregnancies, including 1 abortion All children: born by planned caesarean sections (50% took place with	*No conclusion regarding delivery*	Congenital anomaly of 3 females not reported, patient recruitment via self-help organizations, self-reported outcomes The authors report no conflict of interests.	3 RoB: 5/9

					attendance of a urologist)		research grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009e2012. Statistical calculations are supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013e2015), EB521/2-1 and JE681/4-1 (2015e2018). HR was supported by a grant from the DFG (RE 1723/1-1)	
Dap, 2017 [62]	Retrospective case reports 2000-2016 France	Pregnancy outcomes among patients with prior bladder exstrophy.	n= 3 female patients who had bladder exstrophy diagnosed at birth and who presented with a pregnancy Age: 22-31 y	• Pregnancy outcomes	• Three Patiens with 6 spontaneous pregnancies • 6/6 Cesarean sectio Patient 1: • Planned cesarean • Postpartum period: no adverse events Patient 2: <u>First child:</u>	Based on the results of the present study, it is suggested that women with bladder exstrophy can have a healthy reproductive life. Based on the guidelines proposed by Dy et al., close monitoring of serum creatinine, renal function, ultrasonography, and urine culture is necessary. Cesarean	Study aim not clearly defined, not described if all eligible patients were included, no statistical analysis The authors report no conflict of interests. Funding: no information given	4 RoB: 12/20

					• Emergency cesarean delivery owing to preterm labor • Postpartum period: Urinary incontinence <u>Second & third child</u> • Planned cesarean • Postpartum period: no adverse events Patient 3: <u>First child:</u> • Planned cesarean • Postpartum period: no adverse events <u>Second child</u> • Planned cesarean Postpartum period: Artificial sphincter infection	delivery should be planned and a surgeon with good knowledge of this particular anatomy should be present.		
Ebert, 2011 [63]	Prospective case reports Germany	We reported our operative experience and management during pregnancy in two BEEC patients after urinary diversion and complex functional reconstruction.	n=2 BEEC patients after urinary diversion and complex functional reconstruction Age: 26 and 17 y	• Operative delivery	Case 1: • primary section • no postoperative complications Case 2: • secondary section due to ongoing labor • no postoperative complications	Though care should be intense in pregnant BEEC individuals, patients should not be discouraged to have own children. To facilitate successful pregnancy outcome operative delivery should be done as a interdisciplinary	Patient recruitment not clearly described, no statistical analysis All authors state no financial support and no conflict of interest. supported by a research grant from the	4 RoB: 15/20

						team work and emergency situations should be avoided by meticulous planning and counseling of the BEEC patients.	German Federal Ministry of Education and Research (Deutsches Bundesministeriu m für Bildung und Forschung, BMBF).	
Volkmer, 2002 [64]	Case reports 1995-2000 Germany	Pregnancy in women with ureterosigmoidos-tomy is a rare condition that differs in many ways from pregnancies in women with other forms of urinary diversion.	n=3 bladder exstrophy patients with uretrosigmoidostomy Age: 20-36 y	• Pregnancy and delivery	**Delivery** • 75% (3/4) cesarean section • 25% (1/4) vaginal **Postpartum complications** None **Neonatal complications** None	According to published reports, cesarean section is recommended in patients with former bladder extrophy to reduce the risk of prolapse of the uterus and damage to the anal sphincter from episiotomy.	no statistical analysis performed no information about conflict of interest and funding	4 RoB: 16/20
Mantel, 2001 [65]	Case reports	Three young patients, who had bladder exstrophy, and wanted to have children, were followed-up over a period of more than 10 years.	n=3 bladder exstrophy patients Patients born between 1964 and 1967	• Pregnancy and delivery	**Case 1** • spontaneous rupture of the membranes occurred at 35 weeks of gestation • cesarean section in emergency **Case 2** • 36 weeks of gestation, she pregpresented with a spontaneous labor, a rupture of the membranes,	Beyond a low fertility and a high rate of miscarriages, these pregnancies are exposed to several complications, such as premature labor, pyelonephritis, and most of all the aggravation of a prolapse. A planned cesarean section appears to be justified, in order to preserve urinary continence, often achieved after many previous surgeries.	Patient recruitment was not described, no statistical analysis was performed no information about conflict of interest and funding	4 RoB: 13/20

					and a fetus in a transverse position • cesarean section in emergency **Case 3** not been able to become pregnant			
Skari, 1998 [66]	Retrospective case series 1995-1996	The aim of the present study was to examine the sensitivity of prenatal ultrasound diagnosis in neonates referred for surgery, and to test whether a prenatal versus postnatal diagnosis influenced mode of delivery and neonatal outcome of these infants.	n=36 neonates • congenital diaphragmatic hernia (n=8) • abdominal wall defects (n=12) • bladder exstrophy (n=3) • meningomyelocele (n=13)	• sensitivity of ultrasound diagnosis • neonatal outcome of these infants • mode of delivery	**Bladder exstrophy** <u>Proportion of cesarean deliveries</u> Prenatal diagnosis: 0 Postnatal diagnosis: 0/3	None of our three bladder exstrophy patients were diagnosed prenatally.	no information about patient characteristics, data were collected retrospectively from the referring hospitals and from a semi-structured interview with the mother, no statistical analysis no information about conflict of interest supported by grants from Dr. Alexander Malthe's Foundation and The Norwegian Research Council	4 RoB: 12/20
Schumacher, 1997 [67]	Case reports Germany	We report on our experience with pregnancies and deliveries in patients with a continent ileocecal reservoir with catheterizable	n=6 women mean age 26.8 y • 4 bladder exstrophy • 1 meningomyelocele • 1 urogenital sinus Mean age: 26.8 y (18-33 y)	• Pregnancy and delivery	7/7 cesarean section • 1 elective • 6 chosen due to a breech presentation of the child	In women with Mainz pouch urinary diversion there appears to be no contraindication to pregnancy, while other forms of continent diversion	Patient recruitment was not described, no statistical analysis was performed no information about conflict of	4 RoB: 12/20

		stoma (Mainz pouch).			7/7 healthy children without congenital abnormalities **Pregnancy Complications** • 3/5 none complications • 2/5 Bilateral dilatation	await further evaluation. Urologists and obstetricians should be aware of the potential complications of this high risk pregnancy and delivery, and their interdisciplinary cooperation is essential for successful outcome.	interest and funding	
Stein, 1996 [68]	Retrospective case series 1968-1994 Mean follow-up: 16.7 y (0.2-35 y) Germany	The social integration of patients after urinary diversion, as well as their sexual behaviour and fertility, were of primary interest to this retrospective study.	n=115 patients • 95 patients with bladder exstrophy • 20 with incontinent epispadias Age at delivery: 18-32 y	• Sexual behaviour and fertility • Continence	5 women delivered 7 children • 2/5 fixation of the uterus 7/7 cesarean section **Complications** 6/7 none 1/7 mild upper tract dilatation and uterine prolapse	*No conclusion regarding delivery*	Patient characteristics were not described in detail, no statistical analysis was performed no information about conflict of interest and funding	4 RoB: 12/20
Kennedy, 1993 [69]	Case reports 1985-1992 USA	Pregnancy after orthotopic continent urinary diversion	n=4 bladder exstrophy Age: 19-22 y	• Pregnancy and delivery	4/4 cesarean section • 1/4 emergency sectio (secondary to ruptured membranes with the onset of premature labor) • 1/4 performed semielectively before term because • of severe cervical prolapse and	Women of childbearing age who have an orthotopically placed urinary reservoir are able to conceive and deliver healthy children free of congenital abnormalities. The current experience with four of these patients suggests that close monitoring by a high-risk obstetrician and	Study aim was not clearly described, no statistical analysis no information about conflict of interest and funding	4 RoB: 15/20

					unilateral leg edema **Postpartum complication** 3/4 severe cervical prolapse persisting six months after delivery or greater and will require uterine reparative operation	urologist is essential for a successful gestation and delivery. Consequently, pregnancy is not contraindicated with orthotopic continent urinary diversion.		
Krisiloff, 1987 [70]	Case series	Our purpose ist o clarify these aspects oft he problem by recounting our clinical expierences to enable physicians to provide better-informed patient care to these women.	n=28 women with bladder exstrophy	• Pregnancy	**7 pregnancies with 5 sucessful deliveries** • 2 abortions (spontan and therapeutic because if feared complications) • 4 spontaneous vaginal deliviers • 1 cesarean section because of fetal distress **Complications** 3/5 breech deliveries 6/7 cervival and uterine prolaps 6/7 chronic urinary tract infections **Children** healthy without exstrophy or major congenital anomalies	*No conclusion regarding delivery*	No information about patient recruitment and patient characteristics, no statistical analysis no information about conflict of interest and funding	4 RoB: 8/20

Blakely, 1981 [71]	Case report 1946-1979 United Kingdom	It is with the obstetric and gynaecological problems of these patients that this paper is concerned.	n=16 women • 14 bladder exstrophy • 2 epispadias	• Obstetrics • Gynaecological problems	5 women delivered 8 children by Caesarean sectio It is recommended that the decision between lower segment and classical section be made at operation.	The successful surgical repair of prolapse will make further pregnancy unwise, even though Caesarean section is used for delivery.	unclear if data collection was prospective or retrospective, no statistical analysis no information about conflict of interest and funding	4 RoB: 14/20

Schlüsselfrage Welche Untersuchungen sollten postnatal erfolgen?
Keine Evidenztabelle erstellt, da keine Evidenz zugeordnet werden konnte.

5. AG Therapie

Schlüsselfrage Ist ein Blasenverschluss in den ersten 48-72 Stunden notwendig?									
Referenz	**Studien-charak-terisitika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Morrill, 2023 [72]	Retrospective cohort study 1990-2020	The authors aim to compare single institutional 30-day complication rates between delayed and neonatal closure of classic bladder exstrophy.	n=145 exstrophy-epispadias patients <u>Median age</u> Neonatal: 3 days (2-6 days) delayed: 202 days (111-305) <u>Male</u> Neonatal: 63/95 (66%) delayed: 41/50 (82%)	neonatal closure n=95	delayed closure n=50	**30-day postoperative complication rate** <u>Any complication</u> neonatal: 46/95 (48.4%) delayed: 29/50 (58%) p=0.298 <u>Complication without transfusation</u> neonatal: 33/95 (34.7%) delayed: 13/50 (26%) p=0.349 <u>Clavien I-II complications</u> neonatal: 40/95 (42.1%) delayed: 27/50 (54%) p=0.292 <u>Clavien III complications</u> neonatal: 7/95 (7.4%) delayed: 1/50 (2%)	The majority of the complications associated with delayed closure are a low Clavien-Dindo grade and easily managed during the postoperative inpatient hospital stay. Families should be counseled about the possibility of minor, conservatively managed complications and likelihood of a blood transfusion with osteotomy.	cohorts were different regarding the numbers of osteotomy The authors have no financial or personal relationships with other people or organizations that could inappropriately influence their work. The Kwok Family Foundation of Hong Kong support the exstrophy database and laboratory research. *Studie wurde nach dem Suchzeitraum veröffentlicht, aber aufgrund*	3 RoB: 8/9

						p=0.263 <u>Clavien IV complications</u> neonatal: 3/95 (3.2%) delayed: 1/50 (2%) p=1		*der relevanten Ergebnisse durch die Experten hinzugefügt*	
Chalfant, 2022 [73]	Retrospec-tive cohort study 2012-2019 USA Follow-up is limited to 30 days	The primary aim of this study was to determine complication rates in the classic bladder exstrophy population for bladder closure and advanced urologic reconstruction in national studies compared to single-institutional studies.	n=302 classic bladder exstrophy patients **Bladder closure cohort** (n=152) <u>Median age in days</u> early: 3 (IQR 2-5) delayed: 143 (IQR 52-143) <u>Male</u> early: 12/28 (42.9%) delayed: 74/124 (59.7%)	early bladder closure n=28	delayed bladder closure n=124	**Operation time** early: 275 min (213-352) delayed: 428 min (339-508) **Osteotomy** early: 7/28 (25%) delayed: 60/124 (48.3%) **30-day complications rate** • for bladder closure: 30.3% • for advanced urological reconstruction: 24% • No significant differences between readmission, reoperation, cardiac arrest requiring cardiopulmonary resuscitation, wound disruption, organ/space surgical site infection, systematic sepsis,	Classic bladder exstrophy surgeries carry a higher risk of complications than is generally reported. Infectious complications occur >10% of the time in both bladder closure and advanced urologic reconstruction and should be the source of additional study given the inverse relationship infections pose to surgical success in classic bladder exstrophy patients. These data suggest that reported classic bladder exstrophy complication data may be underrepresented in the literature.	Short follow-up time No information about funding and conflict of interest.	3 RoB: 8/9

						unplanned reintubation, progressive renal insufficiency, superficial incisional surgical site infection, urinary tract infection and deep incisional surgical site infection <u>Bleeding/Transfusions</u> early: 5/28 (17.9%) delayed: 81/124 (65.3)			
Khandge, 2021 [74]	Retrospective cohort study 1975-2019 USA	The authors hypothesize that pelvic osteotomy during exstrophy closure may be performed safely in newborns with few perioperative or post-operative negative sequelae.	n=286 patients with classic bladder exstrophy Male: 204/286 (71.3%) <u>Median age</u> Newborn: 3 (0-28) days Delayed: 198 (30-2893) days	Newborn closure (≤28 days of life) n=186	Delayed Closure (>28 days of life) n=100	**Surgical success rates** Newborn: 68.3% (127/186) Delayed: 88.0% (88/100) **Bladder dehiscence** Newborn: 12.4% (23/186) Delayed: 3.0% (3/100) **Blood transfusion rates** Newborn: 37.7% (26/69) Delayed: 42.6% (29/68) p=0.68	While current trends have moved toward delayed primary closures, there remains a role for osteotomy during exstrophy closure in select newborn patients and can be performed safely with few complications.	Insufficient information about the osteotomy groups (numbers, comparability), no consistent reporting of p-values, no follow-up reported The authors have no conflict of interest declared. The Kwok Family Foundation of Hong Kong supports the	3 RoB: 6/9

						Orthopedic complications Newborn: 3 (2.4%) Delayed: 2 (2.3%)		exstrophy database and laboratory research.	
Bueno-Jimenez, 2020 [75]	Retrospective cohort study 2001-2018 Spain <u>Mean follow-up</u> early: 9 y delayed: 1 y	To analyze short-term results in male patients with bladder exstrophy undergoing delayed primary closure and compare them with early bladder closure as part of staged repair in our healthcare facility.	n=19 male patients BEEC Patients with malformations such as cloacal exstrophy or exstrophy variants were excluded. <u>Mean age</u> early: 25 h delayed: 58 days	early bladder closure n=13	delayed bladder closure n=6	**Closure success** early: 11/13 (85%) delayed: 6/6 (100%) **Complications** <u>Transient hydronephrosis (< 6 m)</u> early: 3/13 (23%) delayed: 2/6 (33%) <u>Maintained hydronephrosis (> 6 m)</u> early: 1/13 (8%) delayed: 1/6 (17%) <u>Repetition urinary tract infections</u> early: 5/13 (38%) delayed: 3/6 (50%)	Delayed primary reconstruction is safe as it allows for closure success without increasing complications as compared to staged repair. A long-term follow-up is required to assess urinary continence, esthetic results, and genital functionality.	small number of patients and a long-term follow-up period, especially in delayed closure patients No information about funding and conflict of interest.	3 RoB: 8/9
Wu, 2020 [76]	Retrospective cohort study <u>Median follow-up</u> early: 8.00 y (1.85 -24.7 y) delayed: 6.5 y (2.24-16.8 y)	To examine consecutive bladder capacities in classic bladder exstrophy patients who had primary closures at differing ages and determine whether there is an optimal age for closure, with reference to bladder capacity.	n=166 classic bladder exstrophy patients <u>Male</u> early: 70.3% delayed: 85.7% <u>Median age at closure</u>	early bladder closure n=128	delayed bladder closure n=38	**Bladder capacity** first three bladder capacity measurements, the delayed group demonstrated lower bladder capacities than the	All patients in the delayed bladder closure group demonstrated a decline in bladder capacity compared to the control neonatal closure group, with significant differences in the 2nd and 4th quartiles. Thus, closing the bladder prior to	patient recruitment was not clearly described, osteotomy was used more frequently in the delayed group, no information about loss to follow-up	3 RoB: 6/9

			early: 3.32 days (SD 4.03) delayed: 261 days (SD 260)			neonatal group (65 cc vs 43.5 cc, p < 0.01; 90.5 cc vs 62.0 cc, p < 0.01; 101 cc vs 80.0 cc, p < 0.01) **Age at acquisition of capacity measurements** no differences between the two groups Linear mixed effects model showed significantly decreased total bladder capacity in delayed closure compared to neonates. The 2nd and 4th quartile groups had the most significant decreases in capacity.	nine months of age is recommended.	The authors have no financial or personal relationships with other people or organizations that could inappropriately influence their work. This study had no funding source.	
Inouye, 2018 [77]	Retrospective cohort study since 1975 USA	Even with contemporary management, patients still have failed primary closures. We sought to understand the role of training, surgical technique, and their impacts on outcomes of CBE closure.	n=722 patients with classic bladder exstrophy Male: 506/722 (70.2%)	early bladder closure n=559	• delayed bladder closure n=111 • unknown n=51	**Successful vs. failed closure** *(bivariate analysis)* • early: 352/559 vs. 207/559 • delayed: 89/111 vs. 22/111 • Unknown: 35/51 vs. 16/51 p=0.002	We found that early time of closure, closure by an adult urologist or pediatric surgeon, closure by CPRE method, not having a concomitant osteotomy, and immobilization with spica cast or mummy wrap were associated with increased odds of failed primary closure.	Comparability of cohorts unclear (patient characteristics and length of follow-up) Funding: This study had no external funding source.	3 RoB: 6/9

						Multivariable logistic regression analysis *(adjusted)* • delayed: Reference • early: 1.56 (0.85-2.88), p=0.15 • Unknown: 0.42, 95% CI: 0.17-1.01, p=0.54		Conflicts of interest: The authors declare no conflicts of interest.	
Ferrara, 2014 [78]	Retrospective cohort study 2000-2012 United Kingdom	This study aims to define the consequence of delayed exstrophy repair on bladder growth in bladder exstrophy patients who underwent routine delayed exstrophy repair, compared with those who underwent immediate postnatal reconstruction.	n=45 patients with bladder exstrophy Male: 25/45 <u>Mean age at cystogram</u> neonatal: 21.9 mo (SD 9.1 mo) delayed: 20 mo (SD 8.3 mo)	neonatal bladder closure n=21	elective delayed exstrophy repair n=24	**Mean bladder volumes** (1 y) neonatal: 72.85 (SD 28.5) ml delayed: 72.87 (SD 34.9) ml p=0.99 **Vesico-ureteric reflux** (1 y) neonatal: 10/21 delayed: 5/21	In the authors' experience, delayed exstrophy repair does not reduce the subsequent bladder capacities compared with neonatal exstrophy closure.	historical control group (neonatal closure: 2000-2005 vs. delayed: 2006-2012), relatively short follow-up The authors declared no conflict of interest No funding received.	4 RoB: 7/9
Baradaran, 2012 [79]	Retrospective cohort study 1970-2006 USA <u>Median follow-up</u> • early: 10.7 y (1.5-24 y) • normal template:	We examined longitudinal growth of the bladder in children who underwent delayed primary closure of bladder exstrophy due to either a small bladder template or a delayed referral, and compared bladder growth in these patients to children undergoing neonatal primary closure.	n=115 patients with classic bladder exstrophy <u>Median age at closure</u> • early: 2 days (0-27 days) • normal template: 172 days (31–676 days)	early bladder closure n=82	delayed bladder closure (more than 30 days) n=33 • small template (n=18) • normal template (n=15)	**Bladder capacity** no significant differences in year 1, 3 and 4 <u>2 Years</u> *(early vs. delayed)* • early: 110 ml (27–260 ml) • normal template: 50 ml (40–65 ml) p=0.01	Delayed primary repair of exstrophy does not compromise the rate of bladder growth. However, children born with smaller templates will have overall smaller capacities and are less likely to undergo bladder neck reconstruction.	significantly different follow-up times, high loss to follow-up in the normal template group (40%) No information about funding and conflict of interest.	3 RoB: 7/9

	10.8 y (4.2-28 y) • small template: 4.2 y (1.2-13.6 y)		• small template: 305 days (86–981 days) <u>Male</u> early: 58/82 delayed: 28/33			• small template: 45 ml (15–157 ml) p=0.02 <u>5 Years</u> *(early vs. delayed)* • early: 100 ml (37–250 ml) • normal template: 104 ml (47–145 ml) p=0.33 • small template: 70 ml (33–175 ml) p=0.04 <u>6 Years</u> *(early vs. delayed)* • early: 116 ml (64–400 ml) • normal template: 88 ml (70–144 ml) p=0.4 • small template: 58 ml (40–80 ml) p=0.03			
Connor, 1989 [80]	Retrospective cohort study 1945-1985 USA Follow-up 2-35 y	Our series spans 40 y during which the principles of modern treatment of bladder exstrophy were formulated and attempts to identify those procedures that have consistently proved successful in the management of this condition.	n=137 patients with classic bladder closure and primary closure <u>Sex</u> Male: 140/207 (68%) Patient age at initial presentation: 1 day-35 y	early primary closure with bladder neck closure n=40	delayed primary closure without staged reconstruction n=97	**Continence** <u>early closure</u> • 25/40 (62%) had an excellent result • 8/40 (20%) had a good result • 7/40 (17%) required urinary diversion • 82% of the patients achieved continence, of these 16 patients must perform clean	Based on our results and those of others we conclude that the most successful operation for bladder exstrophy is primary closure within the first 72 hours of life followed by staged reconstruction of the bladder neck.	Comparability of cohorts unclear (patient characteristics and length of follow-up), continence status not always reported, unclear who measures the continence No information about funding and conflict of interest.	3 RoB: 5/9

						intermittent catheterization <u>delayed closure</u> • 5/97 (5.1%) had excellent continence • 10/97 (10.3%) had a good result • 20/97 (20.6%) had a poor result • 62/97 (64%) totally incontinent and were managed by an external collecting device **Complications** <u>early closure</u> • 6/40 (15%) had some degree of upper tract deterioration (2/6 required subsequent operative intervention) <u>delayed closure</u> • 25 patients (26%) had upper tract deterioration, • 15 patients needed an operative intervention due to reflux or outlet obstruction			

Husmann, 1989 [81]	Cohort study 1964-1989 Canada Minimum follow up: 5 y	To determine what factors could affect the success of initial bladder closure in classical bladder exstrophy.	n=80 patients with classical bladder exstrophy	Closed with iliac osteotomy n=51	Closed without iliac osteotomy n=29	**Closed with iliac osteotomy** <u><72 h after birth (n=15)</u> • with dehiscence: 13% • requiring augmentation: 6% • continent: 73% <u>3-30 days (n=12)</u> • with dehiscence: 16% • requiring augmentation: 16% • continent: 66% <u>31 days to 1 y (n=14)</u> • with dehiscence: 14% • requiring augmentation: 14% • continent: 71% <u>> 1 y (n=10)</u> • with dehiscence: 10% • requiring augmentation: 40% • continent: 60% **Closed without iliac osteotomy** <u><72 h after birth (n=19)</u>	To improve the results in staged bladder reconstruction we recommend use of perioperative antibiotics, adequate postoperative nutritional support to aid in wound healing, closure when the neonate is less than 72 h old if no iliac osteotomy is to be performed, immediate treatment of gastric distension by nasogastric drainage, secure fixation of all urinary diversion catheters with tubes exiting through the suprapubic region and careful preoperative assessment in individuals with a history of delayed closure to confirm the presence of an adequate bladder capacity.	comparability of cohorts unclear No information about funding and conflict of interest.	3 RoB: 8/9

						• with dehiscence: 10% • requiring augmentation: 5% • continent: 84% <u>3-30 days (n=6)</u> • with dehiscence: 16% • requiring augmentation: 16% • continent: 16% <u>31 days to 1 y (n=4)</u> • with dehiscence: 0% • requiring augmentation: 0% • continent: 0% **Bladder dehiscence** • No statistical correlation could be found among the development of bladder dehiscence, age of the child at bladder closure or the performance of iliac osteotomy (p >0.5) • Individuals undergoing delayed bladder closure without			

						iliac osteotomy had no notable difference in the incidence of bladder dehiscence **Bladder augmentation** • 10% of the individuals whose bladder was closed before they were 1 year old required augmentation compared to 40% whose bladder was closed after that age (p <0.02) **Continence** • in neonates whose bladder was closed before 72 h after birth the continence is not affected by the performance of iliac osteotomy (p >0.5) • delayed bladder closure without iliac osteotomy had a statistically significant difference in the ability to gain urinary			

						continence (p <0.01) • patients excluded who underwent closure without iliac osteotomy after they were 72 h old no statistical difference in individuals undergoing early versus delayed closure (p >0.5)			

Schlüsselfrage Ist eine intra- und postoperative Regionalanästhesie sinnvoll?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Bueno-Jimenez, 2020 [75]	Cohort study 2001-2018 Spain <u>Mean follow-up</u> early: 9 y delayed: 1 y	To analyze short-term results in male patients with bladder exstrophy undergoing delayed primary closure and compare them with early bladder closure as part of staged repair in our healthcare facility.	n=19 male patients BEEC Patients with malformatio ns such as cloacal exstrophy or exstrophy variants were excluded. <u>Mean age</u> early: 25 h delayed: 58 days	early bladder closure (n=13)	delayed bladder closure (n=6)	**Closure success** early: 11/13 (85%) delayed: 6/6 (100%) **Postoperative management protocols** <u>Postoperative anesthetic strategy</u> • early: Intubation with muscle relaxation for 5 days • delayed: Extubation; Control of analgesia with epidural catheter	Delayed closure can prove advantageous as it avoids general anesthesia at a time when the newborn is still physiologically immature, and also makes immediate post-birth mother-child separation unnecessary.	small number of patients and a long-term follow-up period, especially in delayed closure patients No information about funding and conflict of interest.	3 RoB: 8/9
Ebert, 2020 [82]	Cohort study 2009-2016 Germany	To evaluate the impact of reconstructive strategies and post-operative management on short- and long-term surgical outcome and complications of classical bladder exstrophy patients' comprehensive data of the multicenter German-wide Network for Congenital Uro-Rectal	**<u>Prospective cohort</u>** n=34 babies with classical bladder exstrophy Median age: 3 mo (IQR 2-4 mo) <u>Sex</u> Female: 10/34 (29%) Male: 24/34 (71%)	Staged approach • n=23 (prospective cohort) • n=60 (cross-sectional cohort)	Single-stage approach • n=11 (prospective cohort) • n=53 (cross-sectional cohort)	**Peridural catheter** <u>Prospective cohort</u> • Staged approach (n=23) yes: 18 (64%) no: 3 (29%) missing data: 2 (7%) • Single-stage approach (n=11) yes: 2 (33%) no: 5 (40%) missing data: 5 (40%) p=0.009 <u>Cross-sectional cohort</u> • Staged approach (n=60)	Only peridural catheters were inserted nearly twice as often in staged than in single-stage approaches in the prospectively observed group. When comparing both patient groups in general, a significantly higher frequency of peridural catheters was found in the prospectively observed than in	patient characteristics of both groups (staged approach and single-stage approach) are not separately described, no information on the length of follow-up supported by a research Grant (01GM08107) from the German Federal	3 RoB: 6/9

		malformations (CURE-Net) were analyzed.	**Cross-sectional cohort** n=113 patients with classical bladder exstrophy Median age: 12 y (IQR 6-21 y) <u>Sex</u> Female: 39/113 (35%) Male: 74/113 (65%)			yes: 22 (39%) no: 30 (43%) missing data: 8 (19%) • Single-stage approach (n=53) yes: 20 (37%) no: 23 (41%) missing data: 10 (22%) p=0.84 <u>Stratification for sex</u> No differences: • peridural catheters use (p=0.55)	the cross-sectional cohort (p = 0.017).	Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations were supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2016), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE 1723/1-1). http://www.cure-net.de.	
Martin, 2019 [83]	Cohort study 2011-2014 USA	We reviewed our experience with infants undergoing major abdominal surgery to determine if epidural catheter use decreased anesthetic and opioid exposure and improved postoperative analgesia.	n=82 infants undergoing major abdominal surgery • bladder exstrophy repair(n=9) • ureteral reimplantation (n=8) • Laparotomy exploratory (n=65)	Epidural anesthesia n=47	no epidural anesthesia n=35	**Bladder exstrophy repair** epidural anesthesia: 9/9 no epidural anesthesia: 0/9 **Ureteral reimplantation** epidural anesthesia: 8/8 no epidural anesthesia: 0/8 **Laparotomy**	Placement of epidural catheters in infants undergoing major abdominal surgery is associated with decreased long-acting opioid requirements intraoperatively. Epidural placement does not preclude opioid exposure however, as opioids may be administered for	no information about sex, patients with epidural use are older, length of follow-up not described Funding for data management and statistical analysis was provided by the Seattle Children's	3 RoB: 6/9

			Median age • epidural anesthesia: 62.0 (IQR 6.0, 177.0) • no epidural anesthesia: 5.0 (IQR 2.0, 55.0)			epidural anesthesia: 30/65 no epidural anesthesia: 35/65 **Overall** Mean intraoperative ET sevoflurane concentration • epidural anesthesia: 1.7 (SD 0.6) • no epidural anesthesia: 1.5 (SD 0.6) P = 0.037 Median intraoperative ET sevoflurane concentration • epidural anesthesia: 1.7 (IQR 1.3, 2.93) • no epidural anesthesia: 1.6 (IQR 1.0, 1.8) P = 0.049 Mean Fentanyl dose (mcg/kg) • epidural anesthesia: 3.3 (SD 4.3) • no epidural anesthesia: 6.2 (SD 7.8) P = 0.033 Median Fentanyl dose (mcg/kg) • epidural anesthesia: 2.6 mcg/kg (IQR 0,4.5) • no epidural anesthesia: 3.3 mcg/kg (IQR 2.4,5.8) P = 0.019	indications other than nociceptive pain in the difficult-to-assess postoperative infant.	Hospital Faculty Research Support Award, Center for Clinical and Translational Research. Adrian Bosenberg is a section editor of this journal (Pediatric Anesthesia). He was not involved in the peer review of this paper. Mixed patient population	

						Morphine use • epidural anesthesia: 3 (6%) • no epidural anesthesia: 9 (26%) No Morphine use • epidural anesthesia: 44 (94%) • no epidural anesthesia: 26 (74%) P = 0.014 **Epidural anesthesia** Complications • no major complications • most common: leaking (8/47, 17%), inadequate blockade (8/47, 17%) Duration ranged from 0 to 5 days postoperatively (50% of infant epidurals removed by postoperative day 3)			
Okonkwo, 2019 [84]	Cohort study 2007-2016 United Kingdom	This review aims to evaluate the efficacy and complication rate associated with continuous caudal epidural analgesia in the management of infants presenting for the delayed primary repair of isolated bladder exstrophy and to	n=42 classic bladder exstrophy undergoing delayed primary closure Male: 32/42 Age epidural: 5.6 mo (1.5-11.5 mo)	isolated caudal epidurals catheters n=27	caudal epidurals supplemented by intravenous opioids n=15	**Overall pain score (day one + day two)** isolated: 18 (0-67) opioid: 53 (11-76) p=0.008 **Day one total pain score** isolated: 8 (0-50) opioid: 15 (0-110) p=0.47 **Day two total pain score**	Early feeding (within the first 12 h) in delayed bladder exstrophy repair is likely to improve patient comfort and consolability without increasing the incidence of gastrointestinal complications.	patient recruitment not clearly described, length of follow-up unclear This study was supported by departmental funds. No additional external funding was utilized.	3 RoB: 7/9

		discuss the impact of early feeding in patients in this group.	opioid: 6.2 mo (2.1-17 mo)			isolated: 32 (0-117) opioid: 65 (11-172) p=0.014 **Complications** <u>Pruritis requiring treatment</u> isolated: 0 opioid: 25% (95% CI: 5-57) p=0.026 <u>Nausea and vomiting requiring intervention</u> isolated: 8% (95% CI: 1-25) opioid: 25% (95% CI: 5-57) p=0.3 No ileus and aspiration requiring interventions in both groups.	Intravenous opioid may be associated with increased postoperative complications that may influence peri-operative outcomes.	No conflict of interest declared.	
Rubenwolf, 2011 [85]	Cohort study 2003-2010 Deutschland	Ziel der vorliegenden Arbeit war es, die lumbale PDA im Hinblick auf ihre Durchführung, Effizienz, Sicherheit und mögliche Vorzüge gegenüber der rein systemi-schen perioperativen Analgesie zu analy-sieren.	n=21 Säuglinge mit kongenitalem Blasenekstrophie-/Epispadiekomplex <u>Alter</u> • mit PDA: 0,25 (SD 0,17–0,38) • ohne PDA: 0,23 (SD 0,16–0,4)	Gruppe mit PDA n=15	Gruppe ohne PDA n=6	**Krankenhausaufenthalt** • mit PDA: 25 Tage (Spanne 21-38) • ohne PDA: 28 Tage (Spanne 24-30) **Operationsdauer** • mit PDA: 342 min (Spanne 240-440) • ohne PDA: 333 min (Spanne 235-500) **Beatmungsdauer** • mit PDA: 479 min (Spanne 330-1000) • ohne PDA: 637 min (Spanne 480-1160) **Extubation nach Operationsende**	Die lumbale PDA stellt im perioperativen Narkose- und Schmerzmanagement bei mittleren und großen plastisch-rekonstruktiven kinderurologischen Eingriffen im Kindesalter ein analgetisch hocheffektives und sicheres Verfahren dar. Durch den signifikant reduzierten Bedarf an Anästhetika und Analgetika begünstigt die PDA eine zeitnahe Extubation mit allen	Nachbeobachtungszeit nicht berichtet Der korrespondierende Autor gibt an, dass kein Interessenkonflikt besteht. Keine Informationen zu Sponsorschaften	3 RoB: 8/9

						• mit PDA: 59 min (Spanne 5-408) • ohne PDA: 210 min (Spanne 120-600) **Intensivaufenthalt** • mit PDA: 1,1 Tage (Spanne 0,75-2,5) • ohne PDA: 1,7 Tage (Spanne 1-3) Der Zeitpunkt der ersten postoperativen Nahrungsaufnahme und des Ingangkommens der enteralen Motilität war bei Kindern mit perioperativer Periduralanästhesie kürzer als in der Gruppe ohne PDA; die beobachteten Unterschiede waren jedoch gering.	weiteren Vorteilen der postoperativen Versorgung.		

Schlüsselfrage Ist eine latexfreie Behandlung hinsichtlich unerkannter Allergien gerechtfertigt?									
Referenz	**Studien-charak-teristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Monitto, 2010 [86]	Case-control study USA	In this study, we tested the hypothesis that single-nucleotide polymorphisms in genes encoding IL13 and IL18 occur at an increased frequency in natural rubber latex allergic patients with spina bifida or bladder exstrophy.	n=120 patients • spina bifida (n=40) • bladder exstrophy (n=40) • control (n=40) whole blood (3 ml)	Serology and genotyping Bladder exstrophy patients (n=40) Male: 26/40 Mean age: 18.3 ± 10.6 y	Serology and genotyping Healthy control (n=40) Male: 18/40 Mean age: 20.7 ± 11.3 y	**Latex-specific IgE positive (%)** Bladder exstrophy: 17/40 (42.5%) Control: 3/40 (7.7%) **History of reaction to latex containing products** Bladder exstrophy IgE (+): 14/17 (82%) Bladder exstrophy IgE (-): 3/23 (13%) Control atopic: 0 Control nonatopic: 0 **Allele Frequencies** • Sensitization (IgE antibody positivity) to natural rubber latex allergens was associated with atopic history and number of prior operations and was prevented	In patients born with spina bifida or bladder exstrophy, environmental factors seem to play a greater role in the development of natural rubber latex sensitization and overt allergic symptoms than the IL polymorphisms in IL13 and IL18 previously shown to be associated with natural rubber latex allergy in health care workers.	recruitment process not clearly described, self-reported latex allergy questionnaire, some differences between the groups (e. g. gender) *only results for bladder exstrophy shown* No information about conflict of interest. Supported by Johns Hopkins Anesthesiology and Critical Care Medicine Clinical Research grant.	4 RoB: 5/9

						by the avoidance of natural rubber latex beginning at birth • the natural rubber latex allergy phenotype was not significantly associated with promoter polymorphisms in IL13 or IL18 when comparing natural rubber latex allergic bladder exstrophy patients with nonsensitized patients and with atopic and nonatopic controls • multivariate analysis in which natural rubber latex - IgE serology and number of prior operations were included: no association between single-nucleotide polymorphisms status and natural rubber latex allergy status • association between the IL18 +113 and			

						IL18 +127 minor frequency allele and natural rubber latex - IgE-positive serology: did not persist in multiple logistic regression model when number of prior operations was considered			
Ricci, 1999 [87]	Case series Italy	To evaluate the prevalence of latex sensitization in a group of patients with bladder exstrophy, and to determine the role of associated risk factors, e.g. atopy, and the number and duration of surgical and anaesthetic procedures.	n=17 patients with bladder exstrophy • children (n=15) • young adults (n=2) Mean age (children): 7.9 y (2-12 y) Male: 13/17	Skin prick-tests and specific IgE		**Latex sensitization** • no significant difference in sex ratio • Overall: 12/17 • Symptomatic: 5/12 • asymptomatic but latex-sensitized: 7/17 • not allergic/sensitized: 5/17 **Intraoperative anaphylactic reaction (had led to life-threatening events)** 1/17 **Latex-specific IgE titre** <u>Symptomatic</u> (n=5) • latex-specific IgE determined by prick test and RAST	A third of patients with bladder exstrophy showed latex symptoms and another third had latex sensitization. Multiple surgical procedures and atopy play a major role in the development of latex hypersensitivity	Patient recruitment, inclusion and exclusion criteria not clearly described, unclear how risk factors were recorded *Only significant risk factors shown* No information about conflict of interest and funding.	4 RoB: 13/20

						• did not correlate with a higher latex-specific IgE titre <u>Asymptomatic but latex-sensitized</u> (n=7) • RAST: positive in all • Skin-prick: 4/7 <u>Not allergic/sensitized</u> (n=5) None of the children without latex antibodies had symptoms of latex allergy **Risk factors** <u>Total hours of operations</u> • Symptomatic: 39.4 (SD 6.6) p<0.001 • Asymptomatic but latex-sensitized: 31.1 (SD 14.4) • Not allergic/sensitized: 18 (SD 7.3) p<0.001 <u>Years of intermittent catheterization</u> • Symptomatic: 5.6 (SD 2.8) p<0.007			

						• Asymptomatic but latex-sensitized: 4.2 (SD 5.5) • Not allergic/sensitized: 0.6 (SD 1.3) p<0.007 <u>Number of cystographic assessments</u> • Symptomatic: 4.8 (SD 1.3) p<0.002 • Asymptomatic but latex-sensitized: 3 (SD 2.8) • Not allergic/sensitized: 2.2 (SD 1.6) p<0.002			
Dormanns, 1997 [88]	Cohort study 1992-1995 USA	Three groups of patients at risk for type I hypersensitivity reaction were identified, and a regimen for prophylaxis developed (based in part on protocols used in preparing patients who are allergic to radiocontrast media).	n=34513 patients who had a general anesthetic	Prophylaxis protocol • n=86 at risk bladder exstrophy (n=41) • myelomening ocele (n=37) • cerebral palsy (n=8)	No prophylaxis protocol n=34427	**Suspected intraoperative latex anaphylaxis** <u>At risk</u> (n=1) • Patient with cerebral palsy, scoliosis, multiple previous operations, a history of intraoperativelatex anaphylaxis, and documented latex-antibody testing had two subsequent intraoperative anaphylactic	It is important that patients at risk for latex allergy be identified during the preoperativeevaluation. A careful preoperative history to elicit signs of latex hypersensitivity in patients considered at risk is the first step in prevention. If latex allergy is suspected, a formal investigationto include allergy consultation and latex-specific IgE test should be requested. Since using this protocol, the incidence of intraoperative	Comparability of cohorts unclear No information about conflict of interest and funding.	3 RoB: 7/9

						reactions during in spite of pharmacologic prophylaxis and avoidance of intraoperative latex (high-risk prophylaxis) • Patient also had allergies to pancuronium, vecuronium, atacurium, midazolam, and thiopental documented by skin testing <u>No prophylaxis</u> (n=2) • One patient has not had further surgery • One patient has two subsequent operations without signs of anaphylaxis with prophylaxis.	anaphylaxis has decreased.		
Kwittken, 1995 [89]	Retrospective case series USA	To better understand the clinical characteristics, diagnosis, and possible prevention of immediate hypersensitivity reactions to latex in a hospitalized, pediatric patient population.	n=35 cases of latex allergy • 48.6% spina bifida • 11.4% bladder exstrophy primary diagnosis of bladder exstrophy (n=4) spina bifida and bladder	IgE		• Severity of reaction (grade I vs. grade IV) could not be correlated with circulation levels of latex-specific IgE, pre-existing clinical history of latex allergy, nor the length of time latex allergy was	Our experience indicates that the incidence of latex hypersensitivity in children is increasing, that the circumstances (patient profile, hospital location, route of exposure) in which life-threatening reactions may occur are more broad than previously reported, and that a better understanding of both	No recruitment time reported, no statistical analysis No information about conflict of interest and funding.	4 RoB: 14/20

			exstrophy (n=1) Male: 22/35 Mean age: 9.6 +/- 4.6 y (21 mo – 17 y)			clinically evident • In vitro: 33/35 detection of latex-specific IgE • When exposure to latex occurs systemically, as through an intravenous line, premedication with steroids and antihistamines may fail to protect against anaphylaxis **Spina bifida & Exstrophy** (n=21) **vs. all others** (n=14) More than six surgeries: 95% vs. 29% Atopy: 67% vs. 93% Previous History: 52% vs. 50% **Patients with bladder exstrophy** (n=5) • 2-47 operations • 2/5 reaction Grade I • 1/5 reaction Grade II • 2/5 reaction Grade IV	environmental sources of latex antigens and host responses to latex exposure are needed for improved prevention of serious reactions.		

Schlüsselfrage Ist eine operative Technik zur BEEK-Behandlung überlegen?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Chalfant, 2022 [73]	Retrospective cohort study 2012-2019 USA Follow-up is limited to 30 days	The primary aim of this study was to determine complication rates in the classic bladder exstrophy population for bladder closure and advanced urologic reconstruction in national studies compared to single-institutional studies.	n=302 classic bladder exstrophy patients **Advanced urologic reconstruction cohort** (n=150) Median age in mo • Bladder augmentation: 121 (IQR 94-150) • Ureteroneocystostomy: 82 (IQR 54-113) • Mitrofanoff procedure: 114 (IQR 74-160) • Bladder neck reconstruction: 76 (IQR 54-113) Male	• Bladder augmentation (n=53) • Ureteroneocystostomy (n=48) • Mitrofanoff procedure (n=34) • Bladder neck reconstruction (n=15)		**Operation time** • Bladder augmentation: 505 min [388-640 min] • Ureteroneocystostomy: 501 min [369-643 min] • Mitrofanoff procedure: 433 min [268-572 min] • Bladder neck reconstruction: 463 min [362-558 min] **30-day complications** • for bladder closure: 30.3% • for advanced urological reconstruction: 24% • No significant differences between readmission, reoperation, wound disruption, systematic sepsis, superficial incisional surgical site infection, urinary tract	Classic bladder exstrophy surgeries carry a higher risk of complications than is generally reported. Infectious complications occur >10% of the time in both bladder closure and advanced urologic reconstruction and should be the source of additional study given the inverse relationship infections pose to surgical success in classic bladder exstrophy patients. These data suggest that reported classic bladder exstrophy complication data may be underrepresented in the literature.	Short follow-up time No information about funding and conflict of interest.	3 RoB: 8/9

			• Bladder augmentation: 41/53 • Ureteroneocystostomy: 30/48 • Mitrofanoff procedure: 19/34 • Bladder neck reconstruction: 8/15			infection and deep incisional surgical site infection <u>Bleeding/Transfusions</u> • Bladder augmentation: 2/53 (3.8%) • Ureteroneocystostomy: 9/48 (18.8%) • Mitrofanoff procedure: 0/34 (0%) • Bladder neck reconstruction: 1/15 (6.7%) p=0.008			
Benz, 2018 [90]	Retrospective cohort study 1993-2016 USA Mean follow-up time: 6.9 y (0.52-23.35 y)	To evaluate HAD as an adjunct during bladder neck transection by comparing surgical outcomes with other types of tissue interposition.	n=147 Exstrophy-Epispadias Complex patients • cloacal exstrophy (n=22) • classic exstrophy (n=124) Male: 94/147 (63.9%) Mean age: 11 y (4.27-53.1 y)	Use of interposed tissue with bladder neck transection: • none (n=26) • native tissue flaps (n=40) • HAD (n=71) • HAD+native tissue flaps (n=10)		**Fistula Frequency** Using either HAD or native tissue flaps resulted in a lower fistulization rate than using no interposed layers (p=0.039) <u>None</u> Classic exstrophy: 3/20 (15%) Cloacal: 2/6 (33%) Total: 5/26 (19%) <u>Native tissue flaps</u> Classic exstrophy: 1/37 (2.7%) Cloacal: 0/3 (0%) Total: 1/40 (2.5%) <u>HAD</u>	Use of soft tissue flaps and HAD is associated with decreased fistulization rates after bladder neck transection. HAD is a simple option and an effective adjunct that does not require harvesting of tissues in patients where a native flap is not feasible.	Comparability of cohorts unclear (patient characteristics and length of follow-up) No information about conflict of interest. The Kwok Family Foundation of Hong Kong supports all clinical and basic science exstrophy research.	3 RoB: 6/9

						Classic exstrophy: 4/58 (7%) Cloacal: 1/12 (8%) Epispadias: 0/1 (0%) Total: 5/71 (7%) <u>HAD+native tissue flaps</u> Classic exstrophy: 0/9 (0%) Cloacal: 1/1 (100%) Total: 1/10 (10%) • The 8.8% fistulization rate when using HAD without fibrin sealant was no different than the 6.5% fistulization rate when using HAD along with fibrin sealant (p=0.695) **Surgical complications** no statistical difference in surgical complications between the use of HAD and native flaps (8.6% vs 5%, p=0.716)			
Kajbafzadeh, 2014 [91]	Retrospective cohort study 1995-2010 Iran	The purpose of this study was to represent our experience of an academic referral center for complex BEEC patients with	n=28 patients with BEEC and small bladder plate in the setting of	SUPER and UAAC technique, and subsequent bladder closure n=12	Total polyp excision along with urothelial covering n=16	**Mean hospital stay** • SUPER and UAAC group: 21.2 days • Simple polyp excision group: 20 days	The final clinical outcome of children with bladder exstrophy polyposis is promising. The combined SUPER and UAAC technique is	self-reported continence status *Several factors such as multiple polyps covered small bladder*	3 RoB. 6/9

	Mean follow-up • SUPER and UAAC group: 28.16 mo (SD=± 18.42 mo) • Simple polyp excision group: 37.18 mo (SD=± 21.53 mo)	several bladder polyps in the setting of small bladder plate surface who underwent this new technique by the name of sub-urothelial polyp enucleation resection and urothelial auto-augmentation cystoplasty.	bladder polyposis Male • SUPER and UAAC group: 8/12 (75%) • Simple polyp excision group: 10/16 (62.5%) Mean age • SUPER and UAAC group: 3.50 y (SD=± 2.06 y) • Simple polyp excision group: 3.25 y (SD=± 1.80 y)			**Mean bladder capacity** • SUPER and UAAC group: 190.62 ml (SD=± 38.18 ml) • Simple polyp excision group: 119.68 ml (SD=±21.71 ml) p=0.04 **Continence rate** • SUPER and UAAC group: 66.7 % • Simple polyp excision group: 31.3 % p=0.03 Socially continent • SUPER and UAAC group: 8/12 • Simple polyp excision group: 5/16 Waiting for toilet training • SUPER and UAAC group: 3/12 • Simple polyp excision group: 2/16 Incontinent • SUPER and UAAC group: 1/12 • Simple polyp excision group: 9/16 **Complications** • All children had an uneventful postoperative period with no	feasible, safe and reproducible option for BEEC patients with bladder plate polyposis. It will add one supplementary operation to the single or staged bladder reconstruction. These patients may warrant further surveillance with histopathological evaluations during the adult life.	*plate, contracted bladder or the lesions engaged 80 % of bladder mucosa was considered as poor bladder plate. These patients were selected for SUPER and UAAC technique.* No conflict of interest exists in relation to the submitted manuscript and there was no source of extra-institutional commercial funding or funding received from National Institutes of Health, Welcome Trust, Howard Hughes Medical Institute and others.	

						major complications or bladder dehiscence • No wound infection, bladder dehiscence or prolapse <u>SUPER and UAAC</u> • 2/12 with urethra–cutaneous/vesico-cutaneous fistula • 10/12 (83.3%) with preserved upper tracts • 2/12 (16.7%) with mild changes in upper tracts • 3/12 had low-grade bilateral VUR • 2/16 had unilateral VUR • 1/12 had high-grade bilateral reflux <u>Simple polyp excision group</u> • 8/16 (50%) with preserved upper tracts • 8/16 (50%) with mild changes in upper tracts • 6/16 had low-grade bilateral VUR • 3/16 had unilateral VUR			

						• 3/16 had high-grade bilateral reflux			
Caione, 2005 [92]	Retrospective cohort study 1990-2022 Italy Follow-up: 24 mo	To stress the use of a bipolar stimulator to detect the perineal muscular complex intraoperatively, and to increase the functional results of reconstruction in exstrophy-epispadias patients.	n=41 exstrophy-epispadias patients • classic bladder exstrophy (n=32) • epispadias (n=9) Male: 31/41 <u>Age</u> • Exstrophy: 3 days to 6 years • Epispadias: 9 months to 16 y	electric bipolar stimulator to detect the perineal muscular complex intraoperatively n=22	without the presented technique n=19	**Mean bladder capacity** <u>Bladder exstrophy</u> stimulator (n=17): 78 cc (30–110 cc) control (n=15): 45 cc (10–65 cc) p<0.05 <u>Male epispadias</u> stimulator (n=5): 123 cc (50–180 cc) control (n=4): 95 cc (55–140 cc) p<0.05 **Dry intervals** <u>Bladder exstrophy</u> stimulator: 11/17 control: 2/15 <u>Male Epispadias</u> stimulator: 5/5 control: 3/4 **Mean dry interval** <u>Bladder exstrophy</u> stimulator (n=17): 75 min (30–120 min) control (n=15): 55 min (35–75 min) p<0.05 <u>Male epispadias</u> stimulator (n=5): 130 min (45–180 min) control (n=4): 90 min (30–140 min)	Proper identification of the anterior perineal muscular complex, using a bipolar stimulator, and its reapproximation at the posterior urethra on the midline was demonstrated to be effective in increasing bladder cycling and in developing adequate bladder volume, anticipating coordinated micturition.	historical control group (1990-1995 vs. 1995-2002), age not reported No information about funding and conflict of interest.	4 RoB: 7/9

						p<0.05 **Day time continence** <u>Bladder exstrophy</u> stimulator: 3/17 control: 0/15 <u>Male Epispadias</u> stimulator: 5/5 control: 2/4 **Febrile urinary tract infection** stimulator: 2/22 control: 6/19 p<0.05 **Upper tract dilatation** stimulator: 8/22 control: 6/19 not significant **Bladder neck deshiscence** stimulator: 0/22 control: 3/19 p<0.05 **Male urethral fistula/stenosis** stimulator: 3/16 control: 9/15 p<0.05 **Female uterus procidentia** stimulator: 0/6 control: 2/4 p<0.05			
Hollowell, 1991	Prospective cohort study	We are doing a prospective study to answer several	n=36 children with BEEC	• Group A: with primary severe		**Group A** • 5/5 were able to initiate a detrusor	These findings suggest that a formal bladder-neck	recruitment of the study group and	3

[93]	United Kingdom	questions regarding bladder function in patients with exstrophy and epispadias. This preliminary report is concerned with the unexpected findings that conventional surgery may be based on false assumptions and that the surgery itself may adversely affect bladder function.	Male: 26/36 Age • Group A: 3-13 y • Group B: 1.5-9 y • Group C: 6-16 y	epispadias after urethral closure but before planned BNR (n=5) • Group B: with exstrophy after bladder and urethral closure but before surgery for continence (n=15) • Group C: who have had BNR (s) (without augmentation) but remain incontinent (secure dry intervals less than 3 h) (n=16)		contraction for voiding • none had involuntary detrusor contractions during filling • normal upper urinary tracts **Group B** • 10/15 showed intermittent involuntary detrusor contractions that were responsible for most of the leakage of urine • 2/11 were able to initiate a detrusor contraction for voiding • 9/11 voided by abdominal straining • 3/15 with leak pressure less than 10 cm H_20, had poor bladder capacity (mean=45 ml) • 8/15 with a leak pressure of 10-30 cm H_2O, 2/8 capacity was better (mean=120 ml) than in 6/8 with involuntary contractions (mean=80 ml). • 4/15 with a leak pressure greater than 30 cm H20	reconstruction may severely damage detrusor function. If this proves to be the case, other management options will need to be evaluated. Possible alternatives are endoscopic submucosal injection of collagen in the bladder neck area or the implantation of an artificial urinary sphincter without first reconstructing the bladder neck.	classification to the groups not described, no follow-up time reported, comparability of cohorts unclear *Number of boys in group C is wrong.* No information about funding and conflict of interest.	RoB: 5/9

						all had involuntary contractions with variable capacity (40-260 ml), 2/4 had upper urinary-tract dilatation **Group C** • 4/16 leaked only with involuntary detrusor contractions • 5/16 had minor leakage at low pressures (10-20 cm H_2O), but their major difficulty was high-pressure (55-165 cm H_2O) detrusor contractions • 7/16 the cause of incontinence was low leak pressure <u>Bladder capacity:</u> • 5/16: <120 ml • 6/16: 120-250 ml • 5/16: 250-500 ml <u>Bladder function – filling:</u> • 10/16: Active • 6/16: Stable <u>Bladder function – voiding:</u> • 2/14: contractile • 12/14: acontractile			

						Leak pressure: • 2/16: >25 cm H20 • 8/16: 15-25 cm H20 6/16: <15 cm H20			
Husmann, 1990 [94]	Retrospective cohort study Canada Mean follow-up: 10.5 y	During the continued long-term follow-up evaluation of patients with classical bladder exstrophy, a significant morbidity associated with inguinal hernias and cryptorchidism in children having this congenital anomaly has been noted. In order to assess the prevalence of these disorders in this patient population, a large series of individuals with CBE presenting for routine follow-up care at our institution were reviewed.	n=134 patients with CBE Male: 81/134 Median age (male population): • staged bladder reconstruction: 5 days • primary cystectomy and diversion: 3 mo	staged bladder reconstruction n=122	primary cystectomy and urinary diversion with no attempt at staged reconstruction n=22	**Comparison of male patients** (n=81) <u>Diagnosis of inguinal hernia, prior to surgery:</u> • Staged reconstruction: 11/59 (19%) • Primary cystectomy and diversion: 3/22 (13%) p=0.5 <u>Diagnosis of inguinal hernia, less than 1 y postsurgery:</u> • Staged reconstruction: 20/59 (34%) • Primary cystectomy and diversion: 1/22 (5%) p=0.017 <u>Diagnosis of inguinal hernia, greater than 1 y postsurgery</u>: • Staged reconstruction: 9/59 (15%) •Primary cystectomy and diversion: 1/22 (5%) p=0.27	We believe the increased incidence of herniation with this congenital anomaly is secondary to a lack of obliquity of the inguinal canal, due to pubic diastasis along with an increased elevation of intraabdominal pressure following initial closure of the abdominal wall and bladder plate. To decrease the attendent morbidity of incarcerated hernias in this population, we stress the need for careful physical examination of the inguinal region and spermatic cord prior to surgery, along with repair of the patent processus vaginalis at the time of initial repair.	patient age between the groups was different *Routine contralateral exploration of the inguinal region was not carried out in our patient population.* No information about funding and conflict of interest.	3 RoB: 7/9

						<u>Patients with inguinal hernias:</u> • Staged reconstruction: 68% •Primary cystectomy and diversion: 23% p<0.001			
Connor, 1989 [80]	Retrospective cohort study 1945-1985 USA Follow-up 2-35 y	Our series spans 40 y during which the principles of modern treatment of bladder exstrophy were formulated and attempts to identify those procedures that have consistently proved successful in the management of this condition.	n=207 patients CBE <u>Sex</u> Male: 140/207 (68%) Patient age at initial presenta-tion: 1 day-35 y	Ureterosigmoi dostomy n=40	Cutaneous urinary diversion n=45 • initial (n=17) • secondary (n=28)	**Continence** <u>Ureterosigmoidostomy</u> no information given <u>Cutaneous urinary diversion</u> Continent diversion was performed in 7 patients as a secondary procedure and all currently are continent with clean intermittent catheterization. **Complications** <u>Ureterosigmoidostomy</u> • 40/40 (100%) experienced some degree of hyperchloremic metabolic acidosis and required systemic alkalization	One also must be prepared to use some of the more innovative techniques currently available to achieve acceptable urinary continence. Long-term close follow-up is essential to ensure that renal function is protected, and since urinary continence may require many operations during a number of years, patient selection is extremely important.	Comparability of cohorts unclear (patient characteristics and length of follow-up), continence status not always reported, unclear who measures the continence No information about funding and conflict of interest. No information about funding and conflict of interest.	3 RoB: 5/9

						• 37/40 (92%) upper tract deterioration • 16/40 (40%) unilateral nephrectomy • 18/40 (45%) significant calculus formation • 3 patients died of causes directly related to this form of diversion <u>Cutaneous urinary diversion</u> • upper tract deterioration (n=16) • stomal stenosis or persistent irritation and bleeding (n=10) • stricture at the site of the ureteroileal anastomosis (n=3) • Colon conduit: Upper tract deterioration occurred secondary to reflux (n=3/11)			
Blasenvergrößerung									
Stewart, 2015 [95]	Retrospective cohort study 1980-2012 Median follow-up: 5 y	This study was designed to identify the incidence of surgical complications among various	n=134 patients with exstrophy–epispadias complex underwent continent	Augmentation n=106	Neobladder n=11	**Complications** <u>Small Bowel Obstruction</u> Augmentation: 6/106 (6%) Neobladder: 0 p=0.422	The increased risk of abdominal and pelvic abscesses in patients who receive a colon continent urinary diversion and	prospectively kept database, comparability of cohorts unclear, small neobladder group	3 RoB: 7/9

		bowel segments typically used for continent urinary diversion.	urinary diversion Male: 81/134 Median age for diversion: 7 y (2-25 y)			<u>Post-Op Ileus</u> Augmentation: 4/106 (4%) Neobladder: 0 p=0.516 <u>Hernia</u> Augmentation: 1/106 (1%) Neobladder: 0 p=0.906 <u>Abscess</u> Augmentation: 1/106 (1%) Neobladder: 3/11 (27%) p=0.002	undergo neobladder compared to augmentation cystoplasty indicates that while surgical complications following major genitourinary reconstruction are rare, they do occur. Practitioners must be wary of potential complications that are best managed by a multi-disciplinary team approach.	No information about funding and conflict of interest.	
Kilic, 1999 [96]	Cohort study 1987-1996 Turkey Mean follow-up: 3.2 y (6 mo-8 y)	To compare the urodynamic findings and clinical outcome in different bladder augmentation techniques.	n=30 patients BEEC (n=28) • posterior urethral valve (n=1) • cloacal exstrophy (n=1) Male: 18/30 Mean age at operation: 8.1 y (1-15 y)	bladder augmentation • colonic (n=11) • gastric (n=9) • ileal (n=6) • ileocaecal (n=2) • rectus abdominis muscle flap (n=4)		**Mean capacity** • colonic: 237 ± 120 ml • gastric: 115 ± 86 ml • ileal: 240 ± 45 ml • ileocaecal: 250 ± 0 ml • rectus abdominis muscle flap: 30 ± 10 ml **Mean compliance** • colonic: 20.6 ± 14 ml/cm H20 • gastric: 10.7 ± 10.4 ml/cm H20 • ileal: 21.6 ± 9 ml/cm H20 • ileocaecal: 25.5 ± 5.5 ml/cm H20 • rectus abdominis muscle flap: 5.8 ± 1.5 ml/cm H20	Comparing these five different techniques, ileal, ileocaecal and colonic groups were in advantage to achieve high volume reservoirs, followed by the gastric group. Regarding complications; in colonic cases. mucus problems, stone formation and surgical complications related to gastrointestinal tract (intestinal obstruction, perforation) were the most common ones. Perineal· dermatitis was the main complication	comparability of cohorts unclear No information about funding and conflict of interest. Two patients are not BEEC cases: 1 patient in the ileocaecal group, 1 patient with unknown group	3 RoB: 7/9

						Complications • colonic: 13 • gastric: 4 • ileal: 2 • ileocaecal: 1 • rectus abdominis muscle flap: 1	in gastric eases. In the ileal group, complication rate was low. Absence of mucus production and the low postoperative complication rates were the two major advantages of rectus abdominis muscle flap technique. However, this technique is not recommended as an augmentation procedure due to its low capacity and compliance rates.		
Komplette Primärreparatur									
Ebert, 2020 [82]	Cohort study 2009-2016 Germany	To evaluate the impact of reconstructive strategies and post-operative management on short- and long-term surgical outcome and complications of classical bladder exstrophy patients' comprehensive data of the multicenter German-wide Network for Congenital Uro-Rectal malformations	**<u>Prospective cohort</u>** n=34 babies with classical bladder exstrophy Median age: 3 mo (IQR 2-4 mo) <u>Sex</u> Female: 10/34 (29%) Male: 24/34 (71%) **Cross-sectional cohort** n=113 patients with	Staged approach • n=23 (prospective cohort) • n=60 (cross-sectional cohort)	Single-stage approach • n=11 (prospective cohort) • n=53 (cross-sectional cohort)	**Perioperative management** **Peridural catheter** <u>Prospective cohort</u> • Staged approach (n=23) yes: 18 (64%) no: 3 (29%) missing data: 2 (7%) • Single-stage approach (n=11) yes: 2 (33%) no: 5 (40%) missing data: 5 (40%) p=0.009	While single-stage approaches tended to have initially more complications such as renal dilatation or urinary tract infections, additional surgery such as augmentations and stomata appeared to be similar after staged and single-stage reconstructions in the long term.	patient characteristics of both groups (staged approach and single-stage approach) are not separately described, no information on the length of follow-up supported by a research Grant (01GM08107) from the German Federal Ministry of Education and Research	3 RoB: 6/9

		(CURE-Net) were analyzed.	classical bladder exstrophy Median age: 12 y (IQR 6-21 y) <u>Sex</u> Female: 39/113 (35%) Male: 74/113 (65%)			<u>Cross-sectional cohort</u> • Staged approach (n=60) yes: 22 (39%) no: 30 (43%) missing data: 8 (19%) • Single-stage approach (n=53) yes: 20 (37%) no: 23 (41%) missing data: 10 (22%) p=0.84 <u>Stratification for sex</u> No differences: • peridural catheters use (p=0.55) No significant differences between both groups: • Postoperative intensive care observation • Wound and tissue infection • Blood transfusion • Anticholinergic medication • Low-dose antibiotic prophylaxis • Transurethral catheter in place • Discharge **Complications**		(Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations were supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2016), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE 1723/1-1). http://www.cure-net.de.	

						Urinary tract dilatation after reconstruction <u>Prospective cohort</u> • Staged approach (n=23) yes: 11 (48%) no: 12 (52%) • Single-stage approach (n=11) yes: 6 (55%) no: 5 (45%) p=0.71 <u>Cross-sectional cohort</u> • Staged approach (n=60) yes: 11 (18%) no: 18 (30%) missing data: 31 (52%) • Single-stage approach (n=53) yes: 24 (45%) no: 19 (36%) missing data: 10 (19%) p=0.0021 **Urinary tract infection** <u>Prospective cohort</u> • Staged approach (n=23) yes: 7 (30%) no: 16 (70%) • Single-stage approach (n=11) yes: 8 (73%) no: 2 (18%) missing data: 1 (9%)			

						p=0.02 <u>Cross-sectional cohort</u> • Staged approach (n=60) yes: 26 (43%) no: 11 (18%) missing data: 23 (38%) • Single-stage approach (n=53) yes: 35 (66%) no: 10 (19%) missing data: 8 (15%) p=0.023 **Disturbed bladder function** <u>Prospective cohort</u> • Staged approach (n=23) yes: 0 no: 20 (87%) missing data: 3 (13%) • Single-stage approach (n=11) yes: 0 no: 9 (82%) missing data: 2 (18%) p=1 <u>Cross-sectional cohort</u> • Staged approach (n=60) yes: 1 (2%) no: 22 (37%) missing data: 37 (62%)			

						• Single-stage approach (n=53) yes: 7 (13%) no: 27 (51%) missing data: 19 (26%) p=0.025 No significant differences between both groups: • Renal deterioration after reconstruction • Unilateral nephrectomy • Epididymitis during follow-up*			
Pathak, 2020 [97]	Systematic review 1989-2018	Does complete primary repair reduce the numbers of procedures for reconstruction of bladder exstrophy?	n=11 articles n=236 patients with bladder exstrophy <u>Sex</u> 153 boys 72 girls 11 sex unreported Timing of the primary closure: from birth to 5.6 years	Complete primary repair		• Infants reported having closure beyond the first 72 h of life (34/236 patients) were most commonly managed with osteotomy and spica cast immobilization **Complications of primary closure** Overall: 63 (*most were considered minor, including superficial infections*) • failure of the closure (n=8) • complete dehiscence (n=2)	Complete primary repair of exstrophy has been suggested as a single procedure for the management of bladder exstrophy. Literature review suggests most patients require multiple procedures to complete reconstruction and attain continence.	No study overview, only one database used, no additional hand search, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment Funding & Conflict of Interest: None declared.	4 RoB: high

						• fistula (n=20, 18 required fistula closure) • death (n=2) **Further reported surgical interventions** • ureteral reimplantation (n=58) • injection of dextranomer/hyaluronidase (n=3) • hypospadias repair (n=11) • bladder neck reconstruction (n=33) • bladder neck bulking procedures (n=7) • revision of epispadias (n=10) **Continence status** *not universally reported* • Volitional voiding (n=34) • dry with only primary bladder closure (n=11) • bladder neck closure (n=7) • intermittent catheterization (n=6)			
Chua, 2019 [98]	Retrospective cohort study	A comparative series of outcomes	n=21 male patients with primary	CPRE n=10	SRBE-BUR N=11	**Operative outcomes**	The SRBE with bilateral ureteral re-implantation is a	Penile cosmetic outcomes were	3 RoB:

	2000-2014 Canada <u>Median follow-up</u> • CPRE: 9.7 y (IQR 2.25-12.75y) • SRBE-BUR: 4 y (2.5-6.9 y)	between CPRE and SRBE-BUR is reported.	exstrophy-epispadias complex <u>Median age</u> • CPRE: 4.5 days (IQR 3-173.25 days) • SRBE-BUR: 2 days (1-4 days)			<u>Median procedure time</u> • CPRE: 580 min (IQR 540-700.25) • SRBE-BUR: 367 min (IQR 340-400) p<0.0001 <u>Estimated blood loss</u> • CPRE: 175 ml (IQR 136.25-485 ml) • SRBE-BUR: 75 (IQR 25-150 ml) p=0.003 <u>Total estimated blood loss</u> • CPRE: 175 ml (IQR 136.25-485 ml) • SRBE-BUR: 100 (IQR 65-175 ml) P=0.012 **Long-term complications** No statistically significant differences were noted **Urinary continence** No significant differences were noted for urinary continence rates and unplanned additional operations.	safe alternative for the repair of the exstrophy-epispadias repair as it prevents the catastrophic complication of penile tissue loss, while having comparable long-term outcomes with the CPRE. Delaying epispadias repair avoids penile injury besides possible improvement of its overall cosmesis.	subjectively assessed by the respective surgeons *Only significant operative outcomes shown* The author group has no conflict of interest to disclose. No direct or indirect financial funding was associated with the work of this research study.	8/9

						Penile appearance SRBE-BUR had approximately 40% better penile appearance and continence rate than CPRE group. **Ischemic injury** CPRE: 2 SRBE-BUR: 0 **Further operation** CPRE: 7/10 SRBE-BUR: 6/11			
Arab, 2018 [99]	Retrospective cohort study 1998-2012 Egypt Median follow-up: 14 y (5-19 y)	To demonstrate the long term outcome of a contemporary series of 64 children who underwent CPRE in a single tertiary referral center	n=60 with classic bladder exstrophy Median age: 9 (0.06-42 y) Male: 45/60	CPRE only	CPRE+ different continence procedures	**Continence** • CPRE only: 14/60 (23%) • CPRE+BNR: 6/10 (10%) • CPRE+BNI: 2/60 (3%) • CPRE+BNR, bladder augmentation & continent cutaneous outlet: 9/60 (15%) • CPRE+multiple BNR, bladder augmentation & continent cutaneous outlet: 29/60 (49%) • volitional voiding via urethra: 22/60 (36%) • CIC: 38/60 (64%)	The percentage of children with classic bladder exstrophy who underwent CPRE who will achieve continence with volitional voiding via the urethra is 36%. The continence results after BNR and BNI is better in de novo cases than in redo ones. Continence in female and de novo cases are more likely to be achieved with lower number of continence procedures.	Comparability of cohorts unclear, no clear continence definition, continence assessment not described, No information about funding and conflict of interst.	3 RoB: 6/9
Inouye, 2018 [77]	Retrospective cohort study since 1975	Even with contemporary management, patients still have	n=722 patients with CBE	CPRE n=159	• MSRE n=406 • Unknown	**Successful vs. failed closure** *(bivariate analysis)*	We found that early time of closure, closure by an adult urologist or	Comparability of cohorts unclear (patient characteristics	3 RoB: 6/9

	USA	failed primary closures. We sought to understand the role of training, surgical technique, and their impacts on outcomes of CBE closure.	Male: 506/722 (70.2%)		n=156	• CPRE: 92/159 vs. 67/406 • MSRE: 323/406 vs. 83/406 • Unknown: 61/156 vs. 95/406 p<0.0001 **Multivariable logistic regression analysis** *(adjusted)* • MSRE: Reference • CPRE: 2.05, 95% CI: 1.29-3.26, p=0.0024 Unknown: 4.81, 95% CI: 2.94-7.86, p<0.0001	pediatric surgeon, closure by CPRE method, not having a concomitant osteotomy, and immobilization with spica cast or mummy wrap were associated with increased odds of failed primary closure.	and length of follow-up) Funding: This study had no external funding source. Conflicts of interest: The authors declare no conflicts of interest.	
Alsowayan, 2016 [100]	Retrospective cohort study 1990-2014 Saudi Arabia Mean follow-up time: 18 y±5 y	We present the long-term treatment outcomes of classic bladder exstrophy patients over 24 years in a low exstrophy-volume centre.	n=16 patients with bladder exstrophy Male: 7/16	CPRE n=10	MSRE n=6	no significant differences between the groups in dehiscence, fistula, urinary tract infections, bladder neck injection, bladder neck reconstruction + bilateral ureteric reimplantation, augmentation cystoplasty, clean intermittent catheterization, urethral voiding, anticholinergics, Hydronephrosis and uroflow **Continence** <u>Continent after bladder exstrophy closure only</u> CPRE: 2/10	Continence following successful BE closure only is low at 12.5%. An auxiliary continence procedure to achieve continence seems to be inevitable. Continence rate after successful auxiliary procedure rose to 93.8%. This might be at the cost of urethral voiding, which was achieved in 60%.	age not reported The authors declare no competing financial or personal interests. No information about funding	3 RoB: 8/9

						MPRE: 0/6 not significant <u>Continent at last follow-up</u> CPRE: 9/10 MPRE: 6/6 not significant <u>Nocturnal enuresis</u> CPRE: 1/10 MPRE: 1/6 not significant **Sexual function** (n=6 sexually active) not statically significant <u>Males</u> (n=3) CPRE • 1 normal MPRE • 1 mild chordee & poor ejaculate • 1 mild chordee & normal ejaculate <u>Females</u> (n=3) CPRE • 1 normal • 1 vaginoplasty MPRE • 1 normal with successful pregnancy			
Braga, 2010 [101]	Retrospective cohort study 1997-2008 Canada	In this study we sought to compare the outcomes of children who underwent	n=38 patients with bladder exstrophy	CPRE n=23	CPRE-BUR n=15	**Postop hydronephrosis grade** p=0.05 <u>I</u> CPRE: 3/23 (13%)	Bilateral ureteral reimplantation can be safely and effectively performed during primary closure of bladder exstrophy	Significant different follow-up times between the groups	3 RoB: 8/9

	Mean follow-up CPRE: 70 mo (23–117 mo) CPRE-BUR: 34 mo (6–54 mo)	CPRE-BUR to those undergoing CPRE alone to appraise the impact of BUR on reducing the frequency of postoperative febrile urinary tract infections in this population.	Median days age at surgery Both: 3 days Male CPRE: 13/23 (57%) CPRE-BUR: 5/15 (33%)			CPRE-BUR: 2/15 (13%) II CPRE: 3/23 (13%) CPRE-BUR: - III CPRE: 3/23 (13%) CPRE-BUR: - IV CPRE: 1/23 (4%) CPRE-BUR: - **Postop febrile urinary tract infections** CPRE: 11/23 (48%) CPRE-BUR: 1/15 (7%) p=0.01 **Postop vesicoureteral reflux** CPRE: 17/23 (74%) CPRE-BUR: - p=0.004	in newborns, potentially reducing postoperative febrile urinary tract infections and hydronephrosis by early correction of vesicoureteral reflux.	No information about funding and conflict of interest.	
Borer, 2005 [102]	Retrospective cohort study 1979-2004 USA	We assessed bladder growth and dynamics following CPRE compared to the staged approach.	n=37 patients with bladder exstrophy Male CPRE: 16/23 staged approach: 8/14	CPRE n=23	staged approach n=14	**Mean % predicted bladder capacity:** *Males* • CPRE (n=14): 46.5 (95% CI 33.5–59.6) • staged approach (n=7): 49.4 (95% CI 29.2–69.7) p=0.81 *Females*	Within the CPRE group bladder stability was universal, and sphincter electromyography was normal suggesting no neuromuscular compromise of the pelvic floor. At early follow-up, our results suggest that percent predicted bladder capacity is	historical control group (1979-1996 vs. 1996-2004), comparability of cases and controls, no information to length and loss to follow-up No information about funding and conflict of Interest.	4 RoB: 4/9

						• CPRE (n=7): 51.4 (95% CI 31.8–71.0) • staged approach (n=6): 48.1 (95% CI 26.5–69.7) p=0.82 **Bladder capacity** *(initially)* • CPRE: 46.5 29.0 ml (95% CI 21.3–39.5) (increased by 28.9% per year thereafter (95% CI 17.4–41.5, p<0.001) • staged approach: 69.8 ml (95% CI 46.7–104.4) (increased by 15.0% per year thereafter (95% CI 6.2–24.5, p=0.002) **Compliance** was 124.4% (95% CI 22.6–310.7, p=0.01) greater in the CPRE group at all times following repair **Detrusor overactivity** CPRE: 0/19 staged approach: 6/13 (46%) p=0.002	equivalent irrespective of gender or management.		
Sujijantararat, 2002	Retrospective cohort study	The aim of the present study was to analyse	n=13 patients	Single stage combined	Staged functional	**Single staged approach** Bladder exstrophy	The results of the present series show that	historical control	4

[103]	1986-2000 Thailand Mean follow-up: 47 mo (1-168 mo)	the results of surgical repairs of this complex by one surgeon during the last 14 years.	• classical bladder exstrophy (n=8) • isolated epispadias (n=4) • superior vesical fissure (n=1) Male: 8/13 <u>Mean age</u> Classical bladder exstrophy: 4.4 y (1 day-14 y)	functional bladder closure and epispadias repair n=5 • classical bladder exstrophy (n=2) • isolated epispadias (n=3)	bladder closure n=4 patients with classical bladder exstrophy	<u>Continence</u> 2/2 continent <u>Complications</u> • no fistula and wound dehiscence • bilateral VUR (n=2) Epispadias <u>Continence</u> 2/3 complete continent 1/3 partial continent <u>Complications</u> • no fistula was found • VUR grade II (n=1) **Staged approach** <u>Complications</u> • urethrocutaneous • fistula (n=1) • urethral obstruction (n=2) • Partial bladder and • abdominal wall dehiscence (n=1) • Bilateral VUR (n=2)	anatomical correction can be achieved with a low acceptable complication rate. Optimum results should be obtained if the surgery is carried out early in life, particularly within 72 h following birth.	group (single staged approach since 1999), recruitment of the study group not clearly described, Comparability of cohorts unclear (e.g. patient characteristic and follow-up time), unclear how continence was defined and measured No information about funding and conflict of Interest.	RoB: 3/9
Blasenhalsrekonstruktionstechniken									
Gupta, 2013 [104]	RCT 2004-2010 India	To evaluate the outcome IPS-ABNR compared to classic YDL-BNR in exstrophy with insufficient bladder capacity	n=16 male patients of exstrophy bladder <u>Mean age at repair</u>	IPS-ABNR n=9	YDL-BNR n=7	**Continence** <u>IPS-ABNR</u> • 0/9 persistent leakage or continuous dribbling	Innervation sparing reconstruction of sphincter with anatomical restoration of bladder neck in exstrophy patients	no information on random sequence generation, allocation concealment and blinding	2 RoB: high

		requiring detubularized-ileocystoplasty.	9.6 y (3-17 y)			• 7/9 dry interval for more than 3 h • 5/9 ability to initiate micturition and stop in midstream • 1/9 stricture urethra with absolute dependence on Mitrofanoff stoma YDL-BNR: • 2/7 incompetent bladder neck with gross incontinence • 4/7 dry interval of more than 3 h without the ability of voiding per urethra • 1/7 stricture urethra with absolute dependence on Mitrofanoff stoma **Urodynamic study** Mean bladder capacity • IPS-ABNR: 252 cc • YDL-BNR: 246 cc **Intraoperative complications** IPS-ABNR • 1/9 excessive bleeding from the detrusor bed after excision of triangular mucosal patch	requiring augmentation cystoplasty can achieve dynamic bladder outlet resistance with adequate leak point pressure resulting in decreased chances of urinary leak. Voluntary voiding with midstream holding capacity is also achieved. Operative accidents are less likely in these patients because of better visualization of entire anatomy during dissection.	Funding: This study had no funding source. Conflicts of interest: The authors declare no conflicts of interest.	

						YDL-BNR • 1/7 injury to urethral strip at verumontanum **Post-operative complications** IPS-ABNR • 2/9 subcutaneous wound dehiscence occurred • 3/9 subcutaneous wound infection YDL-BNR • 2/7 subcutaneous wound dehiscence occurred • 4/7 subcutaneous wound infection • No overall ○ complete dehiscence **Late complications** IPS-ABNR • 2/9 Stone formation • 1/9 stricture formation YDL-BNR • 2/7 Stone formation • 1/7 stricture formation			
Arap, 1988 [105]	Retrospective cohort study 1967-1984 Brazil	We present our personal experience with 38 cases of incontinent epispadias in	n=38 children with incontinent epispadias • penopubic or	BNR techniques used • Tanagho (n=8)		**Continence after BNR** Overall Yes: 22/30 (73.3%)	The results were similar with the 3 techniques.	recruitment of the study group not clearly described, comparability of cohorts unclear	3 RoB: 3/9

	Mean follow up 62 mo (5 mo-18 y)	which we used 3 basic techniques of bladder neck reconstruction with the anterior bladder wall or trigonal flap tubularization.	complete epispadias (n=35) • transitional forms between bladder exstrophy and epispadias (n=3) Male: 28/38	• Leadbetter (n=20) • Young-Dees (n=8)		No: 8/30 (26.7%) <u>Tanagho</u> Yes: 5/8 (73%) No: 3/8 (27%) <u>Leadbetter</u> Yes: 12/16 (75%) No: 4/16 (25%) <u>Young-Dees</u> Yes: 5/6 (83%) No: 1/6 (17%) **Complications** <u>Tanagho</u> • Bladder stones: 3 • Transient reflux: 3 • Persistent reflux: 3 <u>Leadbetter</u> • Ureterovesical obstruction: 4 • Reflux: 5 <u>Young-Dees</u> • Reflux: 4		(patient characteristics and length of follow-up), measurement of continence not described No information given about funding and conflict of interests.	
Vergleich von Prozeduren zur Kontinenzerreichung									
Maruf, 2020 [106]	Retrospective cohort study 1975-2017 USA Median follow-up from the first continence	We investigated surgical approaches to urinary incontinence and long-term continence outcomes after successful bladder reconstruction in a heterogeneous	n=432 patients with CBE Male: 306/432 (70.8%) <u>Median age (range)</u>	Final continence procedures: • BNR alone: 162/432 (37.5%) • BNR with AC and/or continent catheterizable		**Continence Outcomes** (at last follow-up) • Overall continence rate: 266/350 (76%, 95% CI: 71.1-80.3) • BNR: 91/142 (64.1%, 95% CI: 55.6-71.8)	Most patients with CBE who undergo a continence procedure will be dry for more than 3 h without leakage at nighttime, but voiding volitionally per urethra may only be achieved by a quarter of	comparability of cohorts unclear, continence was patient or family reported, length of follow-up after the last continence procedure unclear (at least: 3 mo)	3 RoB: 5/9

	procedure: 7.2 y (IQR 2.3-13.7 y)	patient population with classic bladder exstrophy.	• primary closure: 2 days (0-2.893 days) • first continence procedure: 5.9 y (range 0.2-33.8 y).	stoma: 76/432 (17.6%) • BNC with continent catheterizable stoma: 173/432 (40.0%) • 11/432 neobladder • 7/432 other continent diversions		• BNR with AC or stoma: 38/62 (61.3%, 95% CI: 48.0-73.1) • BNC with continent urinary diversion: 124/133 (93.2%, 95% CI: 87.2-96.7) • Neobladder: 10/10 (100%, 95% CI: 65.5-100) • Other continent urinary diversion/diversion without bladder neck procedure: 3/3 (100%, 95% CI: 31.0-100)	patients seeking urinary continence. Urinary continence after BNR is associated with older age at evaluation. Nevertheless, a large proportion of patients undergoing BNR will end up needing BNC with continent diversion, which provides excellent results. Still, proper patient selection is integral for success of the continence procedure.	No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.	
Kajbafzadeh, 2017 [107]	Retrospective cohort study 2009-2012 Iran Mean follow-up: 72 mo (SD=±6 mo)	The objective of this study is to describe a new surgical technique for obtaining eventual urinary continence at a urology center of excellence with over 20 years of experience in the reconstruction of BEEC.	n=16 female patients with BEEC Mean age: 3.48 y (SD=±1.75 y)	Single-stage bladder closure without osteotomy (group 1) n=9	UUE without osteotomy (group 2) n=7	**Bladder capacity** • Group 1: 123.8 mL (SD=±19.1 mL) • Group 2: 185.5 mL (SD=±22.1 mL) p=0.04 **Continence** <u>Complete continence</u> • Group 1: 5/9 (55.5%) • Group 2: 5/7 (71.42%) p=0.03 <u>Partial continence</u> • Group 1: 3/9 (33.3%) • Group 2: 2/7 (28.57%) p=0.04	The eventual clinical outcomes of BEEC children undergoing the UUE technique were promising. This practicable, safe, and reproducible option will add one complementary stage to the previously used reconstruction techniques.	unclear who measures the continence The authors declare no conflicts of interest and funding.	3 RoB: 8/9

						<u>Partial continence with episodes of nocturnal enuresis</u> • Group 1: 4/9 (44.44%) • Group 2: 2/7 (28.57%) <u>Frequently wet</u> • Group 1: 1/9 (11.1%) • Group 2: 0/7 (0%) **VUR** • Group 1: 0/9 (0%) • Group 2: 3/7 (42.85%) VUR was successfully managed by Deflux injection. All patients in both groups experienced an uneventful postoperative period**.**			
Eftekharzadeh, 2017 [108]	Retrospective cohort study 2009-2014 <u>Mean follow-up:</u> calcium: 38 mo (±5.2 mo) deflux: 33 mo (±4.1 mo)	The aim of this study was to evaluate the efficacy of the endoscopic injection of calcium hydroxyapatite into the bladder neck region of patients with urinary incontinence and BEEC.	n=37 with BEEC Male: 27/37 <u>Mean age</u> calcium: 8.09 y (± 3.5 y) deflux: 7.51 y (± 2.8 y)	endoscopic injection of calcium hydroxyapatite (5.4 ml) n=16	Deflux injection (5.1 ml) n=21	**Continent** calcium: 11/16 (68.75%) deflux: 14/21 (66.66%) **Degree of incontinence was improved** calcium: 4/16 (25%) deflux: 5/21 (23.81%) **No change**	The preliminary results of this study revealed that calcium hydroxyapatite may be applied as an affordable bulking agent in treatment of urinary incontinence in BEEC.	patient recruitment was not clearly described, self-reported continence status None of the authors has direct or indirect commercial financial incentive associating with	3 RoB: 7/9

						calcium: 1/16 (6.25%) deflux: 2/21 (9.52%) no significant difference in continence achievement between the groups (p=0.9)		publishing the article and does not have any conflict of interest. No information about funding.	
Hanna, 2017 [109]	Retrospective cohort study 1981-2014 USA	We review our experience with various strategies for management of urinary incontinence and their outcome in 61 patients born with bladder exstrophy who failed their initial repairs.	n=61 incontinent bladder exstrophy patients Age: 3-18 y	• Reclosure and iliac osteotomy (n=5) • Mainz II pouch (n=16) • Bladder augmentation (n=31) • Bladder substitution (n=10)		**Reclosure and iliac osteotomy** • Voiding and dry: 3/5 • CIC every 4-5 h and dry: 1/5 • Damp/wet: 1/5 **Mainz pouch II** • Voiding and dry: 16/16 **Bladder augmentation** • Voiding and dry: 2/34 • CIC every 4-5 h and dry: 25/34 • Voiding and CIC: 4/35 • Damp/wet: 3/35 <u>Morbidity</u> • Stomal stenosis: 6 • Stomal prolapse: 1 • Bladder stones: 8 • Kidney stones: 4 • Hematuria/dysuria: 1 **Bladder substitutions**	Following failed surgeries the majority of incontinent patients can be salvaged to become continent/dry. It would appear that the Mainz II internal diversion offers a reasonable surgical option for selected patients, especially for females and those who have endured multiple surgical failures.	patient recruitment not clearly described, comparability of cohorts unclear (patient characteristics and length of follow-up), measurement of continence not described The authors declare no conflicts of interest and funding.	3 RoB: 4/9

						• Voiding and dry: 2/34 • CIC every 4-5 h and dry: 25/34 • Voiding and CIC: 4/35 • Damp/wet: 3/35 <u>Morbidity</u> • Stomal stenosis: 1 • Bladder stones: 3 • Kidney stones: 1 • Perforation: 1			
Capoliccho, 2001 [110]	Retrospective cohort study 1988-1998 Canada <u>Mean follow-up</u> Group 1: 6.1 y Group 2: 2 y Group 3: 3.3 y	We report on a comprehensive exstrophy population, focusing on the various procedures required for urinary continence.	n=43 patients • cloacal exstrophy (n=4) • classic bladder exstrophy (n=36) • complex variants (n=3) Male: 26/43	• Group 1 (n=9): Bladder neck reconstruction • Group 2 (n=15) bladder neck reconstruction and augmentation and/or appendicovesicostomy • Group 3 (n=19) bladder neck closure with appendicovesicostomy		**Small bladder plate** Group 1: 1/9 (11%) Group 2: 1/15 (7%) Group 3: 4/19 (21%) **Dehiscence** Group 1: 1/9 (11%) Group 2: 5/15 (33%) Group 3: 6/19 (32%) **Bladder neck stenosis** Group 1: 3/9 (33%) Group 2: 3/15 (20%) Group 3: 2/19 (11%) **Initial osteotomy** Group 1: 1/9 (11%)	All patients with exstrophy can be rendered continent but many may require other procedures following initial bladder neck reconstruction. The adjunctive procedures necessary to achieve continence must often address the issues of inadequate bladder capacity or impaired compliance. When managing a failed BNR the type of surgical repair chosen should be carefully balanced against the potential psychological impact of multiple surgical procedures	age not reported, follow-up times different No information about funding and conflict of Interest.	3 RoB: 7/9

						Group 2: 0 Group 3: 8/19 (42%) **Continence** Group 1: 5/9 (56%) Group 2: 10/15 (67%) Group 3: 19/19 (100%) **Age at continence** Group 1: 4.8 y Group 2: 8.2 y Group 3: 9.2 y Gender was the strongest predictor of continence (94% females vs 69% males p=0.055)	and delay in the age at which continence is achieved.		
Stein, 1995 [111]	Retrospective cohort study 1968-1994 Germany Mean follow-up 16.7 y (0.2-35 y)	To determine the optimal surgical approach in achieving complete urinary continence with preservation of the upper urinary tract in the exstrophy-epispadias complex we reviewed the records of patients treated at our institution.	n=115 patients • epispadias (n=20) • bladder extrophy (n=95)	• Ureterosigmoidostomy (n=32) • Sigma rectum pouch (Mainz pouch II) (n=16) • Other rectal reservoirs (n=3) • Mainz pouch I (n=30) • Modified Young-Dees augmentation (Mainz pouch) (n=3) • Sling plasty (n=2)		**Continence at follow-up** • Ureterosigmoidostomy: 31/32 (97%) • Sigma rectum pouch (Mainz pouch II): 15/16 (94%) • Other rectal reservoirs: 2/3 (67%) • Mainz pouch I: 29/30 (97%) • Modified Young-Dees augmentation (Mainz pouch): 2/3 (67%) • Sling plasty: 1/2 (50%)	Our data on patients with bladder exstrophy and incontinent epispadias indicate that primary urinary diversion results in a continence rate of more than 90% with preservation of the upper urinary tract. After failure of urinary tract reconstruction individualized treatment is necessary.	Comparability of cohorts unclear (patient characteristics and length of follow-up) number of patients which were treated with sling plasty unclear (n=2 in Table 2, n=3 in the text) No information about funding and conflict of Interest.	3 RoB: 6/9

						Complications <u>Ureterosigmoidostomy</u> • 10/35 stenosis of the ureter • 6/35 ureteral reimplantation • 6/35 conversion to a colon conduit to preserve renal function • 2/35 acute abdominal wall dehiscence • 2/35 conversion to an ileocecal pouch due to incontinence • 2/35 nephrectomy • 1/35 ileus <u>Sigma rectum pouch</u> • 3/16 Ureteral stenosis • 1/16 upper tract dilatation of the right kidney • 1/16 stress incontinence <u>Modified Young-Dees procedure with Mainz pouch augmentation</u> • 1/9 reimplantation of both ureters was necessary • 4/9 obstruction of the neourethra <u>Sling plasty</u>			

						• 1/3 complete incontinent • 2/3 stress incontinence • In all 3 patients the upper urinary tract is normal. <u>Colon conduit</u> primary colon conduit: • without ensuing complications and normal upper urinary tract (n=5) secondary colon conduit: • 1/12 stomal stenosis • 2/12 ureteral stenoses • 1/12 slight dilatation of the right upper tract. <u>Mainz pouch I</u> • 1/30 necrosis of the ileum nipple • 2/30 ureteral stenoses • 2/30 stomal stenosis • serum creatinine levels of all patients were within the normal range and none had deterioration of the upper urinary tract			
Hollowell, 1991 [112]	Retrospective cohort study 1978-1990	Surgical management of incontinence bladder exstrophy	n=86 patients with previously closed	BNR without augmentation n=32	BNR with augmentation n=47	**BNR without augmentation** • 20/32 failed	It is realized that there is a need for better methods of assessing the	patient recruitment not clearly described,	3 RoB: 4/9

			classic bladder exstrophy			• 6/32 potentially successful • 5/32 statisfactory continence • 1/32 Mitronoff procedure performed **BNR with augmentation** *(n=71; 47 initial group, 20 failed without bladder augmentation, 4 who underwent primary augmentation)* 3/71 waiting list • 55/68 dry • 13/68 good capacity was achieved, but additional surgery was needed <u>Statisfactory</u> (n=58) • 43/55 CIC/void • 5/55 Mitrofanoff • 3/55 artificial urinary sphincter • 7/55 awaiting CIC <u>Unstatisfactory</u> (n=10) • 2/10 awaiting artificial urinary sphincter • 1/10 awaiting Mitrofanoff • 7/10 wet/unknown	potential of the closed exstrophy bladder and more objective criteria for selevtion for augmentation.	comparability of cohorts unclear (patient characteristics, group changes and length of follow-up), continence status measurement via personal interviews No information about funding and conflict of Interest. Complications	
Operationen bei Epispadias									

Leclair, 2018 [113]	Prospective cohort study 2006-2017 France Median follow-up: 57 mo (15-132 mo)	Our aim was to assess the results of a surgical management using perineal approach in girls with normal bladder capacity, and Kelly radical soft-tissue mobilization in patients with inadequate bladder, based on the assumption that bladder capacity is a reliable marker of epispadias severity.	n=16 girls with primary female epispadias <u>Median age at surgery</u> • Perineal reconstruction: 32 mo (14-102 mo) • Kelly repair: 42 mo (8-93 mo)	Perineal reconstruction (girls with normal bladder) • n=7	Kelly repair (girls with inadequate bladder) n=11	**Continence status** *[Assessed at 5 years or later, after follow-up > 12 months]* <u>Perineal reconstruction</u> • 4/7 (57%): dry day/night • 5/7 (71%): dry by day • 2/7 (29%): still wearing protections <u>Kelly repair</u> • 3/8 (38%): dry day/night • 8/8 (100%): dry by day **Bladder capacity at diagnosis** *[Percentage of expected Bladder capacity for age]* • Perineal reconstruction: 116% (92-143%) • Kelly repair: 56% (10-94%) **Bladder capacity at final evaluation** • Perineal reconstruction: 82% (56-102%) • Kelly repair: 87% (25-103%) **Additional procedure**	A tailored approach to female epispadias, based on perineal reconstruction in favorable cases, and radical soft-tissue mobilization in severe cases, seems to yield good continence outcomes in the long term.	Funding: This study had no funding source. Conflicts of interest: The authors declare no conflicts of interest.	3 RoB: 9/9

						Bladder neck injection • Perineal reconstruction: 3/7 • Kelly repair: 0/8 Bladder augmentation • Perineal reconstruction: 0/7 • Kelly repair: 0/8			
Alyami, 2017 [114]	Retrospective cohort study 2000-2013 Canada Mean follow-up Young-Dees-Leadbetter cervicoplasty bladder neck approach: 12.3 y (8-13 y) Single-stage perineal approach: 6 y (1-10 y)	The aim of the present study was to describe long-term follow-up of patients who underwent the traditional vs alternative approach.	n=12 female patients with epispadias Mean age at first surgery • Young-Dees-Leadbetter cervicoplasty bladder neck approach: 2.9 y (0.5-4 y) • Single-stage perineal approach: 4.3 y (1-17 y)	Young-Dees-Leadbetter cervicoplasty bladder neck approach n=3	Single-stage perineal approach n=9	**Young-Dees-Leadbetter cervicoplasty bladder neck approach** Dry: 0/3 Redo-surgery: 3/3 Need for bladder augmentation: 2/3 Continence post redo-surgery: 3/3 (CIC) **Single-stage perineal approach** Dry: 4/9 Not toilet trained: 2/9 Incontinence: 3/9 Redo-surgery: 3/9 Need for bladder augmentation: 0/9 Continence post redo-surgery: 2/3 **Complication:** No major complications	Female epispadias could be successfully repaired using a single-stage modified perineal approach that achieved good continence with volitional voiding, good cosmetic results and compared favorably with the ones repaired with the Young-Dees-Leadbetter technique. The additional step of performing bladder neck tailoring to achieve a funneling configuration seemed to be useful in improving continence.	Groups are not comparable (age range, other factors unclear) No conflict of interest/ funding declared.	3 RoB: 6/9
Braga, 2008 [115]	Retrospective cohort study 1994-2005	We review our results with isolated male epispadias repair,	n=33 male patients with isolated epispadias	Mitchell-Bagli operation n=12	Cantwell-Ransley operation n=21	**Continence after epispadias repair** Penopubic epispadias	Similar urinary continence rates can be achieved for male penopubic	less information to patient characteristics, it remains	3 RoB: 5/9

	Canada <u>Mean follow-up</u> Mitchell-Bagli: 70 mo (10-120 mo) Cantwell-Ransley: 80 mo (21-144 mo)	comparing the Cantwell-Ransley and Mitchell-Bagli procedures in regard to continence status and postoperative complications.	• glanular (n=3) • penile (n=9) • phenopubic (n=21)	• penopubic (n=7) • glanular and penile (n=5)	• penopubic (n=14) • glanular and penile (n=7)	• Mitchell-Bagli: 4/6 (67%) • Cantwell-Ransley: 0/13 (0%) (p<0.01) **Final continence status** Phenopubic Epispadias: <u>Completely Dry/Dry More Than 4 Hours</u> • Mitchell-Bagli: 5/6 (83%) • Cantwell-Ransley: 8/11 (73%) <u>Dry 2–4 hours/Stress Incontinence</u> • Mitchell-Bagli: 1/6 (17%) • Cantwell-Ransley: 3/11 (27%) p=0.91 7 patients also had nighttime continence, and no patient was dry for less than 2 hours or consistently wet. **Complications** Penile or glanular epispadias: • Mitchell-Bagli: 1/5 Meatal stenosis • Cantwell-Ransley: 0/7 complications	epispadias with both surgical techniques, at the expense of more bladder neck repairs following the Cantwell-Ransley procedure.	unclear if the two cohorts are comparable, continence status was ascertained by patient or family report, unclear why some data were not included in the analysis No information about conflict of interest and funding. *no information about age of glanular and penile epispadias repair*	

						Phenopubic Epispadias: <u>Overall complications</u> • Mitchell-Bagli: 2 (29%) • Cantwell-Ransley: 8 (57%) p=0.44 <u>Residual dorsal curvature</u> • Mitchell-Bagli: 1 (14%) • Cantwell-Ransley: 3 (21%) <u>Urethrocutaneous fistula</u> • Mitchell-Bagli: 1 (14%) • Cantwell-Ransley: 4 (29%) <u>Cosmetic revision</u> • Mitchell-Bagli: 0 (0%) • Cantwell-Ransley: 1 (7%)			
Verfahren nach fehlgeschlagener Reparatur									
Gearhart, 1998 [116]	Retrospective cohort study <u>Mean follow up</u> 87 mo (6-168 mo)	We compared results in boys who underwent combined bladder closure and epispadias repair or staged reconstruction.	n=37 boys with BEEC Mean age: • Study group: 22 mo (6-68 mo)	study group n=16 boys with (combined bladder closure and epispadias repair after previous	matched control-group n=21 patients (had failed, and who underwent standard staged	**Continence** <u>Dry before BNR</u> • Study group: 2/16 • Control group: 0/21 <u>After BNR</u> Study group:	We recommend epispadias repair combined with bladder exstrophy closure for treating failed exstrophy closure or late initial closure. Operative	recruitment of the study and control group not clearly described No information about funding	3 RoB: 7/9

			• Control group: 22 mo (6-62 mo)	closure had failed)	reconstruc-tion)	• Dry day & night: 5/10 • Dry day/occasional wet nights (1-2 per mo): 3/10 • Later augmentation for incontinence 2/10-> dry on CIC Control group: • Dry day & night: 6/13 • Collagen for stress incontinence: 2/13 – dry • Later augmentation 5/13-> dry on CIC <u>After BNR +Augment</u> • Study group: 1/16-> dry on CIC • Control group: 0/21 <u>Awaiting BNR</u> • Study group: 2/16 • Control group: 0/21 <u>Augmentation</u> • Study group: 1/16 awaiting Augmentation • Control group: 2/21-> dry on CIC	complications and results are comparable to those in patients in whom previous exstrophy closure failed and who undergo standard staged repair.	and conflict of interest. No information on timeframe of the gathered data.	

						Complications <u>Study group</u> • fistulas (n=6) • stricture (n=1) • bladder septum was • resected endoscopically (n=1) <u>Control group</u> urethrocutaneous fistula developed at the site of epispadias closure (n=8)			

Schlüsselfrage Ist ein Beckenverschluss obligat?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Abou Ela, 2020 [117]	Randomized controlled trial (with case-control study) 2016-2018 Egypt	Our aim was to evaluate the effectiveness of anterior osteotomy in the restoration of normal pelvic floor anatomy in classic bladder exstrophy repair using pelvic floor MRI as an imaging tool for evaluation.	n=20 infants with classic bladder exstrophy with no history of previous surgical operations <u>Mean age</u> • osteotomy : 5.33 mo±2.06 mo • no osteotomy : 11.12 mo ±9.98 mo <u>Male</u> • osteotomy : 8/12 • no osteotomy : 4/8	complete primary repair + anterior osteotomy n=12	complete primary repair without osteotomy n=8 <u>Case-control study</u>: age & gender-matched control group, with normal pelvic anatomy n=6	***RCT*** **Mean operative time** osteotomy: 4.12±0.38 h no osteotomy: 2.69±0.70 h p=0.001 **Postoperative hemoglobin** osteotomy: 10.54±0.78 mg/dl no osteotomy: 10.24±0.94 mg/dl p=0.259 **Mean hospital stay** osteotomy: 5.67±2.39 days no osteotomy: 5.62±3.46 days p=0.688 **Osteotomy vs. no osteotomy** no statistically significant difference in postoperative symphyseal diastases, puborectalis angle, ischial angle, obturator to levator angle and posterior bladder	Anterior osteotomy did not have a significant difference in the restoration of the normal pelvic floor anatomy when combined with complete primary repair of classic bladder exstrophy in newly diagnosed neonates older than three months, except for a single measurement, posterior bladder neck distance. Future studies needed to determine the effect of osteotomy on continence.	Insufficient information about the randomisation and allocation process, blinding unclear, control group with normal pelvic anatomy was recruited via hospital, different loss to follow-up rates between BEEC patients and normal pelvic patients: 20% of the BEEC group were excluded as they experienced dehiscence No conflict of interest. This research did not receive any specific grant from funding agencies in the public,	RCT: 2 RoB: high Case-con-trol study: 4 NOS: 7/9

						neck distance, posterior anal distance, iliococcygeus angle difference, iliac wing angle, total levator ani muscle length, anterior compartment length, posterior compartment length, muscle in anterior compartment and muscle in posterior compartment **Complications** No statistically significant difference between both groups regarding all complications. <u>Wound infection and partial dehiscence</u> osteotomy: 5/12 no osteotomy: 1/8 <u>Postoperative fever</u> osteotomy: 2/12 no osteotomy: 3/8 <u>Mild lower limb edema</u> osteotomy: 2/12 no osteotomy: 0/8 <u>Suprapubic fistula (1 mo postoperative)</u> osteotomy: 4/12 no osteotomy: 2/8 <u>Wound dehiscence (1 mo postoperative)</u> osteotomy: 4/12		commercial, or not-for-profit sectors.	

						no osteotomy: 0/8 ***Case-Control Study*** **Bladder exstrophy patients** (n=16) **vs. patients with normal pelvic anatomy** (n=6) no statistically significant difference in postoperative puborectalis angle, ischial angle, posterior anal distance, total levator ani muscle length, muscle in anterior compartment and muscle in posterior compartment <u>Symphyseal diastases</u> BEEK: 2.96±1.07 normal: 0.52±0.13 p=0.001 <u>Obturator to levator angle</u> BEEK: 38.11±6.99 normal: 46.48±2.66 p=0.004 <u>Posterior bladder neck distance</u> BEEK: 3.78±0.54 normal: 3.18±0.43 p=0.02 <u>Iliococcygeus angle difference</u> BEEK: 3.35±0.39 normal: 2.62±0.10			

						p=0.002 Iliac wing angle BEEK: 1.35±0.18 normal: 0.72±0.13 p=0.001 Anterior compartment length BEEK: 40.5±3.96 normal: 27.67±5.56 p=0.001 Posterior compartment length BEEK: 59.5±3.96 normal: 72.33±5.56 p=0.001			
Inouye, 2018 [77]	Cohort study since 1975 USA	Even with contemporary management, patients still have failed primary closures. We sought to understand the role of training, surgical technique, and their impacts on outcomes of CBE closure.	n=722 patients with classic bladder exstrophy Male: 506/722 (70.2%)	Concomitant osteotomy n=279	• no osteotomy n=371 • Unknown n=71	**Successful closure** *(bivariate analysis)* • Osteotomy: 205/279 • No osteotomy: 227/371 • Unknown: 44/71 p=0.0035 **Multivariable logistic regression analysis** *(adjusted)* • Osteotomy: Reference • No osteotomy: 1.35, 95% CI: 0.89-2.06, p=0.16 • Unknown: 0.82, 95% CI: 0.43-1.57, p=0.55	We found that early time of closure, closure by an adult urologist or pediatric surgeon, closure by CPRE method, not having a concomitant osteotomy, and immobilization with spica cast or mummy wrap were associated with increased odds of failed primary closure.	Comparability of cohorts unclear (patient characteristics and length of follow-up) Funding: This study had no external funding source. Conflicts of interest: The authors declare no conflicts of interest.	3 RoB: 6/9
Inouye, 2016 [118]	Cohort study 1975-2016	To understand the indications and outcomes of bladder closure with	n=100 with classic bladder exstrophy	Closed with osteotomy n=38	Closed without osteotomy n=62	**Failed primary closure** osteotomy: 4/38 (11%)	Regardless of the type of closure undertaken,	inclusion criteria not described, significant differences	3 RoB: 6/9

	USA <u>Follow-up</u> osteotomy: 13.4 y ± 7.31 y without osteotomy: 8.9 y ± 6.65 y	and without pelvic osteotomy in patients younger than 1 mo of age.	Male: 68/100 <u>Age</u> osteotomy: 8.7 days ± 8.3 days without osteotomy: 2.9 days ± 3.1 days			without osteotomy: 5/62 (7%) p=0.466 **Bladder capacity for bladder neck reconstruction** osteotomy: 31/38 (82%) without osteotomy: 44/62 (71%) p=0.234	there clearly is a role for newborn classic bladder exstrophy closure without pelvic osteotomy in patients considered suitable for closure by both the pediatric urologist and orthopedic consultant.	between the groups (age, pre-closure pubic diastasis), patients receiving osteotomy had a significantly longer follow-up than non-osteotomy patients No funding received. The authors declare no conflict of interest.	
Kenawey, 2014 [119]	Case-control study 1982-2011 Canada Mean follow-up: 10 y ± 4.9 y	Can Neonatal Pelvic Osteotomies Permanently Change Pelvic Shape in Patients with Exstrophy?	n=73 children with classic bladder exstrophy n=164 normal children Male: 45/73 Mean age: 10.5 y ± 5.1 y	classic bladder exstrophy patients with pelvic osteotomy (n=52)	children without osteotomy: • Normal pelvic radiographs (n=164) • pelvic CT (n=21) classic bladder exstrophy patients without pelvic osteotomy (n=9)	**Exstrophy patients** • IP/IS distances did not differ significantly between patients with and without pelvic osteotomies (p = 0.567 and p = 0.892) • IS/IP ratio was significantly higher in the osteotomy group (p = 0.021) • IS/IP ratio increased with age in patients with pelvic osteotomies, whereas it decreased in those without osteotomies **Normal controls** • The IS/IP ratio was significantly smaller	The IS/IP ratio is a useful measure of ischiopubic rotation and can be used to characterize pelvic growth, including the phenomenon of rediastasis in patients with exstrophy. Pelvic rediastasis is a progressive increase in interpubic distance resulting from growth without loss of rotational correction, as shown by the	recruitment of controls was not clearly described, discrepancies of evaluated patients are not sufficiently described, comparability of the exstrophy groups with and without osteotomy unclear The complete Disclosures of Potential Conflicts of Interest submitted by authors.	4 RoB: 6/9

						in patients with exstrophy (2.1 ± 0.7) compared with controls (13.5 ± 6.3, p < 0.0001) • Normal children: the interpubic distance and the ischiopubic divergence angle had a narrow range and were constant with age, whereas the interischial distance and the IS/IP ratio increased progressively and were strongly correlated with age. • Exstrophy patients: the interpubic distance was positively correlated with the interischial distance, whereas the IS/IP ratio was lower than that in normal controls and was not correlated with age.	constancy of the IS/IP ratio with age in these patients. A better rotational position at the time of osteotomy may lead to a better pelvic shape at maturity.	There was no external financial support for this study.	
Petrarca, 2014 [120]	Case-control study 1990-2005 Italy	A direct kinetic gait evaluation has never been performed, nor has the effect of pelvis dimorphism on the upper body been studied.	n=19 bladder exstrophy patients Male: 11/19 n=25 healthy controls	bladder exstrophy patients n=19 • with pelvic osteotomy (n=6) • no osteotomy (n=13)	healthy controls n=25	• Bladder exstrophy significantly affects kinematics and kinetics of trunk, spine, pelvis, knee and foot • Osteotomy: trunk retroversion, pelvic retroversion and rotation, hip adduction angle	Walking in patients with bladder exstrophy is accomplished by retroversion of the pelvis and deviations mainly in the spine angle in no osteotomy	recruitment of the control group unclear, controls only aged-matched The authors declared no conflict of interest.	4 RoB: 7/9

			Age bladder exstrophy: 14 y±8 y controls: 15 y±8 y			and moment, knee flexion and its maximum power during loading response increased • No osteotomy: spine angle, pelvic posterior tilt, hip extension, and the external rotation of the foot progression angle increased • All the kinetics parameters analyzed in the study showed lower values in the patient group than in controls	and in knee flexion in osteotomy.	Financial support: Scientific Direction of Bambino Gesu Childrens Hospital, IRCCS, Rome, Italy	
Baka-Ostrowska, 2013 [121]	Retrospective cohort study 1982-2006 Poland	To analyze complications after primary bladder exstrophy closure with a special consideration of the role of pelvic osteotomy.	n=100 patients with bladder exstrophy Male: 65/100	contemporary iliac osteotomy n=36	bladder was closed without osteotomy n=64	**Patients operated up to 72 h of life** Wound dehiscence without osteotomy: 13/47 with osteotomy: 1/4 p=0.7 **Patients operated above 72 h of life** Wound dehiscence without osteotomy: 11/17 with osteotomy: 6/32 p<0.002	Osteotomy performed at primary bladder exstrophy closure diminishes the risk of wound dehiscence independently of patient's age. Posterior iliac osteotomy is sufficient and safe and could be repeated if necessary.	Comparability of cohorts and length of follow-up unclear No information about funding and conflict of interest.	3 RoB: 6/9
Lavien, 2014 [122]	Retrospective cohort study 1974-2012 USA	The authors' aim is to determine whether pelvic osteotomy reduces the incidence of primary and recurrent inguinal	n=136 patients with classic bladder exstrophy	Primary closure with osteotomy n=73	Primary closure without osteotomy n=63	Incidence of inguinal hernias identified during primary closure • With osteotomy: 24/73 (33%)	Patients undergoing pelvic osteotomy at the time of bladder closure have a lower	number of patients with immediate and delayed primary closure not reported,	3 RoB: 8/9

	Mean follow-up: 8 y (1 mo–35 y)	hernias in patients with classic bladder exstrophy.	Male: 98/136 (72%)			• Without osteotomy: 20/63 (32%) <u>Incidence of hernia recurrence</u> • With osteotomy: 4/24 (17%) • Without osteotomy: 11/20 (55%) p=0.027 <u>Incidence of inguinal hernia following primary closure</u> • With osteotomy: 25% • Without osteotomy: 46% p=0.017 <u>Risk of hernia formation after primary repair</u> (Multivariate regression analysis: OR) • Male sex: 21.649, (95 % CI: 0.006-0.375), p=0.004 • Delayed primary closure: 0.487, (95 % CI: 0.130-1.826), p=0.286 Osteotomy during closure: 0.046, (95 % CI: 0.086-1.001)	incidence of de novo and recurrent inguinal hernia development compared to patients in whom pelvic osteotomy was omitted. Pelvic osteotomy may better correct and stabilize the obliquity of the inguinal canal. A pre-peritoneal approach to the repair of inguinal hernias in this population takes advantage of the surgical exposure afforded during bladder closure but has a higher rate of recurrence compared to a standard inguinal approach.	No information given about funding and conflict of interests.	
Kajbafzadeh, 2010 [123]	Retrospective cohort study 1995-2007	To compare intrapelvic osseous dimensions in classic bladder exstrophy patients who underwent pelvic osteotomy	n=33 classic bladder exstrophy patients Male: 18/33	osteotomy n=14	pubic approximation using metal plates n=19	• Sacroiliac joint angle, pubococcygeal angle, ischiopubic angle, pubic diastasis, and inter-triradiate	Our study suggests that internal fixation of pubic arch using metal plates in bladder exstrophy	patient recruitment not clearly described, age at postoperative 3D-CT vary	3 RoB: 6/9

		and pubic symphysis internal fixation, using metal plates without osteotomy by defining intrapelvic angles and distances using three-dimensional computed tomography scan.	<u>Mean age</u> osteotomy: 70.4 mo (7-180 mo) metal plates: 63.2 mo (1-156 mo)		Control group without exstrophy n=14	distance were different from controls in both techniques • metal plates: Iliac wing angle near normal values • before-after comparison revealed significant changes in iliac wing angle, sacroiliac joint angle, and pubic diastasis in both groups	may be as effective as the currently accepted osteotomy-containing techniques from the standpoint of intrapelvic osseous dimensions and angles. Modification of our new pubic approximation technique is essential to better recapitulate the anatomy of the normal bony pelvis.	widely (1-180 mo) No information about conflict of interest. This study was supported by Deputy of Research, Tehran University of Medical Sciences.	
Castagnetti, 2008 [124]	Cohort study 2005-2006 Italy Median age at evaluation: 9.7 y (3.1-17.8 y)	This study aimed to evaluate the difference in the orthopaedic and urological functional outcomes, also using a standardized questionnaire, in a selected group of patients undergoing bladder exstrophy repair either with or without osteotomy.	n=14 consecutive bladder exstrophy patients	Osteotomy group n=8 • soon after birth (n=5) • 2 mo (n=1) • 1 y (n=2)	No osteotomy group n=6	**Pubic bones dissymmetry** <u>No</u> without osteotomy: 3/6 with osteotomy: 7/8 p=0.2 <u>1-1.5 cm</u> without osteotomy: 3/6 with osteotomy: 1/8 p=0.2 **Bending of the spine** <u>No</u> without osteotomy: 6/6 with osteotomy: 4/8 p=0.08 **Trendelenburg sign**	Although osteotomy is an essential step in the treatment of many bladder exstrophy patients in order to achieve a tension-free closure of the abdominal wall and bladder, our preliminary results suggest that it does not improve the eventual orthopaedic or urological outcomes of bladder exstrophy.	patients' data were partially collected retrospectively, comparability of cohorts unclear, osteotomy was performed in different centers No information about funding and conflict of interest.	3 RoB: 6/9

						Positive both: 0 **Thomas sign** without osteotomy: 1/6 with osteotomy: 0/8 p=0.4 **Out-toeing** without osteotomy: 4/6 with osteotomy: 5/8 p=1 **Bladder-neck reconstruction** without osteotomy: 4/6 with osteotomy: 7/8 p=0.5 **Bladder augmentation** without osteotomy: 2/6 with osteotomy: 4/8 p=0.5 **Creation of Mitrofanoff conduit** without osteotomy: 2/6 with osteotomy: 4/8 p=0.5 **On clean intermittent catheterization** without osteotomy: 3/6 with osteotomy: 4/8 p=0.7			

						Continent without osteotomy: 3/6 with osteotomy: 4/8 p=0.7 **Pediatric Orthopedic Society of North America questionnaire** No difference between group proved statistically significant			
Gugenheim, 1999 [125]	Cohort study 1974-1994 USA	This paper describes a modification of bilateral posterior iliac osteotomies in which a strip of ilium is resected subperiosteally lateral to the sacroiliac joints, allowing easier anterior closure.	n=31 BEEC patients • Classic bladder exstrophy (n=20) • Bladder and cloacal exstrophy (n=11) Age: 1 day – 32 mo	closed reduction and cast application in the newborn period n=4	• classic bilateral posterior iliac osteotomies n=12 • bilateral posterior resection osteotomies n=15	**Dehiscence** • closure without osteotomies: 1/4 • classic osteotomies: 5/12 • resection osteotomies; 1/15 **Continence** • closure without osteotomies: 4/4 • classic osteotomies: 9/12 • resection osteotomies; 9/15 No child had waddling gait.	*no conclusion*	patient recruitment not clearly described, comparability of cohorts unclear, no information about the length of follow-up No information about funding and conflict of interest.	3 RoB: 5/9
Husmann, 1989 [81]	Cohort study 1964-1989 Canada Minimum follow up: 5 y	To determine what factors could affect the success of initial bladder closure in classical bladder exstrophy.	n=80 patients with classical bladder exstrophy	Closed with iliac osteotomy n=51	Closed without iliac osteotomy • n=29	**Closed with iliac osteotomy** <u><72 h after birth (n=15)</u> • with dehiscence: 13% • requiring augmentation: 6% • continent: 73%	To improve the results in staged bladder reconstruction we recommend use of perioperative antibiotics, adequate	comparability of cohorts unclear No information about funding and conflict of interest.	3 RoB: 8/9

						3-30 days (n=12) • with dehiscence: 16% • requiring augmentation: 16% • continent: 66% 31 days to 1y (n=14) • with dehiscence: 14% • requiring augmentation: 14% • continent: 71% > 1y (n=10) • with dehiscence: 10% • requiring augmentation: 40% • continent: 60% **Closed without iliac osteotomy** <72 h after birth (n=19) • with dehiscence: 10% • requiring augmentation: 5% • continent: 84% 3-30 days (n=6) • with dehiscence: 16% • requiring augmentation: 16% • continent: 16% 31 days to 1y (n=4) • with dehiscence: 0%	postoperative nutritional support to aid in wound healing, closure when the neonate is less than 72 h old if no iliac osteotomy is to be performed, immediate treatment of gastric distension by nasogastric drainage, secure fixation of all urinary diversion catheters with tubes exiting through the suprapubic region and careful preoperative assessment in individuals with a history of delayed closure to confirm the presence of an adequate bladder capacity.		

						• requiring augmentation: 0% • continent: 0% **Bladder dehiscence** • No statistical correlation could be found among the development of bladder dehiscence, age of the child at bladder closure or the performance of iliac osteotomy (p >0.5) • Individuals undergoing delayed bladder closure without iliac osteotomy had no notable difference in the incidence of bladder dehiscence **Continence** • in neonates whose bladder was closed before 72 h after birth the continence is not affected by the performance of iliac osteotomy (p >0.5) • delayed bladder closure without iliac osteotomy had a statistically significant difference in the ability to gain urinary continence (p <0.01)			

						• patients excluded who underwent closure without iliac osteotomy after they were 72 h old no statistical difference in individuals undergoing early versus delayed closure (p >0.5)			

Schlüsselfrage Ist die anzuwendende Technik eines Beckenverschlusses vom Alter abhängig?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Khandge, 2021 [74]	Retrospective cohort study 1975-2019 USA	The authors hypothesize that pelvic osteotomy during exstrophy closure may be performed safely in newborns with few perioperative or post-operative negative sequelae.	n=286 patients with classic bladder exstrophy Male: 204/286 (71.3%) Median age Newborn: 3 (0-28) days Delayed: 198 (30-2893) days	Osteotomy (Combined Approach)	Osteotomy (Posterior Approach) Osteotomy (Anterior Innominate)	**Success rate** Overall Newborn (n=142): 98 (69%) Delayed (n=86): 77 (89.5%) p<0.001 Combined Approach Overall: 61/66 (92.4%) Newborn: 20 (80.0%) Delayed: 41 (100%) p=0.006 Posterior Approach Newborn: 31 (60.8%) Delayed: 21 (72.4%) p=0.294 Anterior Innominate Newborn: 47 (71.2%) Delayed: 15 (93.8%) p=0.06 Newborns no significant difference was found in the success rates between the combined, posterior iliac, and anterior innominate approaches (p=0.02) Delayed	While current trends have moved toward delayed primary closures, there remains a role for osteotomy during exstrophy closure in selected newborn patients and can be performed safely with few complications.	Insufficient information about the osteotomy groups (numbers, comparability), lack of consistent reporting of p-values, no follow-up reported The authors declared no conflict of interest. The Kwok Family Foundation of Hong Kong supports the exstrophy database and laboratory research.	3 RoB: 6/9

						comparisons in success rates within the delayed cohort for combined, posterior iliac, and anterior innominate approaches (p < 0.001)			
Baka-Ostrowska, 2013 [121]	Retrospective cohort study 1982-2006 Poland	To analyze complications after primary bladder exstrophy closure with a special consideration of the role of pelvic osteotomy.	n=100 patients with bladder exstrophy Male: 65/100	contemporary iliac osteotomy n=36	bladder was closed without osteotomy n=64	**Age at the primary closure** 1st day without osteotomy: 18/64 with osteotomy: 2/36 2nd day without osteotomy: 25/64 with osteotomy: 1/36 3rd day without osteotomy: 4/64 with osteotomy: 1/36 4-30 days without osteotomy: 8/64 with osteotomy: 11/36 1-12 months without osteotomy: 4/64 with osteotomy: 17/36 >12 months without osteotomy: 0/64 with osteotomy: 3/36 **Wound dehiscence** 1st day	Osteotomy performed at primary bladder exstrophy closure diminishes the risk of wound dehiscence independently of patient's age. Posterior iliac osteotomy is sufficient and safe and could be repeated if necessary.	Comparability of cohorts and length of follow-up unclear No information about funding and conflict of interest.	3 RoB: 6/9

						without osteotomy: 7/18 with osteotomy: 1/2 <u>2nd day</u> without osteotomy: 3/25 with osteotomy: 0/1 <u>3rd day</u> without osteotomy: 3/4 with osteotomy: 0/1 <u>4-30 days</u> without osteotomy: 5/8 with osteotomy: 4/11 <u>1-12 months</u> without osteotomy: 4/4 with osteotomy: 1/17 <u>>12 months</u> without osteotomy: 0/0 with osteotomy: 0/3 **Patients operated up to 72 h of life** <u>Wound dehiscence</u> without osteotomy: 13/47 with osteotomy: 1/4 p=0.7 **Patients operated above 72 h of life** <u>Wound dehiscence</u> without osteotomy: 11/17 with osteotomy: 6/32 p<0.002			
Husmann, 1989 [81]	Retrospective cohort study 1964-1989	To determine what factors could affect the success of initial bladder	n=80 patients with classical bladder exstrophy	Closed with iliac osteotomy n=51	Closed without iliac osteotomy n=29	**Closed with iliac osteotomy** <u><72 h after birth (n=15)</u>	To improve the results in staged bladder reconstruction we recommend	comparability of cohorts unclear, No information about funding	3 RoB: 8/9

	Canada Minimum follow up: 5 y	closure in classical bladder exstrophy.				• with dehiscence: 13% • requiring augmentation: 6% • continent: 73% <u>3-30 days (n=12)</u> • with dehiscence: 16% • requiring augmentation: 16% • continent: 66% <u>31 days to 1y (n=14)</u> • with dehiscence: 14% • requiring augmentation: 14% • continent: 71% <u>> 1y (n=10)</u> • with dehiscence: 10% • requiring augmentation: 40% • continent: 60% **Closed without iliac osteotomy** <u><72 h after birth (n=19)</u> • with dehiscence: 10% • requiring augmentation: 5% • continent: 84% <u>3-30 days (n=6)</u> • with dehiscence: 16% • requiring augmentation: 16% • continent: 16% <u>31 days to 1y (n=4)</u>	use of perioperative antibiotics, adequate postoperative nutritional support to aid in wound healing, closure when the neonate is less than 72 h old if no iliac osteotomy is to be performed, immediate treatment of gastric distension by nasogastric drainage, secure fixation of all urinary diversion catheters with tubes exiting through the suprapubic region and careful preoperative assessment in individuals with a history of delayed closure to confirm the presence of an adequate bladder capacity.	and conflict of interest.	

						• with dehiscence: 0% • requiring augmentation: 0% • continent: 0% **Bladder dehiscence** • No statistical correlation could be found among the development of bladder dehiscence, age of the child at bladder closure or the performance of iliac osteotomy (p >0.5) • Individuals undergoing delayed bladder closure without iliac osteotomy had no notable difference in the incidence of bladder dehiscence **Continence** • in neonates whose bladder was closed before 72 hours after birth the continence is not affected by the performance of iliac osteotomy (p >0.5) • delayed bladder closure without iliac osteotomy had a statistically significant difference in the ability to gain urinary continence (p <0.01) • patients excluded who underwent closure without iliac osteotomy after they			

						were 72 h old no statistical difference in individuals undergoing early versus delayed closure (p >0.5)			

Schlüsselfrage Wie sollte eine Genitalrekonstruktion in Abhängigkeit von Alter und Art des Defektes erfolgen?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Epispadias									
Caione, 2013 [126]	Cohort study 2000-2011 Italy Mean follow-up: 12 mo (9-16 mo)	We describe a technique of male epispadias repair to prevent resultant hypospadias.	n=48 male patients with exstrophy-epispadias complex • pure epispadias (n=12) • bladder exstrophy (n=36) <u>Mean age</u> • Modified: 15 mo (2 mo- 12 y) Standard: 14.5 mo (1 day-11 y)	Modified penile disassembly technique n=29 *Modified by multiple Z-plasties, which enable creation of a funnel-like bladder neck and urethral plate lengthening*	standard penile disassembly technique n=19	**Average penile length** • Modified: 2.4 cm (2-3.4 cm) • Standard: 2.6 cm (1.8-3.6 cm) Not significant **Fistulas** • Modified: 3/29 (10.3%) • Standard: 2/19 (10.5%) Not significant **length of the urethral plate** • Modified: increased by 11 mm (6-18 mm) • Standard: no significant elongation p<0.05 **Creation of an intentional hypospadias** • Modified: reached the tip of the glans in all cases • Standard: creation of an intentional hypospadias became necessary in 6/19 boys (31.5%)	The modified technique was effective in obtaining appropriate meatal location without decreasing the penile length. The complication rate was not changed. Creation of resultant hypospadias at genitalia reconstruction in male epispadias should strongly be prevented.	historical control group (2000-2004 vs. 2004-2011), the follow-up period is not similar in the two groups No information about funding and conflict of interest.	4 RoB: 7/9

						p<0.05			
Caione, 2001 [127]	Cohort study 1984-1999 Italy	We review our experience during the last 16 y, adopting different surgical approaches for epispadias repair, and compare the results of complete penile disassembly technique with perineal muscular complex reassembly since 1995 with previous repairs.	n=58 epispadias repairs Age: 3 days to 13 y	different surgical techniques n=41 • Thiersch-Duplay urethroplasty (n=6) • tubularized reserve island flap (n=15) • onlay buccal mucosa graft (n=3) Cantwell-Ransley caverno-cavernostomy (n=17)	complete penile disassembly technique n=17	**Complications** different techniques: 21/41 (51%) • Thiersch: 4/6 (66%) • reserve island flap: 11/15 (73%) • onlay buccal graft: 1/3 (33%) • Cantwell-Ransley: 5/17 (29%) penile disassembly: 2/17 (11%) • Complete penile disassembly: 1/5 (20%) • Complete penile disassembly with perineal muscular complex reassembly: 1/12 (8%) **Continence** <u>different techniques</u> • 41 patients underwent bladder neck plasty or bladder neck closure with catheterizable continent cutaneous stoma, and bladder augmentation or orthotopic substitution in 13 (32%) • Urethral catheterization was difficult or impossible in 8 patients (19%) <u>penile disassembly</u>	The complete penile disassembly with perineal muscular complex reassembly technique, with deeper positioning of the urethra in the perineal musculature, seems to guarantee a significant step forward in functional epispadias repair.	historical control group (in the last 5-year period the technique of disassembly of penile components was performed), unclear how cosmetic appearance was measured, Comparability of cohorts unclear, length of follow-up unclear No information about funding and conflict of interest.	4 RoB: 4/9

						• 12/17 continent (2 to 3-hour daytime dry interval) without bladder neck surgery **Cosmetic appearance** <u>different techniques</u> • No satisfactory cosmetic appearance of the phallus and persistent significant dorsal curvature: 12 patients (29%) <u>penile disassembly</u> • Good cosmetic results of the external genitalia: 16/17 **Re-treatment** • different techniques: 4/41 (all 4 in the onlay graft group) • penile disassembly: 1/17 The results in terms of surgical revisions between both groups were statistically significant (p=0.0042)			
Kajbafzadeh, 1995 [128]	Cohort study 1978-1993 United Kingdom Mean follow-up: 6 y (1-15 y)	We describe the evolution of epispadias repair techniques in a pediatric urology unit during a 15-year period and the development of the modified Cantwell procedure, which is currently used	n=180 patients with epispadias • bladder exstrophy (n=86) • epispadias (n=94) Mean age of penile	• Group1: 2-stage repair (n=30) • Group 2: pedicled preputial tube urethroplasty with dural patch chordee	• Group 3: pedicled preputial tube urethroplasty with corporeal rotation (n=40)	**Initial epispadias repair result** <u>Good cosmesis</u> Group 1: 40% Group 2: 55% Group 3: 63% Group 4: 84% <u>Fistula</u> Group 1: 56%	We conclude that a good cosmetic result can be achieved in almost all cases using the modified Cantwell technique as a primary procedure in	surgical techniques performed in different time periods, length of follow-up different between the groups, no statement about loss to follow-	4 RoB: 6/9

			reconstruction: 3 y (1-16 y)	correction (n=35)	Group 4: modified Cantwell epispadias repair incorporating complete tubularized intact urethral plate reverse meatal advancement, corporeal rotation and cavernocavernostomy (n=75)	Group 2: 43% Group 3: 37% Group 4: 4% <u>Stricture</u> Group 1: 17% Group 2: 17% Group 3: 15% Group 4: 5.3% <u>Dehiscence</u> Group 1: 10% Group 2: 2.8% Group 3: 2.5% Group 4: 0% <u>Radial revision</u> Group 1: 50%* Group 2: 44%* Group 3: 37%* Group 4: 16%** * Secondary modified Cantwell technique ** Skin revision only with or without fistula or stricture. The results in group 4 were much better than in any of the other groups.	experienced hands. This technique has a low complication rate and can be used as a salvage procedure following previous unsuccessful epispadias reconstruction using other techniques.	ups, cosmesis was evaluated by a combination of observation and patient/ parent opinion No information about funding and conflict of interest.	
Männer									
Berrettini, 2021 [129]	Systematic review 1990-2019 Median follow-up after substitution phalloplasty: 43.5 mo (2-135 mo)	To determine whether patients with bladder exstrophy-epispadias complex might benefit from substitution phalloplasty.	n=7 studies • Case report (n=1) • Case series (n=5) • Cross-sectional (n=1)	substitution phalloplasty		**Free radial forearm flap** • most commonly: 89% • overall complication rate: 15% **Urethroplasty** • performed in 47% patients	Substitution phalloplasty in patients with bladder exstrophy-epispadias complex can achieve good functional, aesthetic, psychological,	No additional hand search, no information if efforts were made to minimise errors in the study selection, data collection and risk of bias assessment	4 RoB: high

			n=47 patients with BEEC • bladder exstrophy (89.4%) • cloacal exstrophy (10.6%) Age at surgery: 11-35 y			• most cases (20/22) a "tube-within-the-tube" technique was performed simultaneously with the phalloplasty (20/47) • overall complication rate: 54% **Penile prosthesis** • performed in 68% patients • overall complication rate: 25% Aesthetic, sexual, and psychological outcomes were satisfactory (no use of validated instruments for assessment)	and sexual outcomes. It requires multiple procedures and carries a high complication rate.	The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. The authors received no specific funding for this work. Studie aus SR-Suche inkludiert	
Harris, 2020 [130]	Cohort study 1992-2020 USA Mean follow-up: 30.7 mo (0.2-194.5 mo)	To describe the use of additional tissue recruited for coverage after penile lengthening in male exstrophy-epispadias complex patients using either local skin from tissue expansion or extragenital skin with a skin graft and report their respective outcomes.	n= 50 patients with exstrophy-epispadias complex and penile reconstruction Mean age: 18.1 y (7-27 y)	local skin from tissue expansion n=27 combination skin graft and tissue expansion n=4	extragenital skin with a skin graft n=19	**Successful primary reconstruction** *(Figure 3 results)* tissue expansion+combination: 24/31 skin graft: 15/19 **Successful secondary reconstruction** *(Figure 3 results)* tissue expansion+combination: 5/7 skin graft: 3/4 **Successful tertiary reconstruction** *(Figure 3 results)* tissue expansion+combination: 1/2	Tissue expansion and skin graft are useful techniques in providing soft tissue coverage following penile lengthening. tissue expansion is the preferred technique for primary reconstruction in a lengthening procedure. When genital skin is not expandable or coverage from tissue expansion is insufficient after	Combination group was not consistently assigned to a group or considered separately, it is therefore unclear whether these groups are comparable The authors declare that they have no relevant financial interests. No information about funding.	3 RoB: 7/9

						skin graft: - **Complications** <u>Tissue expansion</u> • Infection (n = 3) • Extrusion (n = 4) • Erosion (n = 1) • Migration (n = 1) • Leak (n = 3) • Dehiscence (n = 3) • Early removal (n = 9) <u>Skin graft</u> • Infection (n = 1) • Hematoma (n = 3) • Graft loss (n = 3, [5 grafts]) • Erections (n = 9) • Fistula (n = 5) • Chordee (n = 3) • Stricture (n = 1) • Scarring (n = 4)	lengthening, extragenital skin (skin graft) is recruited.	*data for the first successful reconstruction are different (text vs. Figure 3)*	
Frauen									
VanderBrink, 2010 [131]	Retrospective cohort study 1976-2007 Follow-up: 3 mo-31 y	We review our experience with clitoral reconstruction in a classic bladder exstrophy epispadias complex population with an emphasis on aesthetic outcomes.	n=26 female BEEC patients • isolated epispadias (n=3) • classic bladder exstrophy (n=23) n=33 clitoroplasties were performed <u>Age at initial clitroplasty</u>	• Group 1: tularisation of skin between clitoral bodies for urethral reconstruction (n=3) • Group 2: underwent staged exstrophy reconstruction (n=12)	• Group 3: secondary reconstructive surgery with clitoroplasty accompa-nied by puboplasty to reconstruct the fourchette (n=8) • total urogenital sinus mobilisation (n=3)	**Assessment of post-operative aesthetic outcome following clitoroplasty.** <u>Group 1</u> (n=3) Surgeon opinion: • Good: 3 • Poor: 0 Parent/patient opinion: • Good: 3 • Poor: 0 <u>Group 2</u> (n=12) Surgeon opinion: • Good: 5 • Poor: 7 Parent/patient opinion: • Good: 9	Excellent aesthetic outcomes can be achieved following clitoroplasty in classic bladder exstrophy epispadias complex patients using a variety of surgical techniques. During primary clitoroplasty, use of the skin between the	patient collective consists of treated persons of the senior author, Comparability between the groups unclear, different length of follow-up times between the groups The authors do not have any commercial associations or financial disclosures that	3 RoB: 5/9

			• Group 1: 3-48 mo • Group 2: 1 day-2 mo • Group 3: 3.5-12 y • Group 4: 1-2 days			• Poor: 3 <u>Group 3</u> (n=13) Surgeon opinion: • Good: 8 • Poor: 5 Parent/patient opinion: • Good: 9 • Poor: 1 • No opinion: 3 <u>Group 4</u> (n=3) Surgeon opinion: • Good: 3 • Poor: 0 Parent/patient opinion: • Good: 3 • Poor: 0 **Complications** • Group 1: no urethral stricture developed • Group 2: 7/12 secondary clitoroplasty • Group 3: 3 patients partial atrophy of one or both clitoral bodies; 1 patient gap between hemi-clitoral bodies was widely separated and incapable of being joined • Group 4: no complication	clitoral bodies is expedient for reconstruction of the distal urethra, while in secondary clitoroplasty this skin should be excised to unite the clitoral bodies. Reassessment near puberty can identify poor cosmetic outcome and secondary clitoroplasty may help mitigate the psychological effects attributed to aesthetically displeasing genitalia.	might pose or create a conflict of interest with information presented in the submitted manuscript. No funding received. *different numbers of patients in group 3 (abstract: 8; tables: 13)*	
Cheikhelard, 2009 [132]	Cohort study 1997-2007 France	We compared the functional results of 1-stage perineal urethrocervico-plasty and vulvoplasty vs the classic Young-Dees	n=14 patients with female epispadias <u>Median age</u>	Young-Dees procedure n=7	1-stage urethrocervicoplasty with vulvoplasty through a perineal	**Daytime continence** Young-Dees: 87.5% Vulvoplasty: 85% p=1 **Postoperative bladder**	Reconstructing the bladder neck and urethra via a perineal approach for female	historical control group (young-dees: 1996-2004; vulvoplasty since 2005), groups were	4 RoB: 5/9

	<u>Mean follow-up</u> Young-Dees: 8 y (2.5-13 y) Vulvoplasty: 2.5 y (1-3 y)	procedure for incontinent female epispadias.	Young-Dees: 6 y (3-13 y) Vulvoplasty: 4 y (1.5-11 y)		subsymphyseal approach n=7	**capacity** Young-Dees (n=5): 150 ml (110-400) Vulvoplasty (n=2): 175 ml (150-200) p=0.05 **Postoperative course** • was simpler in the vulvoplasty group due to shorter drainage time and easier spontaneous voiding recovery **Additional surgeries** Young-Dees: 5 (8 procedures) Vulvoplasty: 0 p=0.02 **Upper tract dilatation** Young-Dees: 0 Vulvoplasty: 3 p=0.19 **Ureterovesical reimplantation stenosis** Young-Dees: 0 Vulvoplasty: 1 **Febrile urinary tract infection** Young-Dees: 4 (with 8 infections) Vulvoplasty: 2 p=0.25	epispadias is promising. Surgery may be performed earlier with similar continence results, less postoperative morbidity and less need for additional surgery.	comparable except for age at procedure, different follow-up times, missing follow-up data (e. g. postoperative bladder capacity) No information about funding and conflict of interest.	

Schlüsselfrage Was ist das ideale Alter für die operative Korrektur der isolierten Epispadie?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Therapie(n)**	**Endpunkte**	**Ergebnisse**	**Schluss-folgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Acimi, 2019 [133]	Case series 2009-2018 Algeria Mean follow-up: 61 mo	To report current results of complete penile disassembly technique in epispadias repair.	n=31 patients • bladder exstrophy (n=25) • isolated penopubic epispadias (n=7) <u>Median age of the patients:</u> • Overall: 3 y (10 mo – 6 y) • bladder exstrophy: 2-6 y • isolated epispadias: 10-20 mo	complete penile disassembly for proximal epispadias repair	• Postoperative complication • urinary continence	**Median age of the patients with isolated epispadias**: 10-20 mo **Urinary continence** • dry intervals of at least 1 h/day: 3/7 • dry intervals ≥ 3 h: 2/7 **Complications** • Fistula: 1/7 (14.3%) • Meatal stenosis: 1/7 (14.3%) • Glans rotation: 2/7 (28.5%) • Curvature of the penis 4/7 (57%)	*no conclusion to the best age for surgery*	unclear if the design is retrospective or prospective, unclear how continence status was measured, no statistical analysis The authors declare that they have no conflict of interest. No information about funding *unclear documentation of patients with with dry intervals of at least 1 h/day (6 patients reported, only 5 patients classified)*	4 RoB: 14/20
Cendron, 2018 [134]	Retrospective case series 1994-2011 USA	The goal of the current study was therefore to evaluate whether the more proximal	n=26 male epispadias patients Median age of repair:	Initial imaging or endoscopic evaluation	• Corrective surgery for vesicoureteral reflux and bladder neck • Urinary continence	**Median age at the time of initial epispadias repair**: 10.9 mo (6-23 mo)	*no conclusion to the best age for surgery*	no statistical analysis performed, continence status was based on	4 RoB: 15/20

	Median follow-up: 109.1 mo (2-235.3 mo)	forms of epispadias correlated with associated extragenital anatomic anomalies seen on initial imaging or endoscopic evaluation, and whether these pre-operative findings contributed to sub-sequent surgical management aimed at achieving urinary continence.	10.9 mo (6-23 mo)			**Corrective surgery** vesicoureteral reflux treated by ureteroneocystostomy alone or in conjunction with a Young-Dees-Leadbetter • Penopubic: 4/14 (21%) • Penile: 3/4 (75%) • Glanular: 2/2 (100%) sling or Young-Dees-Leadbetter-Politano reconstruction • Penopubic: 8/14 (38%) • Penile: 3/8 Ureteroneocystos-tomy • Penopubic: 4/14 (29%) in conjunction with bladder neck procedure • Glanular: 1/4 (25%) without bladder neck procedure none underwent iliac osteotomies **Urinary continence** • Overall: 17/26 (65%) • Penopubic: 9/14 (64%) • Penile: 5/8 (63%) Glanular: 3/4 (75%)		subjective self-assessment No information about conflict of interest. No funding reported.	

Alyami, 2017 [114]	Retrospective cohort study 2000-2013 Canada <u>Mean follow-up</u> Young-Dees-Leadbetter cervicoplasty bladder neck approach: 12.3 y (8-13 y) Single-stage perineal approach: 6 y (1-10 y)	The aim of the present study was to describe long-term follow-up of patients who underwent the traditional vs alternative approach.	n=12 female patients with epispadias <u>Mean age at first surgery</u> Young-Dees-Leadbetter cervicoplasty bladder neck approach: 2.9 y (0.5-4 y) Single-stage perineal approach: 4.3 y (1-17 y)	• Young-Dees-Leadbetter cervicoplasty bladder neck approach (n=3) Single-stage perineal approach (n=9)	Long-term outcomes: • Postoperative continence • redo-surgery • Further procedures for incontinence • Need for bladder augmentation	**<u>Mean age at first surgery</u>** • Young-Dees-Leadbetter cervicoplasty bladder neck approach: 2.9 y (0.5-4 y) • Single-stage perineal approach: 4.3 y (1-17 y) **Young-Dees-Leadbetter cervicoplasty bladder neck approach** • Dry: 0/3 • Redo-surgery: 3/3 • Further procedures for incontinence: bladder neck, reconstruction, appendicovesicostomy, Bladder neck Deflux injection • Need for bladder augmentation: 2/3 • Continence post redo-surgery: 3/3 (CIC) **Single-stage perineal approach** • Dry: 4/9 • Not toilet trained: 2/9 • Incontinence: 3/9 • Redo-surgery: 3/9 • Further procedures for incontinence: Bladder neck Deflux injection • Need for bladder augmentation: 0/9	*no conclusion to the best age for surgery*	Groups are not comparable (age range, other factors unclear) No conflict of interest/funding declared.	3 RoB: 6/9

						• Continence post redo-surgery: 2/3 **Complication:** No major complications			
Bar-Yosef, 2017 [135]	Retrospective case series 1998 – 2015 Israel Mean follow-up: 6.9 y (range 0.5 y -18 y)	To evaluate our results of epispadias repair with a modified Cantwell-Ransley technique.	n=22 male patients with EEC • n=16 with EEC • n=6 male patients with isolated epispadias Mean age isolated epispadias: 29 mo (7-120 mo)	• modified Cantwell-Ransley technique	complications	**Age** • Procedures were performed after the age of 6 mo in isolated epispadias patients • Mean age: 29 mo (7-120 mo) **Complications** 0/6 (0 %): there were no complications in the isolated epispadias group	*no conclusion to the best age for surgery*	no statistical analysis performed The authors declare that they have no relevant financial interests. No information about funding	4 RoB: 15/20
Gite, 2017 [136]	Case series 2011-2016 India Follow-up: 6 mo-5 y	We evaluate here our experience with modified Cantwell–Ransley technique described by Gearhart for correction of isolated continent epispadias in adults with respect to its long-term functional outcome and complications	n=5 men with isolated continent epispadias • mid-penile : 2 • proximale penile: 2 • penopubic : 1 Age: 15-25 y	modified Cantwell–Ransley • technique described by Gearhart	• long-term functional outcome complications	**Age**: 15-25 y **Post-operative results** • No meatal stenosis, diverticulum, stricture, fistula, pubic diastasis or incontinence • adequate penile length *One patient had a history of repair in childhood, but exact surgical details were not known.*	*no conclusion to the best age for surgery*	unclear if the design is retrospective or prospective, unclear how continence status was measured, no statistical analysis There are no conflicts of interest. Financial support and sponsorship: Nil	4 RoB: 15/20
Shahat, 2017 [137]	Case series 2008-2015	To present our experience with concealed	n=51 male patients with epispadias	primary isolated male	• age at presentation	**Median age at presentation**	Impediment and	unclear if the design is retrospective or	LoE 4

	Egypt	epispadias and to estimate its actual share in the isolated male epispadias cases and its effect on the surgical outcome.	• classic epispadias (n=40) • concealed epispadias (n=11) Median age at presentation : 32 mo	epispadias reconstruction	• meatal location • incontinence • dorsal curvature • success rate • complications	• Concealed epispadias: 28.5 mo • Classic isolated male epispadias: 52 mo p=0.005 **Incontinence** • Concealed epispadias: 21/40 (52.5%) • Classic isolated male epispadias: 1/11 (9.1%) p=0.015 **Successful outcome after initial repair** • Concealed epispadias: 31/40 (77.5%) • Classic isolated male epispadias: 9/11 (81.8%) p=1 **Secondary procedure** • Concealed epispadias: 9/40 (22.5%) • Classic isolated male epispadias: 2/11 (18.2%) p=1 **Successful outcome after secondary procedure**	delay of diagnosis are its main clinical impacts, with insignificant effect on the surgical outcome.	prospective, not described, unclear how continence status was measured The authors declare that they have no relevant financial interests. No information about funding.	RoB: 16/20

						• Concealed epispadias: 7/9 (77.8%) • Classic isolated male epispadias: 2/2 (100%) p=1			
Yadav, 2017 [138]	Case series 2013-2016 India Mean follow-up: 13.17 mo (4-29 mo)	To evaluate the role of infrasymphyseal bladder neck plication and suspension from the pubic bone along with urethrogenitoplasty as a single-stage procedure for treating isolated cases of female epispadias.	n=6 patients with female epispadias Mean age: 5.91 y(3-10 y)	Combined Infrasymphyseal Bladder Neck Plication and Urethrogenito-plasty	• Continence • Cosmetic outcome • Postoperative complications	**Age** 3 y, 3.5 y, 5 y, 6 y, 8 y, 10 y **Preoperative urinary incontinence** Grade of 3: 6/6 **Postoperative continence:** 5/6 One patient (3 years) had urine leakage while playing or crying during the initial postoperative period; however, this patient became continent with a dry period of more than 3 hours after 4 months of follow-up **Cosmetic & Complications** All patients: • excellent cosmetic outcome no considerable postoperative complications	*no conclusion to the best age for surgery*	unclear if the design is retrospective or prospective, not described, if all eligible patients were included, no statistical analysis was performed No information about funding and conflict of interest.	LoE 4 RoB: 12/20
Spinoit, 2016 [139]	Retrospective case series 1998-2014	The technique for primary isolated male epispadias	n=8 male patients with isolated epispadias	primary isolated male epispadias reconstruction	• Complications • Continence •	**Median age at surgery**: 13 mo (7-47 mo)	*no conclusion to the best age for surgery*	patient numbers not reported according to the severity of their	4 RoB: 13/20

	Belgium Median follow-up: 52 mo (9-120 mo)	reconstruction, based on anatomic restoration of the urethra and bladder neck, is here illustrated.	Median age at surgery: 13 mo (7-47 mo)			**Complications** • No early complications **Further surgeries** • because of complications: 2 (initially penopubic epispadias) • esthetic surgeries: 4 **Incontinence** • 1 patient with penopubic epispadias with open bladder neck 1 patient not yet reached a suitable age for potty-training		condition, unclear how continence was defined, no statistical analysis was performed The authors declare that there is no conflict of interests regarding the publication of this article. No information about funding.	
Bhat, 2015 [140]	Retrospective case series 2008-2012 Follow-up postoperatively: 1-5 y	Aim of the study was to evaluate the functional and cosmetic outcome of double breasting of bladder neck and posterior urethra with partial penile disassembly in one stage in isolated incontinent peno-pubic epispadias.	n=7 cases of primary isolated incontinent peno-pubic epispadias Mean age: 10.7 y (10 mo-16 y)	double breasting of bladder neck and posterior urethra	• urinary continence • cosmesis • genital function • Complications	**Mean age**: 10.7 y (10 mo-16 y) **Postoperative continence:** Overall: 7/7 Fully continent: 6/7 Partially continent (with dry interval of 2 h): 1/7 **Cosmesis** • 6/7 (85.7%): excellent cosmetic outcome with complete correction of • chordee and torque and were pleased with the final appearance • 1/7 (14.3%) mild residual chordee postoperatively, relatively satisfied	Double breasting of bladder neck and posterior urethra with sphincteroplasty and partial penile disassembly produces a reliable neourethra, complete chordee correction with emphasis on achievement of continence and near-normal-appearing penile morphology through a	not described, if all eligible patients were included, unclear how continence status and cosmetic results was measured, no statistical analysis was performed Conflict of interest: None. No information about funding.	4 RoB: 12/20

						with the cosmetic result and did not require any surgical intervention **Genital function** • 2/2 successful ejaculations after the surgery • Semen analysis: sluggish motility and oligospermia with adequate volume **Complications** None of the patients developed fistula, stricture, wound dehiscence or necrosis	single-stage surgery.		
Kibar, 2009 [141]	Retrospective case series 1996-2008 USA <u>Mean follow-up:</u> Bladder exstrophy: 58.2 mo Isolated epispadias: 58.6 mo	To present our long-term results with complete penile disassembly for epispadias repair.	n=21 patients • bladder exstrophy (n=12) • isolated epispadies (n=9; 1 penopubic epispadias, 2 midshaft epispadias, 6 distal epispadias) <u>Reconstruction age</u> Bladder exstrophy: 1 day-17 mo	Mitchell technique	• Continence • Complications • Erectile function	**Age:** 2 mo-7 y **Continence** (4 distal epispadias, 2 midshaft epispadias) • 2/6 required bladder neck injection to achieve maximal continence • 6/6 were continent • 0/6 required clean intermittent catheterization **Complications** • 3/9 (33.3%) • all complications occured on distal epispadias: Mild penile torsion, meatal stenosis,	Epispadias reconstruction using the Mitchell repair can achieve total or near complete urinary continence, decreasing the morbidity of multiple procedures, and potentially allowing children to achieve continence at an earlier age.	unclear how continence status and cosmetic results was measured, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 13/20

			Isolated epispadias: 2 mo-7 y			subcoronal fistula, penile angulation • second operation: 2/3 **Erectile function** • 7/9 straight erections, an orthotopic meatus, and a satisfactory cosmetic appearance • 9/9 erectile function was preserved			
Braga, 2008 [115]	Retrospective cohort study 1994-2005 Canada <u>Mean follow-up</u> Mitchell-Bagli: 70 mo (10-120 mo) Cantwell-Ransley: 80 mo (21-144 mo)	We review our results with isolated male epispadias repair, comparing the Cantwell-Ransley and Mitchell-Bagli procedures in regard to continence status and postoperative complications.	n=33 male patients with isolated epispadias • glanular (n=3) • penile (n=9) • phenopubic (n=21)	• Mitchell-Bagli operation (n= 7 penopubic epispadias) Cantwell-Ransley operatin (n=14 with penopubic epispadias)	• Continence status • Postoperative complications	**Phenopubic epispadias** <u>Mean age at epispadias repair</u> • Mitchell-Bagli: 19.3 mo (9-42 mo) • Cantwell-Ransley: 16.8 mo (12-24 mo) followed by bladder neck procedere at age 2.5-7 y <u>Continence</u> 7 patients also had nighttime continence, and no patient was dry for less than 2 hours or consistently wet. • Completely Dry/Dry More Than 4 Hrs Mitchell-Bagli: 5/6 (83%) Cantwell-Ransley: 8/11 (73%)	*no conclusion to the best age for surgery*	less information to patient characteristics, it remains unclear if the two cohorts are comparable, continence status was ascertained by patient or family report, unclear why some data were not included in the analysis No information about conflict of interest and funding. *no information about age of glanular and penile epispadias repair*	3 RoB: 5/9

						• Dry 2–4 Hrs/Stress Incontinence Mitchell-Bagli: 1/6 (17%) Cantwell-Ransley: 3/11 (27%) p=0.91 <u>Complications</u> • Overall Mitchell-Bagli: 2 (29%) Cantwell-Ransley: 8 (57%) • Residual dorsal curvature Mitchell-Bagli: 1 (14%) Cantwell-Ransley: 3 (21%) • Urethrocutaneous fistula Mitchell-Bagli: 1 (14%) Cantwell-Ransley: 4 (29%) • Cosmetic revision Mitchell-Bagli: 0 Cantwell-Ransley: 1 (7%)			
Mokhless, 2008 [142]	Case series Mean follow-up: 8.5 mo	The current study presents our experience in partial penile disassembly for isolated epispadias repair.	n=11 male patients with isolated primary epispadias • penopubic (n=2) • penile (n=6) • glanular (n=3)	modification of Mitchell's technique • of partial penile disassembly	• Cosmetic appearance	**Age**: 4-13 y **Cosmetic appearance** • no significant dorsal chordee • transformed to subcoronal • hypospadias and were managed 6 months later (n=2)	*no conclusion to the best age for surgery*	study aim and patient recruitment not clearly defined, cosmetic apperance reported by the parents No information about funding	4 RoB: 9/20

			Age: 4-13 y <u>Continence</u> • 9 continent • 2 in-continent (peno-pubic)			penopubic urethral fistula, repaired at a later stage (n=1)		and conflict of interest.	
Lottmann, 1999 [143]	Retrospective case series 1989-1997 France Mean follow-up: 3 years	We present our experience using the Cantwell-Ransley epispadias technique, particularly focusing on postoperative anatomical and functional complications.	n=40 male patients n=23 exstrophy n=17 isolated epispadias • penile (n=11) • penopubic (n=6)	Cantwell-Ransley technique	• Continence • postoperative complications	**Age**: 1-28 years **Incidence of partial or complete failure** Exstrophy: 15/23 (65%) Isolated epispadie: 6/17 (28%)	In our series the age at which the procedure was performed varied. In our experience primary epispadias repair may be performed at the end of the first year of life.	not described, if all eligible patients were included, outcome measurement not clearly described, no statistical analysis was performed *unclear if it was the primary procedure: only 11 patients had never undergone surgery previously* No information about funding and conflict of interest.	4 RoB: 10/20
Kajbafzadeh, 1995 [144]	Case series August 1978 – May 1993 Mean follow-up: 6 y (1-15 years)	We describe the evolution of epispadias repair techniques in a pediatric urology unit during a 15-y period and the development	n=180 male patients with epispadias and EEC n=95 EEC n=85 primary epispadias	1) 2-stage epispadias reconstruction with dissection of the corpora n=12 epispadias cases	• Cosmesis • Complications	**Mean age at surgery:** Patients with primary epispadias by surgical group 1) 4.8 y (n=12) 2) 4 y (n=20) 3) 3 y (n=22) 4) 3.3 y (n=40)	*no conclusion to the best age for surgery*	unclear if the design is retrospective or prospective, patient recruitment and outcome measurement not clearly described, no	4 RoB: 10/20

		of the modified Cantwell procedure, which is currently used.	• penile (n=13) • subsymphyseal (n=72)	2) pedicled preputial tube urethroplasty either alone or with a lyophilized human dural patch to the corpora for correction of penile deformity n=20 epispadias cases 3) edicled preputial tube urethroplasty and corporeal rotation n=22 epispadias cases 4) a modified Cantwell epispadias repair incorporating complete tubularized urethroplasty, cavernocavernostomy and corporeal rotation n=40 epispadias cases				statistical analysis was performed No information about funding and conflict of interest.	

Schlüsselfrage Wann ist eine operative Intervention zur Kontinenz bei isolierter Epispadie indiziert?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schluss-folgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Bhat, 2021 [145]	Retrospective case series Reconstruction period: 2015-2018 India Follow-up: 3-18 mo	The objective of the study was to evaluate the func- tional and cosmetic outcome of single-stage modified partial penile disassembly repair in isolated male epispadias.	n=15 male with epispadias • Peno-pubic variant (n=9) • Penile variant (n=6)	Single-stage modified partial penile disassembly repair		**Mean age**: 11 y (4 mo-21 y) • Five patients with partial incontinence in the study group achieved continence after surgery.	Single-stage modified partial penile disassembly repair is an alternative to Cantwell Ransley repair with acceptable results to avoid morbidity and cost associated with multiple procedures.	not described, if all eligible patients were included, method of outcome measurement unclear, no statistical analysis was performed The authors declare that they did not receive funding for this work. The authors declare that they have no conflicts of interest.	4 RoB: 12/20
Acimi, 2019 [133]	Case series 2009-2018 Algeria Mean follow-up: 61 mo	To report current results of complete penile disassembly technique in epispadias repair.	n=31 patients • bladder exstrophy (n=25) • isolated penopubic epispadias (n=7) <u>Median age of the patients:</u>	complete penile disassembly for proximal epispadias repair		**Median age of the patients with isolated epispadias**: 10-20 mo **Urinary continence** • dry intervals of at least 1 h/day: 3/7 • dry intervals ≥ 3 h: 2/7	The complete penile disassembly remains one of the best techniques for epispadias repair. However, we noticed a reappearance of the dorsal curvature of	unclear if the design is retrospective or prospective, unclear how continence status was measured, no statistical analysis The authors declare that they have no	4 RoB: 14/20

			• Overall: 3 y (10 mo – 6 y) • bladder exstrophy: 2-6 y isolated epispadias: 10-20 mo				the penis in a large number of patients treated for isolated epispadias and the impact of this technique on urinary incontinence remains uncertain.	conflict of interest. No information about funding. *unclear documentation of patients with with dry intervals of at least 1 h/day (6 patients reported, only 5 patients classified)*	
Cendron, 2018 [134]	Retrospective case series 1994-2011 USA Median follow-up: 109.1 mo (2-235.3 mo)	The goal of the current study was therefore to evaluate whether the more proximal forms of epispadias correlated with associated extragenital anatomic anomalies seen on initial imaging or endoscopic evaluation, and whether these pre-operative findings contributed to sub-sequent surgical management aimed at	n=26 male epispadias patients	Initial imaging or endoscopic evaluation		**Median age at the time of initial epispadias repair**: 10.9 mo (6-23 mo) **Urinary continence** • Overall: 17/26 (65%) • Penopubic: 9/14 (64%) • Penile: 5/8 (63%) • Glanular: 3/4 (75%) No correlation between urinary continence and either abnormal bladder neck appearance, pubic diastasis or vesicoureteral reflux could be found.	No correlation between urinary continence and either abnormal bladder neck appearance, pubic diastasis or vesicoureteral reflux could be found.	no statistical analysis, continence status was based on subjective self-assessment No information about conflict of interest. No funding reported.	4 RoB: 14/20

		achieving urinary continence.							
Leclair, 2018 [113]	Prospective cohort study 2006-2017 France Median follow-up: 57 mo (15-132 mo)	Our aim was to assess the results of a surgical management using perineal approach in girls with normal bladder capacity, and Kelly radical soft-tissue mobilization in patients with inadequate bladder, based on the assumption that bladder capacity is a reliable marker of epispadias severity.	n=16 girls with primary female epispadias <u>Median age at surgery</u> • Perineal reconstruction: 32 mo (14-102 mo) • Kelly repair: 42 mo (8-93 mo)	Perineal reconstruction (girls with normal bladder) n=7	Kelly repair (girls with inadequate bladder) n=11	**Continence status** *[Assessed at 5 years or later, after follow-up > 12 months]* <u>Perineal reconstruction</u> • 4/7 (57%): dry day/night • 5/7 (71%): dry by day • 2/7 (29%): still wearing protections – <u>Kelly repair</u> • 3/8 (38%): dry day/night • 8/8 (100%): dry by day **Bladder capacity at diagnosis** *[Percentage of expected Bladder capacity for age]* • Perineal reconstruction: 116% (92-143%) • Kelly repair: 56% (10-94%) **Bladder capacity at final evaluation** • Perineal reconstruction: 82% (56-102%) • Kelly repair: 87% (25-103%) **Additional procedure**	A tailored approach to female epispadias, based on perineal reconstruction in favorable cases, and radical soft-tissue mobilization in severe cases, seems to yield good continence outcomes in the long term.	Funding: This study had no funding source. Conflicts of interest: The authors declare no conflicts of interest.	3 RoB: 9/9

						<u>Bladder neck injection</u> • Perineal reconstruction: 3/7 • Kelly repair: 0/8 <u>Bladder augmentation</u> • Perineal reconstruction: 0/7 • Kelly repair: 0/8			
Alyami, 2017 [114]	Retrospective cohort study 2000-2013 Canada <u>Mean follow-up</u> Young-Dees-Leadbetter cervicoplasty bladder neck approach: 12.3 y (8-13 y) Single-stage perineal approach: 6 y (1-10 y)	The aim of the present study was to describe long-term follow-up of patients who underwent the traditional vs alternative approach.	n=12 female patients with epispadias	Young-Dees-Leadbetter cervicoplasty bladder neck approach n=3	Single-stage perineal approach n=9	**<u>Mean age at first surgery</u>** • Young-Dees-Leadbetter cervicoplasty bladder neck approach: 2.9 y (0.5-4 y) • Single-stage perineal approach: 4.3 y (1-17 y) **Young-Dees-Leadbetter cervicoplasty bladder neck approach** • Dry: 0/3 • Redo-surgery: 3/3 • Further procedures for incontinence: bladder neck, reconstruction, appendicovesicostomy, Bladder neck Deflux injection • Need for bladder augmentation: 2/3 • Continence post redo-surgery: 3/3 (CIC) **Single-stage perineal approach** • Dry: 4/9	Female epispadias could be successfully repaired using a single-stage modified perineal approach that achieved good continence with volitional voiding, good cosmetic results and compared favorably with the ones repaired with the Young-Dees-Leadbetter technique. The additional step of performing bladder neck tailoring to achieve a funneling configuration seemed to be useful in improving continence.	Groups are not comparable (age range, other factors unclear) No conflict of interest/ funding declared.	3 RoB: 6/9

						• Not toilet trained: 2/9 • Incontinence: 3/9 • Redo-surgery: 3/9 • Further procedures for incontinence: Bladder neck Deflux injection • Need for bladder augmentation: 0/9 Continence post redo-surgery: 2/3			
Shahat, 2017 [137]	Case series 2008-2015 Egypt	To present our experience with concealed epispadias and to estimate its actual share in the isolated male epispadias cases and its effect on the surgical outcome.	n=51 male patients with epispadias • classic epispadias (n=40) • concealed epispadias (n=11) Median age at presentation : 32 mo	primary isolated male epispadias reconstruction		**Median age at presentation** • Concealed epispadias: 28.5 mo • Classic isolated male epispadias: 52 mo p=0.005 **Incontinence** • Concealed epispadias: 21/40 (52.5%) • Classic isolated male epispadias: 1/11 (9.1%) p=0.015 **Successful outcome after initial repair** • Concealed epispadias: 31/40 (77.5%) • Classic isolated male epispadias: 9/11 (81.8%) p=1 **Secondary procedure**	Impediment and delay of diagnosis are its main clinical impacts, with insignificant effect on the surgical outcome.	unclear if the design is retrospective or prospective, not described, unclear how continence status was measured The authors declare that they have no relevant financial interests. No information about funding.	LoE 4 RoB: 16/20

						• Concealed epispadias: 9/40 (22.5%) • Classic isolated male epispadias: 2/11 (18.2%) p=1 **Successful outcome after secondary procedure** • Concealed epispadias: 7/9 (77.8%) • Classic isolated male epispadias: 2/2 (100%) p=1			
Yadav, 2017 [138]	Case series 2013-2016 India Mean follow-up: 13.17 mo (4-29 mo)	To evaluate the role of infrasymphyseal bladder neck plication and suspension from the pubic bone along with urethrogenitoplasty as a single-stage procedure for treating isolated cases of female epispadias.	n=6 patients with female epispadias	Combined Infrasymphyseal Bladder Neck Plication and Urethrogenitoplasty		**Mean age**: 5.91 (3-10 y) **Preoperative urinary incontinence** Grade of 3: 6/6 **Postoperative continence:** 5/6 One patient (3 years) had urine leakage while playing or crying during the initial postoperative period; however, this patient became continent with a dry period of more than 3 hours after 4 months of follow-up.	The present technique is simple, safe, and effective for achieving urinary continence in patients with female epispadias.	unclear if the design is retrospective or prospective, not described, if all eligible patients were included, no statistical analysis was performed No information about funding and conflict of interest.	LoE 4 RoB: 12/20

Spinoit, 2016 [139]	Retrospective case series 1998-2014 Belgium Median follow-up: 52 mo (9-120 mo)	The technique for primary isolated male epispadias reconstruction, based on anatomic restoration of the urethra and bladder neck, is here illustrated.	n=26 male patients with isolated epispadias	primary isolated male epispadias reconstruction		Median age at surgery: 13 mo (7-47 mo) **Incontinence** • 1 patient with penopubic epispadias with open bladder neck • 1 patient not yet reached a suitable age for potty-training	Anatomical restoration might be sufficient in isolated male epispadias to acquire continence, but inclusion of a larger series of patients is needed to support this statement.	patient numbers not reported according to the severity of their condition, unclear how continence was defined, no statistical analysis was performed No information about funding. The authors declare that there is no conflict of interests regarding the publication of this article.	4 RoB: 13/20
Bhat, 2015 [140]	Retrospective case series 2008-2012 Follow-up postoperatively: 1-5 y	Aim of the study was to evaluate the functional and cosmetic outcome of double breasting of bladder neck and posterior urethra with partial penile disassembly in one stage in isolated incontinent peno-pubic epispadias.	n=7 cases of primary isolated incontinent peno-pubic epispadias	double breasting of bladder neck and posterior urethra		Mean age: 10.7 y (10 mo-16 y) **Postoperative continence:** Overall: 7/7 Fully continent: 6/7 Partially continent (with dry interval of 2 h): 1/7	Double breasting of bladder neck and posterior urethra with sphincteroplasty and partial penile disassembly produces a reliable neourethra, complete chordee correction with emphasis on achievement of continence and near-normal-appearing	not described, if all eligible patients were included, unclear how continence status and cosmetic results was measured, no statistical analysis was performed Conflict of interest None. No information about funding.	4 RoB: 12/20

							penile morphology through a single-stage surgery.		
Kibar, 2009 [141]	Retrospective case series 1996-2008 USA <u>Mean follow-up:</u> Bladder exstrophy: 58.2 mo Isolated epispadias: 58.6 mo	To present our long-term results with complete penile disassembly for epispadias repair.	n=21 patients • bladder exstrophy (n=12) • isolated epispadies (n=9; 1 penopubic epispadias, 2 midshaft epispadias, 6 distal epispadias) <u>Reconstruction age</u> Bladder exstrophy: 1 day-17 mo Isolated epispadias: 2 mo-7 y	Mitchell technique		**Reconstruction age** Isolated epispadias: 2 mo-7 y **Continence** (4 distal epispadias, 2 midshaft epispadias) • 2/6 required bladder neck injection to achieve maximal continence • 6/6 were continent • 0/6 required clean intermittent catheterization • 0/6 required open reconstruction of the urinary tract such as augmentation, bladder neck reconstruction, or a catheterizable stoma	Epispadias reconstruction using the Mitchell repair can achieve total or near complete urinary continence, decreasing the morbidity of multiple procedures, and potentially allowing children to achieve continence at an earlier age.	unclear how continence status and cosmetic results was measured, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 13/20
Cheikhelard, 2009 [132]	Retrospective cohort study 1997-2007 France <u>Mean follow-up</u> Young-Dees: 8 y (2.5-13 y) Vulvoplasty: 2.5 y (1-3 y)	We compared the functional results of 1-stage perineal urethrocervico-plasty and vulvoplasty vs the classic Young-Dees procedure for incontinent female epispadias.	n=14 patients with female epispadias	Young-Dees procedure n=7	1-stage urethrocervicoplasty with vulvoplasty through a perineal subsymphyseal approach n=7	**Median age** Young-Dees: 6 y (3-13 y) Vulvoplasty: 4 y (1.5-11 y) **Daytime continence** Young-Dees: 87.5% Vulvoplasty: 85% p=1	Reconstructing the bladder neck and urethra via a perineal approach for female epispadias is promising. Surgery may be performed earlier with similar continence	historical control group (young-dees: 1996-2004; vulvoplasty since 2005), groups were comparable except for age at procedure, different follow-up times, missing follow-up data (e. g.	4 RoB: 5/9

						Postoperative bladder capacity Young-Dees (n=5): 150 ml (110-400) Vulvoplasty (n=2): 175 ml (150-200) p=0.05	results, less postoperative morbidity and less need for addi-tional surgery.	postoperative bladder capacity) No information about funding and conflict of interest.	
Braga, 2008 [115]	Retrospective cohort study 1994-2005 Canada <u>Mean follow-up</u> Mitchell-Bagli: 70 mo (10-120 mo) Cantwell-Ransley: 80 mo (21-144 mo)	We review our results with isolated male epispadias repair, comparing the Cantwell-Ransley and Mitchell-Bagli procedures in regard to continence status and postoperative complications.	n=33 male patients with isolated epispadias • glanular (n=3) • penile (n=9) • phenopubic (n=21)	Mitchell-Bagli operation n= 7 penopubic epispadias	Cantwell-Ransley operation n=14 with penopubic epispadias	**Phenopubic epispadias** <u>Mean age at epispadias repair</u> • Mitchell-Bagli: 19.3 mo (9-42 mo) • Cantwell-Ransley: 16.8 mo (12-24 mo) followed by bladder neck procedere at age 2.5-7 y <u>Continence</u> 7 patients also had nighttime continence, and no patient was dry for less than 2 hours or consistently wet. • Completely Dry/Dry More Than 4 Hrs Mitchell-Bagli: 5/6 (83%) Cantwell-Ransley: 8/11 (73%) • Dry 2–4 Hrs/Stress Incontinence Mitchell-Bagli: 1/6 (17%) Cantwell-Ransley: 3/11 (27%) p=0.91	Similar urinary continence rates can be achieved for male penopubic epispadias with both surgical techniques, at the expense of more bladder neck repairs following the Cantwell-Ransley procedure.	less information to patient characteristics, it remains unclear if the two cohorts are comparable, continence status was ascertained by patient or family report, unclear why some data were not included in the analysis No information about conflict of interest and funding. *no information about age of glanular and penile epispadias repair*	3 RoB: 5/9

Mollard, 1998 [146]	Case series 1971 – 1993 France Mean follow-up: 8 y (1-20 y)	We evaluate the long-term results of surgery for isolated (without exstrophy) male epispadias.	n=45 male patients with isolated epispadias • n=14 with posterior epispadias with complete urinary incontinence • n=27 with penile epispadias without incontinence • n=4 with glanular epispadias (1/4 with an intact foreskin)	Young-Dees-Leadbetter bladder neck reconstruction n=14 incontinent epispadias patients		**Age** • 11/14 underwent surgery between the age of 4 and 5 y • 3/14 were referred to the study hospital after surgery failed and were operated at the age of 15, 16 and 26 y **Continence** • 84 % (11/13) of the patients are continent • 1 patient is incontinent • 1 underwent a recent reoperation	Our results of surgery for incontinence associated with isolated male epispadias (84%) were better than for male exstrophy (63%).	unclear if the design is retrospective or prospective, no statistical analysis was performed, outcome measurement was not clearly described No information about conflict of interest and funding.	4 RoB: 14/20
Arap, 1988 [105]	Retrospective cohort study 1967-1984 Brazil Mean follow up 62 mo (5 mo-18 y)	We present our personal experience with 38 cases of incontinent epispadias in which we used 3 basic techniques of bladder neck reconstruction with the anterior bladder wall or trigonal flap tubularization.	n=38 children with incontinent epispadias • penopubic or complete epispadias (n=35) • transitional forms between bladder exstrophy and epispadias (n=3) Male: 28/38	BNR techniques used • Tanagho (n=8) • Leadbetter (n=20) • Young-Dees (n=8)		**Patient age at initial operation** 1-2 y: 5 3-4 y: 15 5-10 y: 14 >10 y: 4 **Continence after BNR** <u>Overall</u> Yes: 22/30 (73.3%) No: 8/30 (26.7%) <u>Tanagho</u> Yes: 5/8 (73%) No: 3/8 (27%) <u>Leadbetter</u> Yes: 12/16 (75%) No: 4/16 (25%)	The results were similar with the 3 techniques.	recruitment of the study group not clearly described, Comparability of cohorts unclear (patient characteristics and length of follow-up), measurement of continence not described No information given about funding and conflict of interests.	3 RoB: 3/9

						<u>Young-Dees</u> Yes: 5/6 (83%) No: 1/6 (17%)		3 patients with transitional forms between bladder exstrophy and epispadias	

Schlüsselfrage Welche Rekonstruktionen sind im Adoleszenten- oder Erwachsenenalter zielführend?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Berrettini, 2021 [129]	Systematic review 1990-2019 Median follow-up after substitution phalloplasty: 43.5 mo (2-135 mo)	To determine whether patients with bladder exstrophy-epispadias complex might benefit from substitution phalloplasty.	n=7 studies • Case report (n=1) • Case series (n=5) • Cross-sectional (n=1) n=47 male patients with BEEC • bladder exstrophy (89.4%) • cloacal exstrophy (10.6%) Age range at surgery: 11-35 y	Substitution Phalloplasty		**Free radial forearm flap** • most commonly: 89% • overall complication rate: 15% **Urethroplasty** • performed in 47% patients • most cases (20/22) a "tube-within-the-tube" technique was performed simultaneously with the phalloplasty (20/47) • overall complication rate: 54% **Penile prosthesis** • performed in 68% patients • overall complication rate: 25% Aesthetic, sexual, and psychological outcomes were satisfactory (no use of validated instruments for assessment)	Substitution phalloplasty in patients with bladder exstrophy-epispadias complex can achieve good functional, aesthetic, psychological, and sexual outcomes. It requires multiple procedures and carries a high complication rate.	No additional hand search, no information if efforts were made to minimise errors in the study selection, data collection and risk of bias assessment The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. The authors received no specific funding for this work. Studie aus SR-Suche inkludiert	4 RoB: high
Kiran, 2020 [147]	Retrospective cohort study 2000-2020	To report our single center experience in the management of untreated adult	n=26 patients with classic	Continent catheterizable pouch n=18	Noncontinent diversion n=4 (Ileal conduit)	**Outcomes** • Continent catheterizable pouch:	The various pouches extend the surgical options. Ileal	Comparability of cohorts unclear, self-reported continence	3 RoB: 6/9

	India Mean follow-up: 6-6.5 y	classical bladder exstrophy.	bladder exstrophy Male: 19/26 (76%) Mean age: 25 y (18-46 y)	• Penn pouch (n=9) • Indiana pouch (n=5) • Modified Kock pouch (n=1) • Abol-Enein pouch (n=3)	Complete primary repair n=3	All patients are continent. • Noncontinent diversion: All patients doing well and reported fully satisfied with the surgery. • Complete primary repair: All patients are continent and voiding spontaneously. **Mean operative time** • Continent catheterizable pouch: 360 min • Noncontinent diversion: 210 min • Complete primary repair: 240 min **Average hospital stay** • Continent catheterizable pouch: 14 days • Noncontinent diversion: 5 days • Complete primary repair: 10 days **Complications** • Continent catheterizable pouch: Abdominal wall flap necrosis, Surgical site infection, Left ureteroneocystos-tomy • Noncontinent diversion: -	conduit may be a simple alternative to complex reconstructions in unmotivated patients with poor access to the hospital.	status and non-validated rating scale for satisfaction The authors declare that they have no relevant financial interests No information about funding.	

						• Complete primary repair: Urge incontinence None of the patients required osteotomy.			
Baird, 2005 [148]	Retrospective cohort study USA Mean follow-up: 72 mo (6-259 mo)	This paper examines the indications for and methods of definitive reconstruction in 25 patients who entered adolescence or early adulthood with persistent urinary incontinence, and also reports on the complications encountered.	n=25 BEEC patients • bladder exstrophy (n=19) • cloacal exstrophy (n=4) • epispadias (n=2) Male: 20/25 Mean age: 12.9 y (10-19 y)	• Augmentation and Continent Stoma (n=18) • Bladder Neck Closure (n=5) • Continent Neobladder (n=1) • Mainz II Pouch (n=1)		**Continence** All 25 patients were fully continent of urine (and also of feces in the patient with a Mainz II pouch) at the last follow-up visit. **Complications** Overall: 9/25 • 3 required stoma revisions for stenosis • 1 required stoma revision for prolapse. • 4 occurred pouch stones • 1 developed vesicocutaneous fistula	Some children with exstrophy/epispadias reach adolescence and remain incontinent. For these patients, modern reconstructive techniques provide hope of continence. With careful preoperative assessment, exact surgical precision, and regular follow-up, a successful outcome can be expected in virtually all cases without the need for external urine collection devices.	Comparability of cohorts unclear, unclear how the continence status was determined no information about conflict of interest or funding.	3 RoB: 6/9

Schlüsselfrage Unterscheidet sich das diagnostische und therapeutische Vorgehen bei den Ekstrophievarianten im Vergleich zur klassischen Ekstrophie?								
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Endpunkt/ Intervention**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Ramji, 2021 [149]	Case reports India	This case series describes a group of 4 unique exstrophy variant cases who had an intact phallus, but a completely open bladder plate.	n=4 male patients Age: 3 mo to 8 y	exstrophy repair and concomitant umbilicoplasty	**Case 1** (8 y) • no history of prior repair • bladder was closed • perineal urethrostomy was created • after surgery: dry-intervals of more than 3 hours **Case 2** (1.5 y) • bladder closure without bladder neck reconstruction • after surgery: voiding via urethra with a strong stream without vesicoureteral reflux or hydronephrosis, not yet toilet-trained **Case 3** (14 mo) • failed bladder closure at 8th day of life • right kidney: severe hydroureteronephrosis (nephrecotomy) • left: ureteral reimplantation concurrently with bladder closure and bladder neck tapering • after surgery with 3.2 y: dribbeling, dry intervals of less than 1 h, wide bladder neck, low bladder capacity, no vesicoureteral	We believe that a detailed assessment of bladder neck prior to reconstructive repair and bladder closure would be beneficial in these cases as the extent of bladder neck involvement would affect reconstructive approach.	patient recruitment not clearly described, no statistical analysis performed No conflict of interest declared. No information about funding.	4 RoB: 13/20

					reflux, left side: hydroureteronephrosis **Case 4** (3 mo) • primary bladder closure with bladder neck tapering • after surgery with 4.3: leaking, no dry intervals, patulous bladder neck with normal bladder capacity, no hydroureteronephrosis, grade II vesicoureteral reflux (right side) None of these repairs were complicated by dehiscence or fistula after bladder closure.			
Maruf, 2019 [150]	Retrospective case series USA 1975-2018	To investigate the diagnosis, surgical management, and outcomes in patients with variant exstrophy-epispadias complex. Variant presentations of the exstrophy-epispadias complex span a wide range of abnormalities.	n=44 patients with exstrophy-epispadias complex Male: 27/44	**Therapy** • Closure • Osteotomy	**Skin-covered** (n=19) • Closure: 17/19 (89%) • Age at closure: 112 days (1-921 days) • Pelvic Osteotomy: 11/17 (65%) • Successful primary closure: 15/17 (88%) • procedure for urinary continence: 7/19 • bladder neck reconstruction: 2/19 • bladder neck transections: 5/19 • continent without continence procedure: 3/19 **Duplicate exstrophy (anterior-posterior)** (n=3), • Closure: 3/3 (100%)	Variants of bladder exstrophy are rare. Proper and early recognition of these infrequent presentations if crucial for appropriate management. Surgical repair is often successful and urinary continence can be achieved in many without a continence procedure. Still, assessments of bladder quality, growth and dry intervals are necessary as some bladder exstrophy variants will require an outlet procedure and/or augmentation to be dry.	only one statistical analysis performed The authors declare that they have no relevant financial interests. No information about funding.	LoE: 4 RoB: 16/20

					• Age at closure: 23 days (1-246 days) • Pelvic Osteotomy: 2/3 (67%) • Successful primary closure: 3/3 (100%) • bladder neck reconstruction: 2/3 • continent without continence procedure: 1/3 **Duplicate bladder** (side-side) (n=2) • Closure: 0 • Age at closure: 0 • Pelvic Osteotomy: 2/2 (50%) • Successful primary closure: 0 • continent without continence procedure: 2/2 **Superior vesical fissure** (n=6) • Closure: 6/6 (100%) • Age at closure: 1 days (1-7 days) • Pelvic Osteotomy: 2/6 (17%) • Successful primary closure: 6/6 (100%) • Bladder neck reconstruction: 2/6 (1 awaiting) • Dry: 5/6 (4 void spontaneously per urethra, 1 voids via stomal catheterization) **Epispadias with bladder prolapse** (n=14) • Closure: 8/14 (87%)			

					• Age at closure: 287 days (169-2010 days) • Pelvic Osteotomy: 7/8 (88%) • Successful primary closure: 8/8 (100%) • Bladder neck reconstruction: 3/14 (2 of them are continent) • bladder neck transections, augmentation cystoplasty, continent urinary diversion with appendicovesicostomy : 4/14 continent per stomal catheterization significant delay in median age of bladder repair in patients with epispadias and bladder prolapse when compared to the other variant subtypes (287 vs 23 days; P = 0.014)			
Lowentritt, 2005 [151]	Retrospective case series USA Follow-up: 1 mo-39 y	Patients with variants of classic epispadias or bladder or cloacal exstrophy were identified. Anatomical presentation, surgical management, type of continence procedures and final outcome were evaluated.	n=25 patients with clinically significant exstrophy variants Male: 15/25 (60%) Time until primary bladder closure ranged from 1 day to 4 years.	**Therapy** • Osteotomy • Bladder neck reconstruction • Urinary diversion	**Epispadias with prolapse** (n=7) <u>Osteotomy</u> • 2/7 osteotomy performed • 5/7 no osteotomy performed <u>Bladder neck reconstruction</u> • 4/7 bladder neck reconstruction performed • 2/7 not yet • 1/7 no bladder neck reconstruction performed	The initial presentation of exstrophy variants can be confusing, often delaying initial treatment. Superior vesical fistulas permit continence without bladder neck reconstruction due to an intact urinary sphincter. Variants such as epispadias with bladder prolapse and duplicate or skin covered exstrophy should be closed at birth with standardized techniques to promote bladder growth for later bladder neck reconstruction. These	patient age not reported, no statistical analysis performed No information about funding and conflict of interest.	4 RoB: 13/20

					Urinary diversion • 3/7 none urinary diversion • Sigmoid augmentation with continent appendicovesicostomy (n=1) • Mitrofanoff and augmentation (n=2) • Continent ileal stoma, ileal augmentation (n=1) Urinary continence • 4/7 continent • 2 to young for bladder neck reconstruction • 1 dry day/wet night **Superior vesicle fistula** (n=3) Osteotomy • 3/3 no osteotomy performed Bladder neck reconstruction • 3/3 no bladder neck reconstruction performed Urinary diversion • 3/3 none urinary diversion Urinary continence • 3/3 continent **Duplicate exstrophy** (n=1) Osteotomy • osteotomy performed Bladder neck reconstruction	cases are faced with the same long-term problems as the classic presentation. Cloacal variants can present with intact anal innervation, allowing a later Pena procedure.		

					• bladder neck reconstruction performed <u>Urinary diversion</u> • none urinary diversion <u>Urinary continence</u> • dry day/wet night **Covered exstrophy** (n=3) <u>Osteotomy</u> • 1/3 osteotomy performed • 2/3 no osteotomy performed <u>Bladder neck reconstruction</u> • 1/3 bladder neck reconstruction performed • 2/3 not yet <u>Urinary diversion</u> • 3/3 none urinary diversion <u>Urinary continence</u> • 2/3 to young for bladder neck reconstruction • 1/3 loss to follow-up **Covered exstrophy with sequestered bowel** (n=3) <u>Osteotomy</u> • 3/3 osteotomy performed <u>Bladder neck reconstruction</u>			

					• 3/3 bladder neck reconstruction performed <u>Urinary diversion</u> • 1/3 Mitrofanoff and ileal augmentation <u>Urinary continence</u> • 1/3 continent • 1/3 incontinent • 1/3 social dry/wet night **Duplicate bladder** (n=1) <u>Osteotomy</u> • No osteotomy performed <u>Bladder neck reconstruction</u> • No bladder neck reconstruction performed <u>Urinary diversion</u> • none urinary diversion <u>Urinary continence</u> • continent **Covered cloacal exstrophy** (n=6) <u>Osteotomy</u> • 4/6 osteotomy performed • 2/6 no osteotomy performed <u>Bladder neck reconstruction</u>			

					• 2/6 bladder neck reconstruction performed • 3/6 not yet • 1/6 no bladder neck reconstruction performed <u>Urinary diversion</u> • 1/6 Augmentation with ectopic bowel, Mitrofanoff • 1/6 Ileal augmentation <u>Urinary continence</u> • 3/6 to young for bladder neck reconstruction • 2/3 continent • 1/3 incontinent			
Turner, 1980 [152]	Retrospective case series United Kingdom	This article concerns an even rarer anomaly, in which the usual muculoskeletal findings of exstrophy were present but the bladder was covered with skin and the urethra was intact.	n=14 cases of split symphysis • solitary bladder (n=11) • vesical duplication (n=3) Male: 4/14	• Diagnosis • Therapy	Diagnosis: • excretory urogram • voiding cystogram Therapy: <u>Yound Dees</u> • 2 male single bladder patients • continent: 2/2 <u>Young Dees Leadbetter</u> • 2 male single bladder patients • 4 female single bladder patients • continent: 6/6 <u>Fistula closure</u> • 1 male single bladder patients • continent: 1/1 <u>Cystocystostomy</u> • 1 female double bladder patient	If a single bladder with good or moderate capacity is present, the patient has an excellent prognosis for continence regardless of sex. A guarded prognosis in patients with bladder duplication is suggested insofar as renal damage is concerned, but continence seems to be a reasonable expectation. The risk of reflux with exstrophic variants, reinforced by the damage patterns we noted, suggest that kidneys of affected patients are significant risk and that early antibiotic coverage and antireflux management seem to be indicated.	patient age not reported, unclear how continent status was defined and measured, loss-to-follow-ups or missing data (Fig 8) not explained, no statistical analysis performed No information about funding and conflict of interest.	4 RoB: 8/20

					• continent: 1/1 <u>Ureteroneocystostomy</u> • 1 female double bladder patient • continent: 1/1 <u>Diversion</u> • 1 female single bladder patient • 1 female double bladder patient • continent: no information **Overall results** • continent: 9/14 • renal units were found to be normal: 20/28 • bilateral reflux: 5/14 • unilateral reflux: 1/14 • no reflux: 3/14 • no information of reflux incidence: 5/14			
Covered Exstrophy								
Sahoo, 1997 [153]	Case reports	We report the largest series (3 cases) of covered exstrophy along with a detailed review of the literature.	n=3 patients with covered exstrophy Male: 2/3	• Diagnosis • Therapy	**Case 1** Diagnosis: • clinical examination • urography Therapy: • Anal cut-back was done **Case 2** Diagnosis: • clinical examination • plain x-ray • urography Therapy: • Anal cut-back was done	The treatment in covered exstrophy cases is simple with good results, and usually consists of plastic repair of the anterior abdominal wall defect, which is far less complex than repair of classical bladder exstrophy with epispadias.	patient recruitment not described, unclear how continent status was measured, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 10/20

					• After 1 mo: primary reconstruction of the anterior abdominal wall and pubic bone approximation were performed without osteotomies **Case 3** Diagnosis: • clinical examination • urography Therapy: • Herniotomy and orchidopexy on the right side were done electively after 3 weeks. All three cases were continent.			
Duplicate exstrophy								
Rösch, 2003 [154]	Case reports	Während die Blasenekstrophie keine sehr seltene Fehlbildung ist, sind die Variationen der Minimalformen äußerst ungewöhnlich und werden deshalb gelegentlich auch nicht erkannt.	n=2 Patienten mit seltenen Varianten des Ekstrophie-Epispadie-Komplexes Fall 1: 24-jähriger Mann mit Pseudoekstrophie Fall 2: männliches Neugeborenes mit gedoppelter Ekstrophie	• Diagnostik • Therapie	**gedoppelter Ekstrophie** (Fall 2) Diagnostik: • klinische Untersuchung • Sonographie • Auffüllen der Blase mit Kochsalz Therapie: • Das polypöse Gebilde wurde komplett exzidiert • postoperative Verlauf war komplikationslos.	**Gedoppelte Ekstrophie**: Finden sich außer dem oberflächlichen Gewebe keine Anomalien von Blasé und Urethra, so ist die alleinige komplette Exzision des ekstrophen Anteils bei der gedoppelten Ekstrophie ausreichend. Ansonsten kommen je nach Befund die klassischen Rekonstruktionstechniken des epispaden Genitale und ggf. für den Blasenhals zur Anwendung	no clear study aim reported, patient recruitment not described, inclusion and exclusion criteria unclear, no statistical analysis performed No information about funding and conflict of interest.	4 RoB: 8/20

Nielsen, 1980 [155]	Case reports	Two different cases of duplicate exstrophy are presented	n=2 patients with duplicated bladder Case 1: boy, 1 day Case 2: boy, 1 day	• Diagnosis • Therapy	**Case 1** <u>Diagnosis</u> • Examination • Pyelography • Cysto-urethrography <u>Therapy</u> • operation with 2 mo • 2 years after: no complaints, voiding stream was free, continent **Case 2** <u>Diagnosis</u> • Examination • palpation • Pyelography • lapratomy <u>Therapy</u> • first operation: 6 mo • second operation: 18 mo • 6 years later: bladder muscosa with slight secreation, vesicoureteric reflux -> reimplant the ureter and excise the remnant of the bladder • 11 years: symptomefree, continent, intravenous pyelography is normal, scoliosis of the lumbar spine	*no conclusion to diagnosis and therapy*	patient recruitment not described, subjective evaluation of aesthetic endpoints, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 9/20
Arap, 1986 [156]	Case reports	Three cases of duplicate exstrophy are described and the theoretical mechanisms of embryogenesis discussed.	n=3 cases of duplicated exstrophy Male: 2/3 Age: 37 days, 3 mo, 14 mo	• Diagnosis • Therapy	**Case 1** <u>Diagnosis</u> • physical examination • urinalysis • plain abdominal roentgenograms • intravenous pyelogram • cystourethrogram	*no conclusion to diagnosis and therapy*	patient recruitment not described, intervention not clearly described, subjective evaluation cosmetic results,	4 RoB: 10/20

					• cystoscopy Therapy • excision of the exstrophic tissues and an abdominal wall plasty in a vertical linear fashion **Case 2** Diagnosis • physical examination • abdominal roentgenography • intravenous pyelogram • urethrogram Therapy • ablation of the extopic bladder muscosa and, afterwards, abdominoplasty with good cosmetic results • at 3 mo: complete urinary control **Case 3** Diagnosis • physical examination • retrograde cystometrogram • intravenous pyelogram • plain roentgenogram Therapy • surgical exercision of the rudimentary ectopic bladder mucosa • plastic repair of the abdominal wall defect by bilateral groin flaps • postponed: penile reconstruction and		no statistical analysis was performed No information about funding and conflict of interest.	

					surgical treatment of urinary incontinence			
Pseudoexstrophy								
Jhanwar, 2016 [157]	Case reports	This report describes two newborn girls with single perineal opening (cloaca), and pseudoexstrophy in the form of divergent pubic bones and rectus muscles, and a low-set umbilicus	n=2 newborn girls with pseudosxstrophy Case 1: 20 days, 3.1 kg Case 2: preterm 32 weeks, 1.8 kg	Therapy: Congenital Pouch Colon	**Case 1** <u>Diagnosis</u> • Hematological and biochemical parameters • renal function tests • Plain X-ray abdomen • Abdominal ultrasound • Lapratomy <u>Therapy</u> • divided ileostomy was constructed proximal to the colonic pouch • Postoperative recovery was uneventful **Case 2** <u>Diagnosis</u> • Clinical and radiological examination • Ultrasound abdomen • Laparotomy <u>Therapy</u> • Meckel's diverticulum was present just 4-5 cm proximal to the cecum. • The grossly distended pouch was decompressed by a small incision on its anterior surface, which was closed subsequently. • A divided ileostomy was constructed proxi-mal to the pouch and a suprapubic cystostomy	*no conclusion to diagnosis and therapy*	no clear study aim reported, unclear if the design is retrospective or prospective, patient recruitment not described, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 8/20

					per-formed with a No. 10 Fr Foley's catheter. • Postoperative recovery was uneventful			
Rösch, 2003 [154]	Case reports	Während die Blasenekstrophie keine sehr seltene Fehlbildung ist, sind die Variationen der Minimalformen äußerst ungewöhnlich und werden deshalb gelegentlich auch nicht erkannt.	n=2 Patienten mit seltenen Varianten des Ekstrophie-Epispadie-Komplexes Fall 1: 24-jähriger Mann mit Pseudoekstrophie Fall 2: männliches Neugeborenes mit gedoppelter Ekstrophie	• Diagnostik • Therapie	**Pseudoekstrophie** (Fall 1) Diagnostik: • Anamnese (Kontinenz, Miktionsstörungen, Harnwegsinfekte, Operationen) • klinische Untersuchung • Sonographie • Urographie	Die Pseudoekstrophie ist die mildeste Ekstrophievariante und bedarf in den allermeisten Fällen keiner operative Therapie.Die Indikation zur Osteotomie und Symphysenadaptation ist vom Ausmaß des Spaltbeckens abhängig und sollte sehr zurückhaltend gestellt werden. Es ist anzunehmen, dass die Pseudoekstrophie häufiger auftritt, als sie bislang beschrieben wurde, da sie weitgehend unbekannt und meist völlig asymptomatisch ist.	no clear study aim reported, patient recruitment not described, inclusion and exclusion criteria unclear, no statistical analysis performed No information about funding and conflict of interest.	4 RoB: 8/20
Ignatoff, 1971 [158]	Case reports	Two cases of variants of bladder exstrophy are presented and discussed.	n=2 patients with incomplete exstrophy Case 1: 18 mo, girl, vesical fissure Case 2: 1 mo, boy, pseudoexstrophy	• Diagnosis • Therapy	<u>Diagnosis</u> • examination • urine culture • roentgenogram <u>Therapy</u> • herniorrhaphy	As in our other case, recognition of an anomalous complexe is necessary to achieve successful repair of the presenting clinical problems, which in this patient were bilateral inguinal hernias. There have been no cases reported of pseudo-exstrophy and functional impairment of the lower urinary tract.	patient recruitment not described, inclusion and exclusion criteria unclear, no statistical analysis was performed No information about funding and conflict of interest.	4 RoB: 10/20
Vesical fissure								
Ignatoff, 1971	Case reports	Two cases of variants of bladder exstrophy are	n=2 patients with incomplete exstrophy	• Diagnosis • Therapy	<u>Diagnosis</u> • examination • complete blood count	Once this variant of the epispadias-exstrophy complexe is recognized,	patient recruitment not described,	4 RoB:

[158]		presented and discussed.	Case 1: 18 mo, girl, vesical fissure Case 2: 1 mo, boy, pseudoexstrophy		• routine urinalysis • roentgenogram • urography • cystography <u>Therapy</u> • fistula surgically excised • bladder neck defect was closed • after surgery: voiding normal, 22 mo: continent for up to 2 hours	conservative therapy directed at obliterating the fistula generally yields a beneficial long-term result. In this case, as in similar reported cases, the existence of other concomitant features of exstrophy such as pubic diastasis, does not preclude successful closure of the urinary tract resulting in total urinary continence and preservation of renal function.	inclusion and exclusion criteria unclear, no statistical analysis was performed No information about funding and conflict of interest.	10/20

Schlüsselfrage Welche Managementstrategien sind bei postoperativen Komplikationen zielführend?									
Referenz	**Studien-charakteris-tika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schluss-folgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Haffar, 2023 [159]	Cohort study 1974-2020	The authors hypothesize that the addition of external fixation (pelvic immobilization) inpatients with any form of limb immobilization will be associated with improved outcomes.	n=747 classic bladder exstrophy patients <u>Sex</u> Male: 508 (68%) Female: 239 (32%)	• external fixation with no lower limb immobilization (n=33) • external fixation with any form (n=184) • external fixation with spica casting/mummy wrapping (n=42) • spica casting with no external fication (n=148) • no form of immobilization (n=87)		**Failures** <u>Total closures</u> • external fixation with no lower limb immobilization: 11/33 (33.3%) • external fixation with any form: 13/184 (7.1%) • external fixation with spica casting/mummy wrapping: 14/42 (33.3%) • spica casting with no external fication: 81/148 (54.7%) • no form of immobilization: 60/87 (69%) <u>Closure with osteotomy</u> • external fixation with no lower limb immobilization: 10/31 (32.3%) • external fixation with any form: 11/174 (6.3%) • external fixation with spica casting/mummy wrapping: 12/39 (30.8%) • spica casting with no external fication: 30/74 (40.5%)	The results of this study clearly suggest the use of external fixation can be protective against bladder closure failure. The use of pelvic immobilization, in addition to post-operative lower limb immobilization should bestrongly considered	patient characteristics for the immobilization techniques not clearly describes, The authors declare no conflict of interest. The Kwok Family Foundation of Hong Kong supports the exstrophy database and laboratory research *Studie wurde nach dem Suchzeitraum veröffentlicht, aber aufgrund der relevanten Ergebnisse durch die Experten hinzugefügt*	3 7/9

						• no form of immobilization: 10/20 (50%) <u>Closeure without osteotomy</u> • external fixation with no lower limb immobilization: 1/2 (50%) • external fixation with any form: 2/10 (20%) • external fixation with spica casting/mummy wrapping: 2/3 (67%) • spica casting with no external fication: 51/74 (68.9%) • no form of immobilization: 59/67 (74.6%) **Succesful closure** associated with • osteotomy use ($p < 0.0001$) • limb immobilization ($p < 0.0001$) specifically • combined anterior innominate with posterior vertical iliac osteotomy ($p < 0.0001$) • modified Buck's traction with external fixation ($p < 0.0001$) • immobilized with mummy wrap, spica casting, or knee immobilizers, external fixation was associated with 3.76			

						increased odds of successful closure (p = 0.0005, 95% CI 1.79-7.90)			
Morrill, 2023 [72]	Retrospective cohort study 1990-2020	The authors aim to compare single institutional 30-day complication rates between delayed and neonatal closure of classic bladder exstrophy.	n=145 exstrophy-epispadias patients Median age Neonatal: 3 days (2-6 days) delayed: 202 days (111-305) Male Neonatal: 63/95 (66%) delayed: 41/50 (82%)	neonatal closure • n=95	delayed closure n=50	**30-day postoperative complication rate** Any complication neonatal: 46/95 (48.4%) delayed: 29/50 (58%) p=0.298 Complication without transfusation neonatal: 33/95 (34.7%) delayed: 13/50 (26%) p=0.349 Clavien I-II complications neonatal: 40/95 (42.1%) delayed: 27/50 (54%) p=0.292 Clavien III complications neonatal: 7/95 (7.4%) delayed: 1/50 (2%) p=0.263 Clavien IV complications neonatal: 3/95 (3.2%) delayed: 1/50 (2%) p=1	The majority of the complications associated with delayed closure are a low Clavien-Dindo grade and easily managed during the postoperative inpatient hospital stay. Families should be counseled about the possibility of minor, conservatively managed complications and likelihood of a blood transfusion with osteotomy.	cohorts were different regarding the numbers of osteotomy The authors have no financial or personal relationships with other people or organizations that could inappropria-tely influence their work. The Kwok Family Foundation of Hong Kong support the exstrophy database and laboratory research. *Studie wurde nach dem Suchzeitraum veröffentlicht, aber aufgrund der relevanten Ergebnisse durch die Experten hinzugefügt*	3 RoB: 8/9

Ebert, 2020 [82]	Cohort study 2009-2016 Germany	To evaluate the impact of reconstructive strategies and post-operative management on short- and long-term surgical outcome and complications of classical bladder exstrophy patients' comprehensive data of the multicenter German-wide Network for Congenital Uro-Rectal malformations (CURE-Net) were analyzed.	**Prospective cohort** n=34 babies with classical bladder exstrophy Median age: 3 mo (IQR 2-4 mo) Sex Female: 10/34 (29%) Male: 24/34 (71%) **Cross-sectional cohort** n=113 patients with classical bladder exstrophy Median age: 12 y (IQR 6-21 y) Sex Female: 39/113 (35%) Male: 74/113 (65%)	Staged approach • n=23 (prospective cohort) • n=60 (cross-sectional cohort)	Single-stage approach • n=11 (prospective cohort) • n=53 (cross-sectional cohort)	**Operations due to complications** (*Cross-sectional cohort*) Closure of urethral penile fistula • Staged approach yes: 11 (18%) no: 49 (82%) • Single-stage approach yes: 12 (39%) no: 39 (73%) missing data: 2 (4%) p=0.64 Scar correction • Staged approach yes: 17 (28%) no: 43 (72%) • Single-stage approach yes: 10 (19%) no: 39 (73%) missing data: 4 (8%) p=0.38 Vaginal introitus plasty • Staged approach yes: 6 (38%) no: 10 (62%) • Single-stage approach yes: 6 (27%) no: 16 (73%) p=0.73 Hysterectomy • Staged approach yes: 0 no: 16 (100%)	In the cross-sectional, no significant differences occurred in regard to additional surgery between the two operative approaches.	patient characteristics of both groups (staged approach and single-stage approach) are not separately described, no information on the length of follow-up supported by a research Grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations were supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2016), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE 1723/1-1).	3 RoB: 6/9

						• Single-stage approach yes: 0 no: 22 (100%) p=1 <u>Uterine sacropxy</u> • Staged approach yes: 0 no: 16 (100%) • Single-stage approach yes: 1 (5%) no: 21 (95%) p=1 <u>Penile deflexion</u> • Staged approach yes: 22 (58%) no: 14 (37%) missing data: 2 (5%) • Single-stage approach yes: 13 (35%) no: 22 (60%) missing data: 2 (5%) p=0.07 **Inguinal hernia repair** Cross-sectional cohort: 52% • significantly more often done in males (66%) than in females (26%) p<0.0001 • bilateral repair 76% • redo surgery: 4% • Symphysis diastasis (with inguinal hernia vs. no inguinal hernia): p=0.06		http://www.cure-net.de.	

						Prospective cohort: 44% • Performed equally between girls (40%) and boys (46% • bilateral repair: 87% • Symphysis diastasis (with inguinal hernia vs. no inguinal hernia): p=0.76			
James Sam, 2020 [160]	Retrospective cohort study 2001-2019 India Mean follow-up: 53 mo	The aim of this study is to assess the outcome of dehisced exstrophy, using a rectus abdom- inis muscle flap flap assisted redo closure (without pubic bone approximation) with concomitant or subsequent further reconstruction.	n= 55 children who presented with dehisced exstrophy after repair Male: 34/55 <u>Mean age</u> • No augmentation: 12 mo • augmentation: 69 mo	no concominant bladder augmentation n=26	no bladder augmentation n=29	**No augmentation group** • Awaiting bladder augmention/BNS: 16 • dry with voiding: 2 • subsequent bladder augmentation: 8 (7 dry, 1 wet) **Augmentation group** • no BNS: 2 (1 dry, 1 awaiting BNS) • concomitant BNS: 27 (26 dry, 1 wet)	We present a simple and reliable method of repair of dehisced exstrophy using RAM flap with the feasibility of concomitant bladder augmentation. Dryness was achieved with stable upper tracts in 36/39 children, 27 of them with a single reconstructive attempt.	sex not reported for the groups, length of follow-up in the no augmentation group too short (16 patients awaiting further surgery) The authors declare no conflict of interests and funding.	3 RoB: 7/9
Okonkwo, 2019 [84]	Retrospective cohort study 2007-2016 United Kingdom	This review aims to evaluate the efficacy and complication rate associated with continuous caudal epidural analgesia in the management of infants presenting for the delayed primary repair of isolated	n=37 classic bladder exstrophy undergoing delayed primary closure Male: 29/37 <u>Age</u>	early feeding n=18	late feeding n=19	**Overall pain score (day one + day two)** Early: 26 (0-82) Late: 55.5 (0-172) p=0.015 **Day one total pain score** Early: 17.5 (0-67) Late: 31 (0-76) p=0.156 **Day two total pain score**	Early feeding (within the first 12 h) in delayed bladder exstrophy repair is likely to improve patient comfort and consolability without increasing the incidence of	patient recruitment not clearly described, length of follow-up unclear This study was supported by departmental funds. No additional	3 RoB: 7/9

		bladder exstrophy and to discuss the impact of early feeding in patients in this group.	Early: 6.9 mo (2.9-11.0) Late: 5.2 mo (1.5-17.0)			Early: 5.5 (0-50) Late: 15 (0-110) p=0.045 **Complications** <u>Nausea and vomiting</u> Early: 6.3% Late: 20% p=0.06 No ileus, aspiration and re-intubation aspiration in both groups	gastrointestinal complications. Intravenous opioid may be associated with increased postoperative complications that may influence peri-operative outcomes.	external funding was utilized. No conflict of interest declared. *In 2012, we introduced early feeding for patients with caudal epidural catheters.*	
Zaman, 2019 [161]	Retrospective cohort study 1975-2018 USA	This study investigates the success rates of primary and secondary bladder closures based on various immobilization techniques from a high-volume exstrophy center.	n=577 patients with classic bladder • primary closures (n=476 • secondary closures (n=101) <u>Male</u> • Primary closure: 323/476 (67.9%) • Secondary closure: 62/101 (61.4%) <u>Median age at closure</u> • Primary closure: 2 days (1-2893 days) • Repeat closure: 417 days	**Immobilization Technique** <u>Primary closure</u> • Modified Bryant's traction: 169/476 (35.5%) • Modified Buck's traction with external fixation: 100/476 (21%) Spica cast: 139/476 (29.2%) • Mummy wrap: 40/476 (8.45%) • Other: 28/476 (5.9%) <u>Repeat closure</u>		**Successful primary closure** • Overall: 343/476 (72.1%) • Modified Bryant's traction: 134/169 (79.3%) • Modified Buck's traction with external fixation: 95/100 (95%) • Spica cast: 69/139 (49.6%) • Mummy wrap: 23/40 (57.5%) • Other: 22/28 (78.6%) **Successful secondary closure** • Overall: 92/101 (92.1%) • Modified Bryant's traction: 12/16 (75%) • Modified Buck's traction with external fixation: 73/75 (97.3%)	The findings from this study demonstrated that the success rates for primary closures were highest using modified Buck's traction with external fixation and lowest for spica casting. Similarly, for secondary closures, the best outcomes were achieved using Buck's traction and external fixation and the lowest success rates were associated with spica casting.	recruitment of the study group not clearly described, patient characteristics for the immobilization techniques and follow-up not reported Funding: This study had no funding source. Conflicts of interest: The authors declare no conflicts of interest. The Kwok Family Foundation of Hong Kong supported the exstrophy database and laboratory research.	3 RoB: 6/9

			(7-4142 days)	• Modified Bryant's traction: 16/101 (15.8%) • Modified Buck's traction with external fixation: 75/101 (74.3%) • Spica cast: 9/101 (8.9%) Mummy wrap: 1/101 (1%)		• Spica cast: 6/9 (66.7%) • Mummy wrap: 1/1 (100%) **Effect of immobilization (primary closure)** *A propensity score-adjusted logistic regression* Modified Buck's traction vs. spica casting OR= 5.60, 95% CI: 1.74-23.1, p<0.008 Modified Bryant's traction vs. spica casting OR=1.13, 95% CI: 0.60-2.12, p=0.699 **Median length of immobilization** Primary closure • Overall: 30 days, IQR: 28-35 days • Modified Buck's traction: 35.5 days, IQR: 30-42 days • Modified Bryant's traction: 28 days, IQR: 28-30 days Repeat closure • Overall: 42 days, IQR: 41-47 days • Modified Buck's traction: 43 days, IQR: 41-48 days • Modified Bryant's traction: 27.5 days, IQR: 25.8-31.5 days			

						Median length of hospital stay Primary closure • Overall: 36 days, IQR: 32-44.8 days • Modified Buck's traction: 45 days, IQR: 37-47 days • Modified Bryant's traction: 34 days, IQR: 31-36 days Repeat closure • Overall: 45 days, IQR: 43-50 days • Modified Buck's traction: 45 days, IQR: 44-50 days • Modified Bryant's traction: 45 days, IQR: 34.5-55.5 days **Orthopedic complications** Primary closure Overall: Four patients had a total of four complications (2.2%) related to their immobilization Modified Bryant's traction: • Lower extremity nerve palsy (n=1) • Skin breakdown (n=1) Modified Buck's traction with external fixation:			

						• Lower extremity nerve palsy (n=1) • Hip infection (n=1) <u>Repeated closure</u> Overall: four patients had a total of five complications (4.7%) Modified Bryant's traction: • Lower extremity nerve palsy (n=1) • Skin breakdown (n=1) Modified Buck's traction with external fixation: • Lower extremity nerve palsy (n=1) • Pin-site infection (n=1) • Readjustment (n=1)			
Mushtaq, 2014 [162]	Retrospective cohort study 2007-2011 United Kingdom Follow-up: 12-72 mo	We describe a novel approach to neonatal bladder exstrophy closure that challenges the role of postoperative immobilization and pelvic osteotomy.	n=74 patients with primary closure without osteotomy Age at closure: 3 days (1-152 days) Males: 42/74	managed on the ward (n=48)	managed to the intensive care unit (n=26)	**Complications** • ward: 5 (10.4%, 1 bladder rupture, 4 urethral stenosis) • intensive care unit: 3 (11.5%, 1 bladder prolapse, 2 urethral stenosis) p=0.583 **Redo closure** • ward: 2 (4.2%) • intensive care unit: 2 (7.7%) p=0.609 **Median days from closure to full oral feeding** • ward: 3 (2-13) • intensive care unit: 11 (6-27)	Primary closure of bladder exstrophy without lower limb immobilization and osteotomy is feasible. Postoperative care on the surgical ward using epidural analgesia results in shorter hospitalization.	No information about funding and conflict of interest.	3 RoB: 9/9

						p<0.00001 **Median days length of stay** • ward: 11 (6-17) • intensive care unit: 18 (14-41) p<0.00001			
Shnorhavorian, 2010 [163]	Retrospective cohort study since 1998 USA	We hypothesized that spica casting is a safe and effective alternative to Bryant's traction after complete primary repair of exstrophy.	n=39 children with complete primary repair of exstrophy Male: 22/39 <u>Median age at closure</u> • Bryant's: 1 days • Spica: 1 days • Spica+osteotomy: 4 days	Bryant's traction without osteotomy n=13	spica casting without osteotomy n=14 spica casting with osteotomy n=13	**Mean operative time** • Bryant's: 185 min • Spica: 249 min • Spica+osteotomy: 401 min **Mean estimated blood loss** • Bryant's: 33.8 ml • Spica: 53.2 ml • Spica+osteotomy: 67.7 ml **Urinary incontinence** • Bryant's: 12/12 • Spica: 5/7 • Spica+osteotomy: 3/3 p=0.09 **Length of stay** Use of Bryant's traction was associated with double the length of stay (p>0.001). **Complications** No correlation of major complications to the type of immobilization used.	Spica casting compared to Bryant's traction is associated with shorter hospitalization following complete primary repair of exstrophy and does not have a significant difference in the rate of complications. In our longitudinal cohort study with long-term followup spica cast was safe and effective for patients with bladder exstrophy, and should be considered an acceptable method of immobilization.	Median age at closure and male-female ratio in the third group were different regarding the other groups, length of follow-up not reported No information about funding and conflict of interest.	3 RoB: 7/9

Silver, 1997 [164]	Case-control study USA Mean follow-up: 15.3-9.9 y	We sought to determine the incidence of urolithiasis in patients with the exstrophy epispadias complex, associated risk factors and guidelines for the proper clinical management of this problem.	n=530 patients with exstrophy-epispadias complex	patients with exstrophy-epispadias complex and urinary tract stones classic exstrophy n=77	patients without stone episodes n=390	**Risk of stone formation** • associated with augmentation cystoplasty (p <0.001) and a bladder neck procedure to increase • outlet resistance (p <0.001) • Other risk factors included urinary tract infection, foreign bodies, • vesicoureteral reflux and urinary stasis • no risk factors: acidosis or immobilization **Stone removal techniques** • Endoscopic surgery: 32/77; recurrence: 12 (38%) • Open surgery: 27/77; recurrence: 10 (37%) • Endoscopic and open surgery: 2/77 • Extracorporeal shock wave lithotripsy: 4/77; recurrence: 3 (75%) • Stone passed: 7/77; recurrence: 5 (71%) • None: 5	These data suggest that urolithiasis in the exstrophy-epispadias complex is related to risk factors associated with surgical reconstruction of this condition. Standard treatment is effective but stone recurrence remains a significant problem. Urine chemistry data may provide information to help minimize stone development in this patient population.	unclear why only 390 patients without stone episodes were included in the study, comparability of the groups unclear, assessment of outcome was record linkage No information about funding and conflict of interest.	4 RoB: 3/9

Schlüsselfrage

Welchen Einfluss hat die Rekonstruktionstechnik auf den oberen Harntrakt?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolger-ungen des Autors	Methodische Bemerkungen	LoE/ RoB

Jarosz, 2022 [165]	Retrospective cohort study 2013-2019 USA <u>Mean follow-up</u> • BUR-CPRE group: 46.33 mo (SD=10.26) • CPRE group: 53.76 mo (SD=26.05)	We hypothesize that BUR at time of CPRE will decrease the rate of recurrent pyelonephritis, post-operative VUR, and the need for subsequent ureteral surgery.	n=64 patients with classic bladder exstrophy <u>Mean Age</u> • BUR-CPRE group: 3.2 mo (SD=2.01) • CPRE group: 2.12 mo (SD=1.71) <u>Male</u> • BUR-CPRE group: 10/15 (66.6%) • CPRE group: 29/49 (59.2%)	cephalotrigonal BUR-CPRE n=15	CPRE alone n=49	**Post-Operative Outcomes** <u>Recurrent pyelonephritis</u> • BUR-CPRE: 3/15 (20%) • CPRE: 17/47 (36.2%) p=0.346 <u>Post-operative VUR</u> • BUR-CPRE: 6/15 (40%) • CPRE: 39/47 (83%) p=0.002 <u>Dilating Reflux</u> • BUR-CPRE: 2/14 (14.3%) • CPRE: 14/45 (31.1%) p=0.310 <u>Subsequent Ureteral Surgery due to persistent VUR and associated recurrent pyelonephritis</u> • BUR-CPRE: 1 (6.7%) • CPRE: 17 (34.7%) p=0.048 <u>Gender and recurrent pyelonephritis</u> Female gender was found to be a significant independent predictor of recurrent pyelonephritis irrespective of BUR status (p=0.005) **Sub-analysis** <u>Refluxing Renal Units</u> *mean (SD)*	BUR-CPRE reduces the incidence of VUR, the number of refluxing renal units, and the need for subsequent ureteral surgery. With BUR-CPRE there is a trend toward reduction in recurrent febrile urinary tract infections and dilating reflux. The reduction in recurrent pyelonephritis was most notable among male bladder exstrophy patients in our cohort. Surgeons should consider BUR-CPRE, when technically feasible, to decrease the adverse outcomes associated with recurrent pyelonephritis.	*Patient selection was based on surgeon judgement that the procedure was technically feasible and that the benefits of the additional procedure outweighed the risks on an individual patient basis.* Funding: This study had no funding source. Conflicts of interest: The authors declare no conflicts of interest.	3 RoB: 8/9

						• BUR-CPRE: 0.6 (0.83) • CPRE: 1.5 (0.77) p=0.001			
Ramji, 2021 [166]	Retrospective cohort study 2009-2019 Median follow-up: 4.4 y (IQR 2.4-6.4 y)	We aimed to determine the impact of BUR-CPRE on reflux rates, renogram findings and bladder capacity.	n=147 patients with BEEC Median age: 1.1 y (IQR 0.6-1.9 y) Male: 37/52 Median age at closure: 1.1 y (IQR 0.6-1.9 y)	BUR at the time of CPRE n=20	No BUR at time of CPRE n=28	**Any VUR present** • BUR: 9 (45%) • No BUR: 23 (82%) p=0.007 **Bilateral VUR** • BUR: 4 (20%) • No BUR: 19 (68%) p=0.004 **High-grade VUR (grad 4 or 5)** • BUR: 2 (10%) • No BUR: 11 (44%) p= 0.016	BUR-CPRE decreases the incidence and severity of VUR after CPRE, but the clinical significance of this remains unclear.	recruitment process not clearly described (e. g. location) There are no conflicts of interest and funding.	3 RoB: 7/8
Bueno-Jimenez, 2020 [75]	Retrospective cohort study 2001-2018 Spain <u>Mean follow-up</u> early: 9 y delayed: 1 y	To analyze short-term results in male patients with bladder exstrophy undergoing delayed primary closure and compare them with early bladder closure as part of staged repair in our healthcare facility.	n=19 male patients BEEC Patients with malformations such as cloacal exstrophy or exstrophy variants were excluded. <u>Mean age</u> early: 25 h delayed: 58 days	early bladder closure (n=13)	delayed bladder closure (n=6)	**Closure success** early: 11/13 (85%) delayed: 6/6 (100%) **Complications** <u>Transient hydronephrosis (< 6 m)</u> early: 3/13 (23%) delayed: 2/6 (33%) <u>Maintained hydronephrosis (> 6 m)</u> early: 1/13 (8%) delayed: 1/6 (17%) <u>Repetition urinary tract infections</u> early: 5/13 (38%) delayed: 3/6 (50%)	Delayed primary reconstruction is safe as it allows for closure success without increasing complications as compared to staged repair.	small number of patients and a long-term follow-up period, especially in delayed closure patients No information about funding and conflict of interest.	3 RoB: 8/9
Ebert, 2020 [82]	Cohort study 2009-2016	To evaluate the impact of reconstructive strategies and	**<u>Prospective cohort</u>** n=34 babies with classical	Staged approach	Single-stage approach	**Complications** **Renal deterioration after reconstruction** <u>Prospective cohort</u>	While single-stage approaches tended to have	patient characteristics of both groups (staged	3 RoB: 6/9

	Germany	post-operative management on short- and long-term surgical outcome and complications of classical bladder exstrophy patients' comprehensive data of the multicenter German-wide Network for Congenital Uro-Rectal malformations (CURE-Net) were analyzed.	bladder exstrophy Median age: 3 mo (IQR 2-4 mo) Sex Female: 10/34 (29%) Male: 24/34 (71%) **Cross-sectional cohort** n=113 patients with classical bladder exstrophy Median age: 12 y (IQR 6-21 y) Sex Female: 39/113 (35%) Male: 74/113 (65%)	• n=23 (prospective cohort) • n=60 (cross-sectional cohort)	• n=11 (prospective cohort) • n=53 (cross-sectional cohort)	• Staged approach (n=23) yes: 0 no: 21 (91%) missing data: 2 (9%) • Single-stage approach (n=11) yes: 0 no: 10 (91%) missing data p=1 Cross-sectional cohort • Staged approach (n=60) yes: 2 (3%) no: 28 (47%) missing data: 30 (50%) • Single-stage approach (n=53) yes: 4 (7%) no: 37 (70%) missing data: 12 (23%) p=0.42 **Unilateral nephrectomy** Prospective cohort • Staged approach (n=23) yes: 2 (9%) no: 21 (91%) • Single-stage approach (n=11) yes: 0 no: 10 (91%) missing data: 1 (9%) p=1 Cross-sectional cohort	initially more complications such as renal dilatation or urinary tract infections, additional surgery such as augmentations and stomata appeared to be similar after staged and single-stage reconstructions in the long term..	approach and single-stage approach) are not separately described, no information on the length of follow-up supported by a research Grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations were supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2016), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE 1723/1-1). http://www.cure-net.de.	

						• Staged approach (n=60) yes: 2 (3%) no: 58 (97%) • Single-stage approach (n=53) yes: 0 no: 49 (93%) missing data: 4 (7%) p=0.5			
Ellison, 2017 [167]	Retrospective cohort study 1990-2017 USA Median follow-up: 9.7 y (3.9-22.3 y)	We sought to assess our long-term experience with CPRE and investigate factors that may influence upper-tract deterioration.	n=30 patients with classic bladder exstrophy Male: 17/30 Age at CPRE: • reimplant: 4.1 (SD 11.9) days • no reimplant: 2.6 (SD 2.6) days	<u>First comparison:</u> ureteral reimplant n=22 <u>Second comparison:</u> bladder neck reconstruction n=15	<u>First comparison:</u> no ureteral reimplant n=8 <u>Second comparison:</u> no bladder neck reconstruction n=15	**Ureteral reimplant** <u>Creatinine, mg/dL</u> • reimplant: 0.51 (0.2-1.0) • no reimplant: 0.40 (0.3-0.7) p=0.36 <u>eGFR, mL/min/1.73 m2</u> • reimplant: 105 (73-159) • no reimplant: 112 (87-131) p=0.68 <u>Hydronephrosis</u> • reimplant: 12 (55%) • no reimplant: 4 (50%) p=0.83 No significant differences between The Society of Fetal Urology grades, Upper Tract Dilation grades and the renal length. **Bladder neck reconstruction** <u>Creatinine, mg/dL</u>	<u>Ureteral reimplant</u> Ureteral reimplantation and the status of the lower urinary tract were not associated with differences in upper-tract outcomes. <u>Bladder neck reconstruction</u> Neither continence status nor bladder neck reconstruction was associated with differences in measurable renal function	age only reported for the ureteral reimplant groups, continence status measurement not clearly described There are no conflicts of interest and funding.	3 RoB: 7/9

						• bladder neck reconstruction: 0.41 (0.3-1.0) • no bladder neck reconstruction: 0.55 (0.2-0.6) p=0.08 <u>eGFR, mL/min/1.73 m2</u> • bladder neck reconstruction: 110 (74-159) • no bladder neck reconstruction: 105 (87-132) p=0.7 <u>Hydronephrosis</u> • bladder neck reconstruction: 7 (47%) • no bladder neck reconstruction: 9 (60%) p=0.71 No significant differences between The Society of Fetal Urology grades and the renal length.			
Hanna, 2017 [109]	Retrospective cohort study 1981-2014 USA	We review our experience with various strategies for management of urinary incontinence and their outcome in 61 patients born with bladder exstrophy who failed their initial repairs.	n=61 incontinent bladder exstrophy patients Age: 3-18 y	• Reclosure and iliac osteotomy (n=5) • Mainz II pouch (n=16) • Bladder augmentation (n=31)		**Bladder augmentation** <u>Morbidity</u> • Kidney stones: 4/31 **Bladder substitutions** • Kidney stones: 1/10	*no conclusion for the upper urinary tract*	patient recruitment not clearly described, comparability of cohorts unclear (patient characteristics and length of follow-up), measurement of	3 RoB: 4/9

				• Bladder substitution (n=10)				continence not described The authors declare no conflicts of interest and funding.	
Kajbafzadeh, 2017 [107]	Retrospective cohort study 2009-2012 Iran Mean follow-up: 72 mo (SD=±6 mo)	The objective of this study is to describe a new surgical technique for obtaining eventual urinary continence at a urology center of excellence with over 20 years of experience in the reconstruction of BEEC.	n=16 female patients with BEEC Mean age: 3.48 y (SD=±1.75 y)	Single-stage bladder closure without osteotomy (group 1) n=9	UUE without osteotomy (group 2) n=7	**VUR** • Group 1: 0/9 (0%) • Group 2: 3/7 (42.85%) VUR was successfully managed by Deflux injection. All patients in both groups experienced an uneventful postoperative period.	The eventual clinical outcomes of BEEC children undergoing the UUE technique were promising. This practicable, safe, and reproducible option will add one complementary stage to the previously used reconstruction techniques.	unclear who measures the continence The authors declare no conflicts of interest and funding.	3 RoB: 8/9
Alsowayan, 2016 [100]	Retrospective cohort study 1990-2014 Saudi Arabia Mean follow-up time: 18±5 y	We present the long-term treatment outcomes of classic bladder exstrophy patients over 24 years in a low exstrophy-volume centre.	n=16 patients with bladder exstropy Male: 7/16	CPRE n=10	MSRE n=6	no significant differences between the groups in dehiscence, fistula, urinary tract infections, bladder neck injection, bladder neck reconstruction + bilateral ureteric reimplantation, augmentation cystoplasty, clean intermittent catheterization, urethral voiding, anticholenergics, Hydronephrosis and uroflow	*no conclusion for the upper urinary tract*	age not reported The authors declare no competing financial or personal interests. No information about funding	3 RoB: 8/9

Tourchi, 2015 [168]	Retrospective cohort study USA Median follow-up: 8.94 y (2-22.66 y)	This study evaluates a single referral center's experience in exstrophy epispadias complex patients who underwent MSRE and pre-BNR management of VUR.	n=199 patients with exstrophy epispadias complex Median age at time of closure: 3 mo (0-72 mo)	osteotomy n=126	no osteotomy n=73	**VUR grade** *(multivariate analysis)* History of osteotomy: OR 0.3 (CI 0.12-0.74) p=0.009 Osteotomy was the protective factor against high-grade VUR. Reasons for ureteral reimplantation (n=22, 11%): • pyelonephritis (n=5; 21.7%) • recurrent UTI (n=12; 52.2%) • worsening hydronephrosis (n=2; 8.7%) • deterioration of renal function (n=4; 17.4%)	Closure without osteotomy and patients who develop outlet obstruction after closure are at increased risk for developing high-grade VUR.	Patient recruitment not clearly described, patient characteristics not clearly described (e.g. number of male/ female), comparability of cohorts unclear (patient characteristics and length of follow-up), loss to follow-up not reported The authors declare that they have no relevant financial interests. No information about funding.	3 RoB: 4/9
Ferrara, 2014 [78]	Retrospective cohort study 2000-2012 United Kingdom	This study aims to define the consequence of delayed exstrophy repair on bladder growth in bladder exstrophy patients who underwent routine delayed exstrophy repair, compared with those who underwent immediate postnatal reconstruction.	n=45 patients with bladder exstrophy Male: 25/45 <u>Mean age at cystogram</u> neonatal: 21.9 (9.1) mo delayed: 20 (8.3) mo	neonatal bladder closure n=21	elective delayed exstrophy repair n=24	**VUR** (1 y) neonatal: 10/21 delayed: 5/21	Bladder exstrophy patients who underwent a delay bladder closure showed similar cystographic capacities at the age of 1 year compared with those who underwent neonatal bladder closure.	historical control group (neonatal closure: 2000-2005 vs. delayed: 2006-2012), relatively short follow-up The authors have no conflict of interest declared. No funding received.	4 RoB: 7/9

Kajbafzadeh, 2014 [91]	Retrospective cohort study 1995-2010 Iran <u>Mean follow-up</u> • SUPER and UAAC group: 28.16 mo (SD=± 18.42 mo) • Simple polyp excision group: 37.18 mo (SD=± 21.53 mo)	The purpose of this study was to represent our experience of an academic referral center for complex BEEC patients with several bladder polyps in the setting of small bladder plate surface who underwent this new technique by the name of sub-urothelial polyp enucleation resection and urothelial auto-augmentation cystoplasty.	n=28 patients with BEEC and small bladder plate in the setting of bladder polyposis <u>Male</u> • SUPER and UAAC group: 8/12 (75%) • Simple polyp excision group: 10/16 (62.5%) <u>Mean age</u> • SUPER and UAAC group: 3.50 y (SD=± 2.06 y) • Simple polyp excision group: 3.25 y (SD=± 1.80 y)	SUPER and UAAC technique, and subsequent bladder closure n=12	Total polyp excision along with urothelial covering n=16	**Complications** • All children had an uneventful postoperative period with no major complications or bladder dehiscence • No wound infection, bladder dehiscence or prolapse <u>SUPER and UAAC</u> • 2/12 with urethra–cutaneous/vesico-cutaneous fistula • 10/12 (83.3%) with preserved upper tracts • 2/12 (16.7%) with mild changes in upper tracts • 3/12 had low-grade bilateral VUR • 2/16 had unilateral VUR • 1/12 had high-grade bilateral reflux <u>Simple polyp excision group</u> • 8/16 (50%) with preserved upper tracts • 8/16 (50%) with mild changes in upper tracts • 6/16 had low-grade bilateral VUR • 3/16 had unilateral VUR • 3/16 had high-grade bilateral reflux	Postoperative follow-up revealed that the outcomes were more promising in those patients who underwent reconstruction with this new technique. As an obvious consequence of satisfactory bladder dynamic and capacity, hydronephrosis was less prevalent in this group with milder upper tract changes.	self-reported continence status *Several factors such as multiple polyps covered small bladder plate, contracted bladder or the lesions engaged 80 % of bladder mucosa was considered as poor bladder plate. These patients were selected for SUPER and UAAC technique.* No conflict of interest exists in relation to the submitted manuscript and there was no source of extra-institutional commercial funding or funding received from National Institutes of Health, Welcome Trust, Howard Hughes Medical Institute and others.	3 RoB. 6/9
Schaeffer, 2013	Case-control study	To compare the eGFR in bladder exstrophy	n=57 exstrophy patients	glomerular filtration rate	glomerular filtration rate	**Primary Closure** *mean eGFR (SD) (ml/min/1.73 m2)*	The staged reconstruction of exstrophy	normative values are guideline based,	4

[169]	USA <u>Mean follow-up after BNR</u> Males (n=21): 9.3 (1.6–20.9) y. Females (n=6): 11.3 (1.6–23.5) y	patients with published normative GFR estimates.	Male: 43/57	of exstrophy patients	of normative values	<u>0-7 days (n=20)</u> Exstrophy: 42.5 (14.5) Population: 40.6 (14.8) p=0.55 <u>8-56 days (n=20)</u> Exstrophy: 44.8 (12.0) Population: 65.8 (24.8) p< 0.0001 <u>57 days-2 y (n=9)</u> Exstrophy: 68.0 (24.8) Population: 95.7 (21.7) p=0.01 <u>>2 y (n=4)</u> Exstrophy: 108.8 (56.1) Population: 133 (27) p=0.45 **BNR** <u>2–12 y (n=13)</u> Exstrophy: 137.1 (49.6) Population: 133 (27) p= 0.77 **Post-BNR follow-up** <u>2–12 y (n=9)</u> Exstrophy: 124.5 (23.3) Population: 133 (27) p= 0.31 <u>Males ≥ 13 y (n=15)</u> Exstrophy: 175.6 (61.2) Population: 140 (30) p= 0.04 <u>Females ≥ 13 y (n=3)</u> Exstrophy: 128.8 (27.2) Population: 126 (22)	does not appear to negatively impact renal function in most patients. As eGFR detects only significant changes, surgical reconstruction may still cause more subtle renal damage.	comparability of cases and control values unclear There are no disclosures or financial conflicts associated with this study or any of the authors. There was not outside financial support provided for this article.	RoB: 5/9

						p= 0.87			
Braga, 2010 [101]	Retrospective cohort study 1997-2008 <u>Mean follow-up</u> CPRE: 70 mo (23–117 mo) CPRE-BUR: 34 mo (6–54 mo)	In this study we sought to compare the outcomes of children who underwent CPRE-BUR to those undergoing CPRE alone to appraise the impact of BUR on reducing the frequency of postoperative febrile urinary tract infections in this population.	n=38 patients with bladder exstrophy Median days age at surgery Both: 3 days <u>Male</u> CPRE: 13/23 (57%) CPRE-BUR: 5/15 (33%)	CPRE n=23	CPRE-BUR n=15	**Postop hydronephrosis grade** <u>I</u> CPRE: 3/23 (13%) CPRE-BUR: 2/15 (13%) p=0.05 <u>II</u> CPRE: 3/23 (13%) CPRE-BUR: - <u>III</u> CPRE: 3/23 (13%) CPRE-BUR: - <u>IV</u> CPRE: 1/23 (4%) CPRE-BUR: - **Postop febrile urinary tract infections** CPRE: 11/23 (48%) CPRE-BUR: 1/15 (7%) p=0.01 **Postop VUR** CPRE: 17/23 (74%) CPRE-BUR: - p=0.004	Bilateral ureteral reimplantation can be safely and effectively performed during primary closure of bladder exstrophy in newborns, potentially Reducing postoperative febrile urinary tract infections and hydronephrosis by early correction ofVUR.	Significant different follow-up times between the groups No information about funding and conflict of interest.	3 RoB: 8/9
Cheikhelard, 2009 [132]	Retrospective cohort study 1997-2007 France <u>Mean follow-up</u> Young-Dees: 8 y (2.5-13 y)	We compared the functional results of 1-stage perineal urethrocervico-plasty and vulvoplasty vs the classic Young-Dees procedure for incontinent	n=14 patients with female epispadias <u>Median age</u> Young-Dees: 6 y (3-13 y) Vulvoplasty: 4 y (1.5-11 y)	Young-Dees procedure n=7	1-stage urethrocervico plasty with vulvoplasty through a perineal subsymphysea l approach n=7	**Upper tract dilatation** Young-Dees: 0 Vulvoplasty: 3 p=0.19 **Ureterovesical reimplantation stenosis** Young-Dees: 0 Vulvoplasty: 1	Reconstructing the bladder neck and urethra via a perineal approach for female epispadias is promising. Surgery may be	historical control group (young-dees: 1996-2004; vulvoplasty since 2005), groups were comparable except for age at procedure, different follow-	4 RoB: 5/9

	Vulvoplasty: 2.5 y (1-3 y)	female epispadias.					performed earlier with similar continence results, less postoperative morbidity and less need for addi-tional surgery.	up times, missing follow-up data (e. g. postoperative bladder capacity) No information about funding and conflict of interest.	
Sujijantararat, 2002 [103]	Retrospective cohort study 1986-2000 Thailand Mean follow-up: 47 mo (1-168 mo)	The aim of the present study was to analyse the results of surgical repairs of this complex by one surgeon during the last 14 years.	n=13 patients • classical bladder exstrophy (n=8) • isolated epispadias (n=4) • superior vesical fissure (n=1) Male: 8/13 <u>Mean age</u> Classical bladder exstrophy: 4.4 y (1 day-14 y)	Single stage combined functional bladder closure and epispadias repair n=5 • classical bladder exstrophy (n=2) • isolated epispadias (n=3)	Staged functional bladder closure n=4 patients with classical bladder exstrophy	**Single staged approach** <u>Bladder exstrophy</u> • bilateral VUR (n=2) <u>Epispadias</u> • VUR grade II (n=1) **Staged approach** • Bilateral VUR (n=2)	The results of the present series show that anatomical correction can be achieved with a low acceptable complication rate. Optimum results should be obtained if the surgery is carried out early in life, particularly within 72 h following birth.	historical control group (single staged approach since 1999), recruitment of the study group not clearly described, Comparability of cohorts unclear (e.g. patient characteristic and follow-up time), unclear how continence was defined and measured No information about funding and conflict of Interest.	4 RoB: 3/9
Stein, 1995 [111]	Retrospective cohort study 1968-1994 Germany	To determine the optimal surgical approach in achieving complete urinary continence with preservation of the upper urinary	n=115 patients • epispadias (n=20) • bladder extrophy (n=95)	• Ureterosigmoidostomy (n=32) • Sigma rectum pouch (Mainz		**Ureterosigmoidostomy** • 6/35 conversion to a colon conduit to preserve renal function • 2/35 nephrectomy	Our data on patients with bladder exstrophy and incontinent epispadias indicate that primary urinary	Comparability of cohorts unclear (patient characteristics and length of follow-up)	3 RoB: 6/9

	Mean follow-up 16.7 y (0.2-35 y)	tract in the exstrophy-epispadias complex we reviewed the records of patients treated at our institution.		pouch II) (n=16) • Other rectal reservoirs (n=3) • Mainz pouch I (n=30) • Modified Young-Dees augmentation (Mainz pouch) (n=3) Sling plasty (n=2)		**Sigma rectum pouch** • 1/16 upper tract dilatation of the right kidney **Modified Young-Dees procedure with Mainz pouch augmentation** *no information to the upper tract* **Sling plasty** In all 3 patients the upper urinary tract is normal. <u>Colon conduit</u> primary colon conduit: • without ensuing complications and normal upper urinary tract (n=5) secondary colon conduit: • 1/12 slight dilatation of the right upper tract. <u>Mainz pouch I</u> Serum creatinine levels of all patients were within the normal range and none had deterioration of the upper urinary tract	diversion results in a continence rate of more than 90% with preservation of the upper urinary tract. After failure of urinary tract reconstruction individualized treatment is necessary.	number of patients which were treated with sling plasty unclear (n=2 in Table 2, n=3 in the text) No information about funding and conflict of Interest.	
Connor, 1989 [80]	Retrospective cohort study 1945-1985 USA	Our series spans 40 y during which the principles of modern treatment of bladder exstrophy were	n=207 patients CBE Patient age at initial	• Ureterosigmoidostomy (n=40) • Cutaneous urinary		**Ureterosigmoidostomy** • 37/40 (92%) upper tract deterioration	One also must be prepared to use some of the more innovative techniques currently	Comparability of cohorts unclear (patient characteristics and length of follow-up),	3 RoB: 5/9

	Follow-up 2-35 y	formulated and attempts to identify those procedures that have consistently proved successful in the management of this condition.	presentation: 1 day-35 y <u>Sex</u> Male: 140/207 (68%)	diversion (n=45) • primary closure (n=137)		• 16/40 (40%) unilateral nephrectomy **Cutaneous urinary diversion** • upper tract deterioration (n=16) • stomal stenosis or persistent irritation and bleeding (n=10) • stricture at the site of the ureteroileal anastomosis (n=3) • Colon conduit: Upper tract deterioration occurred secondary to reflux (n=3/11) **Primary closure** <u>early closure</u> • 6/40 (15%) had some degree of upper tract deterioration (2/6 required subsequent operative intervention) <u>delayed closure</u> • 25 patients (26%) had upper tract deterioration, • 15 patients needed an operative intervention due to reflux or outlet obstruction	available to achieve acceptable urinary continence. Long-term close follow-up is essential to ensure that renal function is protected, and since urinary continence may require many operations during a number of years, patient selection is extremely important.	continence status not always reported, unclear who measures the continence No information about funding and conflict of interest.	
Husmann, 1988 [170]	Retrospective cohort study 1963-1988 Canada	To assess the long-term efficiency in preserving renal function after surgery for bladder	n=91 patients with classic bladder exstrophy	• Staged reconstruction (n=68) • Ileal conduits (n=11)		**Complications** <u>Staged reconstruction</u> • Progressive hydroureteronephrosis (Secondary to bladder outlet obstruction following	Based on these results we believe that staged reconstruction of the patient with classical	Patient recruitment not clearly described and exclusion criteria not reported,	3 RoB: 4/9

	Median follow-up: 12.7 y	exstrophy, we analyzed the renal function of several patients with classical bladder exstrophy treated during the last 25 years.	Median age at closure: 10 days (1 day-5 y)	• Nonrefluxing colonic conduits (n=9) • Ureterosigmoidostomy (n=3)		first stage procedure): 9/68 (11.8%) • Progressive hydroureteronephrosis (Secondary to bladder outlet obstruction following second stage procedure): 7/68 (9.2%) • Persistent vesicoureteral reflux: 3/68 (4%) • Renal scarring: 10/68 (13%) • Renal insufficiency: 3/68 (4%) <u>Ileal conduits</u> • Renal lithiasis: 2/11 (18%) • Renal scarring: 9/11 (82%) • Renal insufficiency: 4/11 (36%) <u>Nonrefluxing colonic conduits</u> • Bilateral ureteroenteric reflux: 1/9 (11%) • Renal scarring: 2/9 (22.2%) • Renal insufficiency: 0% <u>Ureterosigmoidostomy</u> • Renal scarring: 1/3 (33%) • Renal insufficiency: 0%	bladder exstrophy offers a low risk for renal injury, an excellent chance for urinary continence and a more acceptable cosmetic appearance	comparability of cohorts unclear, measurement of continence not described, follow-up times different No information about funding and conflict of interest.	
Arap, 1988 [105]	Retrospective cohort study	We present our personal experience with	n=38 children with	BNR techniques used		**Complications** <u>Tanagho</u> • Bladder stones: 3	The results were similar with the 3 techniques.	recruitment of the study group not clearly	3

	1967-1984 Brazil Mean follow up 62 mo (5 mo-18 y)	38 cases of incontinent epispadias in which we used 3 basic techniques of bladder neck reconstruction with the anterior bladder wall or trigonal flap tubularization.	incontinent epispadias • penopubic or complete epispadias (n=35) • transitional forms between bladder exstrophy and epispadias (n=3) Male: 28/38	• Tanagho (n=8) • Leadbetter (n=20) • Young-Dees (n=8)		• Transient reflux: 3 • Persistent reflux: 3 <u>Leadbetter</u> • Ureterovesical obstruction: 4 • Reflux: 5 <u>Young-Dees</u> • Reflux: 4		described, Comparability of cohorts unclear (patient characteristics and length of follow-up), measurement of continence not described No information given about funding and conflict of interests.	RoB: 3/9

6. AG Nachsorge

Schlüsselfrage Was sollte eine geschlechtsspezifische Nachsorge beinhalten?									
Referenz	**Studien-charak-teristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Direkte Evidenz									
Ebert, 2010 [171]	Case-control study Germany Mean follow-up: 24 y	To investigate whether established pelvic floor variables can be used to predict the risk of uterine prolapse after surgery and to compare two different operative strategies, pelvic adaptation with functional reconstruction and an open pelvis with urinary diversion, as a congenital bony pelvis and pelvic floor defect predisposes females with BEEC to uterine prolapse.	n=24 n=19 **women** with BEEC • 16 classical exstrophy • 2 epispadias • 1 cloacal exstrophy control: n= 5 age-matched controls Mean age US+MRI: 27.3 y (15.5-49 y) Mean age control: 35.4 y (29.8–41 y)	BEEC n=19 • Symphysis closure (n=12) • Open pelvis (n=7) perineal 3D-US+ MRI	Control n=5 perineal 3D-US+MRI	**Symphysis diastasis, cm** (MRI) Symphysis closure: 4.50 (2.40) Open pelvis: 9.04 (4.28) Control: 0.49 (0.05) **Levator hiatus, cm** (MRI) Symphysis closure: 4.12 (1.03) Open pelvis: 7.55 (2.39) Control: 3.17 (0.41) **Levator hiatus, cm** (3D-US) Symphysis closure: 4.88 (0.89) Open pelvis: 5.86 (1.03) Control: 4.20 (0.70)	This is the first study showing that perineal 3D-US is useful for pelvic floor imaging in BEEC. Established pelvic floor variables might be useful for predicting the risk of pelvic organ prolapse in BEEC.	recruitment via German self-support group, recruitment of the control group not described, no information on patient characteristics of the control group (except age) No conflict of interest reported. No information about funding.	4 RoB: 5/9

						Levator angle (°) (MRI) Symphysis closure: 87.31 (16.57) Open pelvis: 101.33 (27.29) Control: 45.45 (8.75) **Levator angle (°)** (3D-US) Symphysis closure: 86.56 (17.34) Open pelvis: 104.06 (18.08) Control: 71.34 (12.53) **Risk of prolapse** 4/7 patients without pelvic reconstruction had total prolapse and only 1/12 after functional reconstruction had mild uterine prolapse (p=0.02) **Possible predictors of the risk of prolapse** no further significant correlations were detected			
Sabethkish, 2017 [172]	RCT 2000-2012 Iran	To investigate the effect of low-dose HCG administration on structural changes in the lower urinary tract in boys with	n=30 **male** patients with BEEC previously undergone	250 IU HCG intramuscularly 3 times per week during a 4-week period n=15	no intervention n=15	**Incontinence Score** improvement was significantly higher in the HCG group (P=.01)	Our preliminary results suggest the role of low-dose HCG in boys with BEEC suffering from urinary	no information on random sequence generation, allocation	2 RoB: high

	Mean follow-up: 4 y	urinary incontinence in the setting of BEEC.	bladder neck reconstruction using the modified Young-Dees-Leadbetter as explained by Mollard and Mure HCG group: • 6/15 (40%) epispadias • 9/15 (60%) classic bladder exstrophy Control group: • 5/15 (33.3%) epispadias • 10/15 (66.6%) classic bladder exstrophy Median age: 7.5 y (5.5 - 11 y)			**Prostate Size, Bladder Capacity, and Penile Length** • total prostate size (P<.0001) and bladder capacity (P<.0001) increased significantly in all patients of the HCG group • no significant change in the control group **Hormonal Changes** • Basal serum testosterone level increased significantly after the first (P = .001) and last (P < .001) injections with no significant increase 3 months after the last injection (P > .05). **Secondary Changes and Complications** • HCG group: 2/15 single episodes of urinary tract infection • Increased penile size was the	incontinence. The data also reveal the role of prostate enlargement in the improvement of urinary incontinence. Chronic treatment with HCG increases bladder capacity that may facilitate future reconstructive surgery.	concealment and blinding No conflict of interest reported. No information about funding.	

						only observed ancillary finding • HCG group: No significant side effect on secondary sexual characteristics • All children showed normal developmental changes **HRQoL in the HCG group** <u>Children</u> Before: 57.8 ± 5.83 final Follow-up: 66.6 ± 5.3 p<0.001 <u>Parents</u> Before: 53.4 ± 5.06 final Follow-up: 64.2 ± 4.78 p<0.001			
Ebert, 2012 [173]	Retrospective case series 2004-2009 Germany	We identified males with sonographic intratesticular abnormalities or testicular tumor in exstrophy-epispadias complex.	n=22 **men** with BEEC • 19 classical bladder exstropy • 3 epispadias Mean age: 24.8 (18.3-39.9 y)	Sonographical examination		**Sonographical examination** 41% no pathological findings 59% single or multiple pathological findings • Unilateral or bilateral small testicles (27.3%) • hydrocele (18.2%) • varicocele (9.1%)	The observation of comorbid testicular tumor in males with exstrophy-epispadias complex should prompt a preventive health examination after puberty, which gives these patients the opportunity for further appropriate diagnostics and treatment if necessary. Biopsy is recommended for sonographically	recruitment via German self-support group, outcome assessment not clearly described, no statistical analysis No information about conflict of interest. Supported by Grant	4 RoB: 12/20

						• spermatocele (4.5%) **Biopsy** (n=3) • testicular intraepithelial neoplasia (n=1 bladder exstrophy) • benign testicular stromal tumors (n=2, 1 bladder exstrophy & 1 epispadias) **Follow-up visits**: 10, 28, 68 mo	detected intratesticular lesions.	01GM08107 from the German Federal Ministry of Education and Research (Deutsches Bundesministerium für Bildung und Forschung, BMBF).	
Gearhart, 1993 [174]	Case series	A total of 13 men born with classical bladder exstrophy underwent magnetic resonance imaging examination of the pelvis to evaluate the size and configuration of the prostate and pelvic organs.	n=13 **men** with classical bladder exstrophy Age: 25.2 y (19-38)	Magnetic resonance imaging		• Mean prostatic cross sectional area: 10.1 +/- 3.4 cm^2 • Mean estimated prostatic volume: 20.7 +/- 8.2 cc • Mean estimated prostatic weight 21.7 +/- 8.6 gm • Mean seminal vesicle length: 2.1 +/- 0.99 • Mean seminal vesicle width: 1.1 +/- 0.38 cm Volume, weight and maximum cross sectional area of the prostate appear normal compared to published norms.	The attainment of continence in this complex group of patients is multifactorial and prostate growth as evaluated by magnetic resonance imaging may not influence continence in these patients.	No information about patient recruitment and detailed inclusion and exclusion criteria, no statistical analysis No information about conflict of interest and funding.	4 RoB: 10/20

Indirekte Evidenz									
Weibliche Nachsorge									
Holmdahl, 2020 [175]	Systematic review 2015-2019	The aim of this review is to summarize and discuss the latest 5 years of published reports on HRQOL in children and adults with the BEEC and its relationship to incontinence and sexual factors.	n=546 patients with BEEC (children & adults)	**Outcome** Sexual Function on HRQOL		**Women and Impact of Sexual Function on HRQOL** • suggests a relationship between sexual function and overall psychological wellbeing (n=1) • females with epispadias: only one-fifth patients had a lackof self-confidence and a fear of rejection in relationships (n=1) • pelvic organ prolapse causes effects on sexual function and incontinence with significant reductions in HRQOL (n=1)	Overall HRQOL in individuals born with the BEEC appears good, but urinary incontinence and sexual dysfunction may have a negative impact.	No information if an additional hand search was made, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment No conflict of interest reported. No information about funding.	4 RoB: high
Alyami, 2017 [114]	Retrospective cohort study 2000-2013 Canada Mean follow-up	The aim of the present study was to describe long-term follow-up of patients who underwent the traditional vs alternative approach.	n=12 female patients with epispadias Mean age at first surgery Young-Dees-Leadbetter cervicoplasty bladder neck	Young-Dees-Leadbetter cervicoplasty bladder neck approach n=3	Single-stage perineal approach n=9	**Young-Dees-Leadbetter cervicoplasty bladder neck approach** Dry: 0/3 Redo-surgery: 3/3	Female epispadias could be successfully repaired using a single-stage modified perineal approach that achieved good continence with volitional voiding, good cosmetic results and compared favorably with the ones	Groups are not comparable (age range, other factors unclear) No conflict of interest/ funding declared.	3 RoB: 6/9

	Young-Dees-Leadbetter cervicoplasty bladder neck approach: 12.3 y (8-13 y) Single-stage perineal approach: 6 y (1-10 y)		approach: 2.9 y (0.5-4 y) Single-stage perineal approach: 4.3 y (1-17 y)			Need for bladder augmentation: 2/3 Continence post redo-surgery: 3/3 (CIC) **Single-stage perineal approach** Dry: 4/9 Not toilet trained: 2/9 Incontinence: 3/9 Redo-surgery: 3/9 Need for bladder augmentation: 0/9 Continence post redo-surgery: 2/3 **Complication:** • No major complications	repaired with the Young-Dees-Leadbetter technique. The additional step of performing bladder neck tailoring to achieve a funneling configuration seemed to be useful in improving continence.		
Anusionwu, 2012 [176]	Retrospective case serie USA	We investigated whether osteotomy is associated with a decreased risk of pelvic organ prolapse in females with classic bladder exstrophy.	n=67 females with classic bladder exstrophy Median age: 23 y (13-60 y) Osteotomy: 25/67 (37.3%)	**Outcome** Pelvic organ prolapse		**Characteristics of patients with and without pelvic organ prolapse** <u>Mean ± SD diastasis (cm)</u> Prolapse: 9.1 ± 3.7 No Prolapse: 6.9 ± 2.7 p=0.016 <u>Mean ± SD age (y)</u> Prolapse: 28.1 ± 12.4 No Prolapse: 25 ± 11.5 p=0.19	Osteotomy does not decrease the risk of pelvic organ prolapse in patients with classic bladder exstrophy. Rather, degree of diastasis is significantly associated with pelvic organ prolapse.	No conflict of interest reported. Supported by Award T32DK007552 from the National Institute of Diabetes and Digestive and Kidney Diseases	4 RoB: 17/20

						<u>Osteotomy</u> Prolapse: 36.8% No Prolapse: 42.9% p=0.66 <u>Parous</u> Prolapse: 11.9% No Prolapse: 10% p=0.36 <u>Vaginoplasty</u> Prolapse: 45% No Prolapse: 31.9% p=0.31 **Multivariate analysis** *(only significant results shown)* <u>Diastasis (cm)</u> • OR: 1.31 (1.01–1.73) p=0.044			
Nakhal, 2012 [177]	Retrospective case series 1983-2010 United Kingdom Mean follow-up: 8 y (1-15 y)	The aim of this paper is to study the incidence and risk factors for genital prolapse in adult women with bladder exstrophy and to describe the long-term outcome of the Gore-Tex wrap procedure for genital prolapse	n=52 women with bladder exstrophy Mean age: 39 y (23-63 y)	**Outcome** Incidence and risk factors for genital prolaps		**Pelvic organ prolaps** 27/52 (52%) • treated surgical: 23/27 (83%) • Gore-Tex wrap group: 16/23 (12 successful after first repair) • Others: 7/23 (2 successful after first repair) **Risk factors for prolaps** pregnancy: 10/27 (37%) • introitoplasty: 1/10 (4%)	Prolapse is a common gynaecological complaint in adult women with bladder exstrophy and the majority will require treatment. At present the Gore-Tex wrap offers good results with a low rate of serious complications.	no statistical analysis performed No conflict of interest reported. No information about funding *different mean ages reported*	4 RoB: 15/20

Männliche Nachsorge									
Holmdahl, 2020 [175]	Systematic review 2015-2019	The aim of this review is to summarize and discuss the latest 5 years of published reports on HRQOL in children and adults with the BEEC and its relationship to incontinence and sexual factors.	n=546 patients with BEEC (children & adults)	**Outcome** Sexual Function on HRQOL		**Men and Impact of Sexual Function on HRQOL** • no studies so far reported a significant impact of sexual function on HRQOL • sexual dysfunction is common (n=4) • A common concern is dissatisfaction with genital appearance and the size of the penis (n=3) • HRQOL and sexual function are similar to the generel population (n=2) reduced erectile function and psychological aspects of sexuality resulted in low self-esteem in terms of sexual relationships (n=1)	Overall HRQOL in individuals born with the BEEC appears good, but urinary incontinence and sexual dysfunction may have a negative impact.	No information if an additional hand search was conducted, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment No conflict of interest reported. No information about funding.	4 RoB: high
Cendron, 2018 [134]	Retrospective case series 1994-2011 USA	The goal of the current study was therefore to evaluate whether the more proximal forms of epispadias correlated with	n=26 male epispadias patients Median age of repair: 10.9 mo (6-23 mo)	Initial imaging or endoscopic evaluation		**Urinary continence** Overall: 17/26 (65%) Penopubic: 9/14 (64%) Penile: 5/8 (63%)	The findings highlight the importance of a thorough initial baseline evaluation for all levels of epispadias, demonstrating an	no statistical analysis, continence status was based on subjective self-assessment	4 RoB: 14/20

	Median follow-up: 109.1 mo (2-235.3 mo)	associated extragenital anatomic anomalies seen on initial imaging or endoscopic evaluation, and whether these pre-operative findings contributed to sub-sequent surgical management aimed at achieving urinary continence.				Glanular: 3/4 (75%) No correlation between urinary continence and either abnormal bladder neck appearance, pubic diastasis or vesicoureteral reflux could be found.	association between the level of the epispadiac urinary meatus and a widened pubic diastasis, but not bladder neck appearance. The prevalence of vesicoureteral reflux appeared higher in less severe epis-padias, which may be related to greater outlet resistance and thus possibly higher backpressure, but appeared not to be associated with a worse outcome.	No information about conflict of interest. No funding reported.	
Beide Geschlechter									
Jarosz, 2022 [165]	Retrospective cohort study 2013-2019 USA Follow-up: BUR-CPRE: 46.33 (10.26) mo CPRE: 53.76 (26.05) mo	We hypothesize that cephalotrigonal BUR-CPRE will reduce the rate of post-operative pyelonephritis, post-operative VUR, and need for subsequent ureteral surgery.	n=64 patients with classic bladder exstrophy Mean age: BUR-CPRE: 3.2 (SD 2.01) mo CPRE: 2.12 (SD 1.71) Gender (Male): BUR-CPRE: 10/15 (66%) CPRE: 29/49 (26%)	cephalotrigonal BUR-CPRE n=15	CPRE alone n=49	**Recurrent pyelonephritis** Gender (Overall) Male: 7/38 (0%) Female: 13/24 (60%) p=0.005 BUR-CPRE Male: 0/10 (0%) Female: 3/5 (60%) p=0.158 CPRE Male: 7/29 (24.1%) Female: 10/19 (52.7%) p=0.769	Female gender was found to be a significant independent predictor of recurrent pyelonephritis irrespective of BUR status (p=0.005). The reduction in recurrent pyelonephritis was most notable among male bladder exstrophy patients in our cohort. Surgeons should consider BUR-CPRE, when technically feasible, to decrease the adverse outcomes associated with recurrent pyelonephritis.	Reasons for loss to follow up were not described No conflict of interest and funding reported.	3 RoB: 8/9

Ebert, 2020 [82]	Cohort study 2009-2016 Germany	To evaluate the impact of reconstructive strategies and post-operative management on short- and long-term surgical outcome and complications of classical bladder exstrophy patients' comprehensive data of the multicenter German-wide Network for Congenital Uro-Rectal malformations (CURE-Net) were analyzed	**<u>Prospective cohort</u>** n=34 babies with classical bladder exstrophy Median age: 3 mo (IQR 2-4 mo) <u>Sex</u> Female: 10/34 (29%) Male: 24/34 (71%) **Cross-sectional cohort** n=113 patients with classical bladder exstrophy Median age: 12 y (IQR 6-21y) <u>Sex</u> Female: 39/113 (35%) Male: 74/113 (65%)	Staged approach • n=23 (prospective cohort) • n=60 (cross-sectional cohort)	Single-stage approach • n=11 (prospective cohort) • n=53 (cross-sectional cohort)	**Post-Operative Management** <u>Stratification for sex</u> No differences: • incidence of post-operative intensive care observation (p = 0.49) • peridural catheters use (p=0.55) • wound infection (p = 1.0) • medication such as anticholinergic drugs (p = 1.0) • antibiotic prophylaxis (p = 0.25) <u>Differences</u>: • blood transfusions (p=0.002, males more often) Blood transfusions were predominant in males after a singlestage approach (p = 0.004) compared to a staged approach (p= 0.22)	*No conclusion regarding sex differences*	patient characteristics of both groups (staged approach and single-stage approach) are not separately described, no information on the length of follow-up supported by a research Grant (01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) 2009-2012. Statistical calculations were supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013-2016), EB521/2-1 and JE681/4-1 (2015-2018). HR was supported by a grant from the DFG (RE	3 RoB: 6/9

								1723/1-1). http://www.cure-net.de.	
Taskinen, 2020 [178]	Retrospective case serie 1967-2005 Finland	To evaluate to what extend urinary continence develops during puberty in patients with classic bladder exstrophy and epispadias.	n=65 patients with epispadias or classic bladder exstrophy • 37 classic bladder exstrophy • 28 epispadias <u>Sex</u> Classic bladder exstrophy • Female: 16 • Male: 21 Epispadias • Female: 7 • Male: 21 Median age of latest control: 19 y (IQR 17-21 y)	**Outcome** Urinary continence		**Development of urinary continence** <u>Bladder exstrophy</u> Male: 3/9 Female: 3/5 p=0.58 <u>Epispadias</u> Male: 10/13 Female: 0/4 p=0.02 **Development of urinary continence with bladder neck reconstruction** Male (n=2): • became continent with volitional voiding before the age of 10 y (bladder exstrophy) • bladder augmentation at the age of 10 y Female (n=3): • daily incontinence with volitional voiding at the age of 10 y (all) • 2/3 full continent • 1/3 rare incontinence after puberty **Last control** • one male and one female underwent	We conclude that approximately half of incontinent classic bladder exstrophy and epispadias patients without clean intermittent catheterization can achieve continence during pubertal development. The prognosis was especially good in patients with rare incontinence and male epispadias. Accordingly, bladder augmentation should be postponed at least in patients without total incontinence	No conflict of interest reported. No information about funding *only sex differences reported*	4 RoB: 17/20

						bladder augmentation after puberty because of persisting incontinence <u>Clean intermittent catheterization</u> (n=3) • 2 continent females with baldder exstrophy • 1 continent male with baldder exstrophy **Continence or rare incontinence** <u>Bladder exstrophy</u> Male: 5/21 (24%) Female: 7/16 (44%) p=0.28 <u>Epispadias</u> Male: 17/19 (89%) Female: 4/7 (57%) p=0.1 no statistical difference between males and females neither among classic bladder exstrophy or epispadias patients			
Pettersson, 2013 [179]	Prospective case series Recruitment: 1944-1961 Period end: 2010	We studied clinical outcomes, especially regarding colorectal adenocarcinoma, in patients who underwent ureterosigmoidostomy in early childhood	n=25 children 21 BEEC • 2 myelomening ocele • 1 Bladder • papillomatosis	Ureterosigmoidostomy		**8 died** • 5 colorectal adenocarcinoma (3 male, 2 female) • 1 ovarian carcinoma • 1 chronic obstructive	*No conclusion regarding sex differences*	No information about conflict of interest. Supported by the Anna-Lisa and Bror Björnsson	4 RoB: 19/20

	Sweden	between 1944 and 1961.	• 1 Cystovaginal fistula Ureterosigmoidostomy: 3.1 y (0.5-8 y) Sex Male: 13/25 Female: 12/25			pulmonary disease (1 male) • Uremia (1 female) **3 alive with colorectal adenocarcinoma** (3 male) **Re-Diversion** (n=20) Male: 10/13 Female: 10/12		Foundation, and the Märta and Gustav Ågren Foundation.	
Gargollo, 2008 [180]	Retrospective case series 1994-2007 USA Median follow-up: 5 y (3 mo-13 y)	We present our median 5-year data on patients who have undergone complete primary repair of bladder exstrophy	n=32 patients with bladder exstrophy Sex Female: 9/32 (28%) Male: 23/32 (72%) • n=28 underwent closure within 72 hours of life n=4 underwent it after 72 hours (7 days-12 mo)	complete primary repair of bladder exstrophy		**Continence** • Relative to males the females had a decreased need for bladder neck reconstruction (p=0.05). **Continent intervals** Males: 2.1 ± 1.2 Females: 1.8 ± 1.1 p=0.55 *see preoperative and postoperative follow-up protocol in figure 1*	*No conclusion regarding sex differences*	no information about funding and conflict of interest.	4 RoB: 16/20
Mesrobian, 1988 [181]	Case serie 1918-1983 USA Follow-up: 13 y (1-61 y)	We review our experience with and long-term follow-up of 103 patients with bladder exstrophy.	n=103 patients with bladder exstrophy Sex Female: 40/103 (39%) Male: 63/103 (61%)	**Outcomes** • Urinary continence • Renal function • Urinary tract infections • Malignant lesions • Associated anomalies • Mortality		**Urinary continence** Vesical neck reconstruction (n=18) Complete continence • Male: 10/18 • Female: 2/18 Partial continence • Male: 2/18	*No conclusion regarding sex differences*	unclear if the design is retrospective or prospective, no statistical analysis no information about funding and conflict of interest.	4 RoB: 14/20

			Patient age: 1 day to 52 y Primary closue: 32/103 Urinary diversions: 71/103			• Female: 1/18 Incontinent: 3 <u>Ureterosigmoidostomy</u> (n=40) Continent of urine and stool: 33/40 Incontinent • Male: 5/40 • Female: 2/40 **Factors that led to urinary diversion after primary closue** <u>Massive reflux with hydronephrosis</u> • Male: 1/4 • Female: 3/4 <u>Wound dehiscence</u> • Male: 0/2 • Female: 2/2 <u>Vesical neck contracture</u> • Male: 1/1 • Female: 0/0 <u>Staged colon conduit (Arap)</u> • Male: 1/1 • Female: 0/0 **Factors that led to re-diversion after primary diversion** <u>Ureterosigmoidostomy: Bilateral obstruction</u> • Male: 3/8 • Female: 5/8		*only sex differences reported*	

						Ureterosigmoidostomy: Urinary incontinence • Male: 0/1 • Female: 1/1 Ureterosigmoidostomy: Colonic polyp • Male: 0/1 • Female: 1/1 Cutaneous ureterostomy: Bilateral obstruction • Male: 0/2 • Female: 2/2 Heitz Boyer-Hovelacque: Urinary incontinence • Male: 1/1 • Female: 0/1 Heitz Boyer-Hovelacque: Bilateral obstruction • Male: 1/1 • Female: 0/1			

Schlüsselfrage

Was sollte eine geschlechtsspezifische Nachsorge beinhalten?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Therapie(n)	Endpunkte	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Weibliche Sexualität									
Canalichio, 2021 [182]	Retrospective case series from January 1989 to	We aim to update the continence outcomes as well as describe gynecological outcomes for	n=18 females with classic bladder exstrophy	complete primary repair exstrophy	Primary outcomes: • urinary continence • vaginal stenosis	**Gynecological outcomes** (n=11) **Menses** • 54.5 % (6/11) reported painful	Vaginal stenosis and menstrual irregularities are unfortunately prevalent in this population, but both are manageable with	Outcome measurement was not clearly described	4 RoB: 17/20

	December 2019 USA	females having undergone complete primary repair exstrophy.	• postpubertal women (n=11) <u>Median age at last follow-up</u> • Overall: 15.9 y (IQR 13.1, 18.4) Postpubertal women: 18.0 y (IQR 15.2, 21.4y)		Gynecological outcomes were assessed only in post pubertal patients and included: • menstrual irregularities • vaginal stenosis • ability to use a tampon • participation in penetrative intercourse	and irregular menses • 6/6 (100 %) were managed with hormonal therapy **Vaginal stenosis** • 6/11 (54.5 %) had vaginal stenosis • 5/6 (83 %) had painful and irregular menses that overlapped Vaginal stenosis managed with: • vaginal dilation alone (33.3 %, 2/6) • flap vaginoplasty (66.7 %, 4/6) **Ability to use tampons** • yes: 3/11 (27.3 %) • not interested: 2/11 (18.2 %) • not recorded: 6/11 (54.5 %) **Penetrative intercourse** • yes: 4/11 (36.4 %) • no: 5/11 (45.5 %) • not recorded: 2/11 (18.2 %)	expectant surgery or medical management.	The authors received no specific funding for this work. The authors declare that they have no conflicts of interest. *different median ages at last follow-up for postpubertal women reported*	

						Bicornuate uterus • 2/11 (18.2 %) **Uterine prolapse** • 2/11 (18.2 %) <u>Median age at vaginal intercourse</u> 19.7 y (IQR 17.8, 21.5 y)			
Ebert, 2017 [61]	Prospective cohort study 2009-2014 Germany	The aim of this study was to investigate sexual function using the standardized FSFI, and to assess the influence of bladder and vaginal reconstruction and the presence of incontinence on FSFI results.	n=21 females with exstrophy-epispadias-complex • 52 % (11/21) classical bladder exstrophy • 19 % (4/21) cloacal exstrophy • 14 % (3/21) Epispadias Mean age: 26 y (SD = 5.1 y)	• bladder in use (n=9) primary or secondary urinary diversion (n=8)	• Functional outcome • Sexuality and pregnancy • Female Sexual Function Index	**Mean FSFI** *Mean Bladder in use (SD) vs. mean primary or secondary urinary diversion (SD)* **Desire** 4.2 (0.8) vs. 3.7 (1.2), p = 0.22 **Arousal** 3.3 (1.7) vs. 4.1 (1.7), p=0.21 **Lubrication** 3.1 (2.0) vs. 5.0 (1.7), p=0.0008 **Orgasm** 2.9 (1.9) vs. 4.0 (2.1), p=0.1 **Satisfaction** 2.7 (2.0) vs. 3.6 (2.4), p=0.26	The risk for sexual dysfunction seems to be lower in patients reconstructed with primary or secondary urinary diversion than patients with bladder in use. It is surprising that lubrication was better after urinary diversion than after bladder neck surgery. Incontinence and in some parts the history of an introitus plasty may play an additional role in development of sexual dysfunction in exstrophy-epispadias-complex. Although most of the female exstrophy-epispadias-complex patients lived in a committed partnership and had sexual intercourse, total FSFI values <26.55 clearly indicate a risk of sexual dysfunction. Although continence itself played a major role, females	Congenital anomaly of 3 females not reported, patient recruitment via self-help organizations, self-reported outcomes, comparability of the groups unclear This work was done in the context of the "Network for Systematic Investigation of the Molecular Causes, Clinical Implications and Psychosocial Outcome of Congenital Uro-Rectal Malformations (CURE-Net)" and supported by a research grant	3 RoB: 5/9

						Pain 3.2 (2.1) vs. 3.4 (2.2), p=0.89 **Total score** 19.5 (1.9) vs. 23.7 (2.0), p=0.0012	reconstructed with urinary diversion seem to have better sexual function.	(01GM08107) from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung) 2009e2012. Statistical calculations are supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), funding signs JE681/3-1 (2013e2015), EB521/2-1 and JE681/4-1 (2015e2018). HR was supported by a grant from the DFG (RE 1723/1-1). The authors declare that they have no conflicts of interest.	
Dap, 2017 [62]	Retrospective case reports 2000-2016 France	Pregnancy outcomes among patients with prior bladder exstrophy.	n= 3 female patients who had bladder exstrophy diagnosed at birth and who presented with a pregnancy	• Enterocystoplasty (n=2) • Enterocystoplasty and artificial sphincter (n=1)	• Conception • Previous spontaneous abortion • Cesarean deliveries • Complica-tions	**Conception** 100 % spontaneous (6/6) **Previous spontaneous abortion**	Based on the results of the present study, it is suggested that women with bladder exstrophy can have a healthy reproductive life	Study aim was not clearly defined, not described, if all eligible patients were included	4 RoB: 12/20

			• 6 pregnancies Age at first conception: 22-24 y			0 % **Mode of delivery** 100 % cesarean (planned n=5, emergency = 1)		Funding: Not reported. The authors declare that they have no conflicts of interest.	
Rubenwolf, 2016 [183]	Retrospective cohort study Reconstruction period: 1969 - 2014 Germany Mean follow-up: 22.3 y (2 – 45 y)	We evaluated the outcome in female patients with classic bladder exstrophy and continent urinary diversion for sexual function and fertility.	n=29 women with classic bladder exstrophy Mean age: 38 y (22 – 61 y)	• primary CUD (n=18) secondary CUD after failed reconstruction of the exstrophic bladder (n=11)	• Sexual function • Social integration • Maternity	**Mean FSFI** *primary (SD) vs. secondary (SD)* 27.8 (5.02) vs. 30.5 (3.7); p=0.14 **Desire** 3.52 (0.9) vs. 3.8 (1.2); p=0.45 **Arousal** 4.53 (1.26) vs. 5.12 (0.7); p=0.17 **Lubrication** 4.52 (1.28) vs. 5.64 (0.42); p=0.01 **Orgasm** 4.37 (1.68) vs. 5.23 (1.0); p=0.14 **Satisfaction** 5.1 (0.75) vs. 5.16 (1.09); p=0.86 **Pain** 4.9 (1.6) vs. 5.45 (1.1); p=0.33 **Pregnancy**	Interestingly, sexual function was comparable irrespective of whether patients had undergone primary or secondary CUD, or continent cutaneous or continent anal UD. The sexuality and fertility of female patients with exstrophy after continent urinary diversion appears to be comparable with those in previously reported series of patients in whom the bladder was preserved. Management of sexual function, gynecologic pathologies and fertility should be an active part of long-term follow-up.	Comparability of the groups unclear, self-reported outcomes Funding: not reported. The authors declare that they have no conflicts of interest	3 RoB: 7/9

						Primary CUD: 44 % (8/18) Secondary CUD: 27 % (3/11); p=0.6			
Amesty, 2016 [184]	Retrospective case series Treatment period: 1976–2013 Spain	To evaluate the results of its treatment in terms of continence, sexuality, and impact of incontinence on quality of life.	n=9 female patients with pure epispadias Age: 5-39 y	• women were treated with a bladder neck reconstruction and genitoplasty, performing both procedures at the same time	• Urinary continence • Sexuality • Quality of life	**Sexuality** • 4/9 reported to have a normal sex life, with good self-confidence and satisfaction in their relationships 3/9 report to have adequate sexual satisfaction, however, reported to having lack of self-confidence and fear of rejection in relationships, because of her incontinence	Patients with female epispadias have good long-term results regarding quality of life and sexuality, despite having some degree of urinary incontinence.	Not described, if all eligible patients were included, self-reported outcomes were used Funding: not reported. The authors declare that they have no conflicts of interest	4 RoB: 14/20
Ebert, 2011 [63]	Prospective case reports Germany	We reported our operative experience and management during pregnancy in two BEEC patients after urinary diversion and complex functional reconstruction	n=2 women with BEEC Age 17 & 26 y	Case 1: had a urinary diversion with an ileocecal pouch including pelvic adaptation done after ten previous failed abdominal surgeries Case 2: had an ileum augmentation and a catheterizable Mitrofanoff	• Urological history • Pregnancy • Delivery course	**Pregnancy complications** • case 1 & 2 had bilateral mild upper tract dilatation monitored from the 8th week onward without any further clinical significance **Mode of delivery** • case 1 & 2: cesarean section without	An elective cesarean section is recommended in all BEEC patients irrespective of the type of reconstruction to avoid pelvic floor disorders. Surgical complications may be minimized by the type of operative approach.	Patient recruitment was not clearly described supported by a research grant from the German Federal Ministry of Education and Research (Deutsches Bundesministerium für Bildung und Forschung, BMBF).	4 RoB: 15/20

				stoma after functional reconstruction of the exstrophic • bladder		any complications case 1 & 2: No clinical and sonographic signs for prolapse occurred **Abdominal incision** • Case 1: Pfannenstiel • Case 2: Median laparotomy **Case 2:** In our case a midline abdominal incision allowed to push the vascular supply of the augmented ileum and the stoma positioned in the right lower abdomen away and so avoid accidental injury.		The authors declare that they have no conflicts of interest.	
Gobet, 2009 [185]	Case series Switzerland 1937-1968	We describe the long-term psychosocial and sexual outcomes of patients born with bladder exstrophy treated with ureterosigmoidostomy at our institution.	n=35 patients with bladder exstrophy Mean age: 50 y (39-67 y) Female: 4/35	Ureterosigmoidostomy according to the Mathisen technique	• long-term psychosocial and sexual outcomes	**Gynecological and andrological outcomes** • Duplicated vagina/uterus: 1/4 • Uterine prolapse: 1/4 • Breast cancer: 1/4 • Early menopause (age 37): 1/4 • Premenstrual syndrome: 1/4	A third of the followed patients in this study experienced some fertility or sexual dysfunction. Intervention in the form of counseling may help patients to discover alternative ways in which to ease these problems.	Partially self-reported outcomes (no information about the use of validated instruments), no statistical analysis was performed Financial interest and/or other relationship	4 RoB: 14/16

						• Salpingitis (1 episode): 1/4 **Sexual intercourse** • ability to achieve sexual intercourse: 3/4 • never tried: 1/4 **Masturbatory** • no answer: 3/4 • no mastrubation; 1/4 **Sexual active** • yes: 3/4 • no: 1/4 **Age at first sexual experience vs peers:** • Normal: 2/4 • Later: 1/4 • Never: 1/4 **Children** • After normal conception: 1/4 (delivered by cesarean section)		with Health Vision. Funding: not reported.	
Mathews, 2003 [186]	Retrospective case series USA Mean follow-up: 14.1 y	To review of the sexual and urogynaecological issues faced by a large cohort of women with the exstrophy-epispadias complex.	n= 34 female with the exstrophy-epispadias complex • classic bladder exstrophy (n=24)	<u>Subgroup of classic bladder exstrophy on sexual function</u> (n=24) • no further genital reconstructive surgery	• Continence • Urinary stones • Vaginal uterine and rectal prolapse • Pregnancy & complica-tions	**Classic bladder exstrophy** <u>Satisfaction with genital reconstruction</u> (n=16) • 10/16 satisfied • 5/16 dissatisfied • 1/16 ambivalent	Women with the exstrophy-epispadias complex after successful reconstruction can lead productive and satisfactory lives. The goal of reconstruction should be to improve	Patient recruitment was not clearly described, self-reported outcome assessment (no information about the use of validated	4 RoB: 8/20

			• female epispadie (n=6) • cloacal exstrophy (n=6) Mean age: 24 y (13-52 y)	after initial bladder closure (n=8) • further genital reconstructio n (n=16)	• Urinary tract infections • Sexual function	**Pregnancy and complication** 6 women with initial closure had 11 pregnancies • 2/11 abortion • 2/11 miscarriage 5 women delivered 7 children • 6/7 Caesarean section • 1/7 vaginal delivery • 7/7 healthy infants with none having exstrophy 1/7 pregnancies uterine prolapse occurred and required surgery because a pessary failed	the cosmetic and functional outcomes.	instruments), no statistical analysis was performed Funds and conflict of interest: not reported.	
Stein, 1997 [187]	Case series Germany Reconstruction period: 1968 until July 1994 Mean follow-up: 16.7 y (0.2-35 y)	To determine the late outcome concerning urinary continence, late complications, sexuality, and fertility in patients with the exstrophy-epispadias complex	n=115 patients with exstrophy-epispadias complex • bladder exstrophy (n=95) • incontinent epispadias (n=20) Mean age: 20.2 y (1-48) Females: 41/115	• urinary diversion (n=88) • modified Young-Dees procedure (n=8) • sling plasty (n=3) genital reconstruction alone (n=3)	• Renal function • Continence • Late complication s • Social development • Sexual behavior • Fertility •	**Sexual behavior** All women engage in sexual intercourse **Pregnancy** 5/41 women delivered children <u>Mainz pouch I</u> • n=3 women with 4 children • Fixation of the uterus: 3/3 • No complications: 4/4 pregnancies	Reconstruction of the external and internal genitalia in women enables good cosmetic results; however, the risk of uterine prolapse should always be kept in mind. Fertility is not problematic, even in women with urinary diversion.	Unclear if data collection was prospective or retrospective, partially self-reported outcomes (no information about the use of validated instruments), no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 11/20

						• Mode of delivery: 4/4 sectio <u>Colon conduit</u> • n=1 woman with 2 children • Fixation of the uterus: no • No complications: 2/2 pregnancies • Mode of delivery: 2/2 sectio <u>Sling plasty</u> • n=1 woman with 1 child • Fixation of the uterus: no • complications: mild upper tract, dilatation and uterine prolapse Mode of delivery: 1/1 sectio			
Lattimer, 1978 [188]	Case series USA	Long-term followup after exstrophy closure	n=17 patients with anatomically reconstructed exstrophy Females: 35 % (6/17) <u>Age</u> Male: 17-30 y Female: 21-38 y	• later ileal conduit diversion (n=8) • non-diverted (n=9)	• Sexual experience • Marriage • Children • Work success • College attendance	**Sexual function** <u>Successful sexual experience</u> • Diverted (5/5) • Non-Diverted (0/1) <u>Children</u> • Diverted (2/5) Non-Diverted (0/1)	Most of these patients are healthy, attractive, well educated adults and have achieved emotional maturity and stability, despite their many problems.	Study aim was not defined, patient recruitment process was not reported, partially self-reported outcomes, no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 8/20

Bennett, 1973 [189]	Retrospective case series Recruitment period: 1931-1963 USA Mean follow-up: 17.9 y (5-35 y)	The controversy concerning the appropriate procedure for the infant with exstrophy has prompted us to review our experience in 94 patients treated by ureterosigmoidostomies to determine survival, renal function, growth and development, and long-term health of these children.	n=94 children with exstrophy of the bladder Female: 26/94 Mean age at point of operation: 4.6 y	ureterosigmoidostomies	• Survival • Renal function • Growth • Development • Long-term health	6 women have 8 children	The efficacy of any procedure in the treatment of a child with such a congenital anomaly must be related to the long-term results, including mortality rate, morbidity, and function.	Not described, if all eligible patients were included, outcome measurement were not clearly described, no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 11/20
Männliche Sexualität									
Systematische Reviews									
Berrettini, 2020 [129]	Systematic review n=7 studies • Case report (n=1) • Case series (n=5) • Cross-sectional (n=1) January 1st, 1990, to December 31st, 2019	We performed a systematic review of the literature with the aim of determining which technique is the best to perform in this population, and what risks and benefits there are for patients, especially in terms of psychosexual outcomes.	n=47 patients with BEEC • 89.4 % (42/47) bladder exstrophy • 10.6% (5/47) cloacal exstrophy Median follow-up after substitution phalloplasty: 43.5 mo (2-153 mo)	• Free radial forearm flap (89 %; 42/47) • Urethroplasty (47 %; 22/47) • Penile prosthesis (68 %; 32/47)	• Aesthetic outcomes • Sexual function • Psychological outcomes • Complications	**Aesthetic outcomes** • Almost all the patients were satisfied with the final cosmesis and size of the phallus, and with their body image, and confirmed they would opt for phalloplasty again **Sexual function** • all the patients reported a satisfying erogenous	Substitution phalloplasty in patients with bladder exstrophy-epispadias complex can achieve good functional, aesthetic, psychological, and sexual outcomes. It requires multiple procedures and carries a high complication rate. A concomitant urethroplasty is not mandatory because it carries a higher complication rate and most of these patients	No additional hand search was conducted, no information if efforts were made to minimise errors in the study selection, data collection and risk of bias assessment The authors received no specific funding for this work. The authors declare that they have no	4 RoB: high

						sensation with the ability to achieve orgasm • 50 % (16/32) of the patients who underwent penile prosthesis implantation reported successful penetrative sexual intercourse and no patient complained of the inability to perform **Psychological outcomes** • Good psychological satisfaction was reported by almost all the patients **Complications** • Free radial forearm flap: 15 % • Urethroplasty: 54 % Penile prosthesis: 25 %	do not usually use their native urethra for micturition. Penile prosthesis implantation remains a technically difficult procedure with a high complication rate and might not contribute to patient satisfaction. It was not possible to determine whether patients with penile prosthesis had better results in terms of sexual function than those without because no clear distinction between these patients was apparent in the results.	conflicts of interest.	
Primärstudien									
Harris, 2022 [190]	Retrospective cohort study 1997-2020 USA	The aim of this study was to assess sexual health outcomes before and after skin graft or tissue expansion assisted	n=28 male patients with exstrophy-epispadias complex, who underwent	• skin graft (n=14) • tissue expansion (n=6) • Phalloplasty (n=8)	• Patient perception of penile appearance • Sexual Health	**Patient perception of penile appearance** PPS score *ranging from 0-12 (median IQR)*	All three surgical methods improved patient perception of penile appearance and length though one third of patients remain dissatisfied, underlining	No detailed information on patient recruitment , median time after reconstruction	3 RoB: 6/9

	Median time after reconstruction: 4.4 y (1.2–13.2 y)	lengthening and neophalloplasty.	penile reconstruction • epispadias (n=4) • classical bladder • exstrophy (n=23): • cloacal exstrophy (n=1) Median age at reconstruction: 18.2 y (15.1 – 23.9 y)		• Ejaculatory dysfunction • Satisfaction with penile length, straightness upon erection • Overall satisfaction from masturba-ting	• Overall (n=24) Before: 4.5 (4.25) After: 7.5 (3) ($p < 0.05$) • Skin graft (n=12) Before: 4.5 (4.25) After: 8 (3) • Tissue expansion (n=6) Before: 7 (2.5) After: 7 (1.5) • Phalloplasty (n=6) Before: 2.5 (2.75) After: 7 (2.75) There was no significant difference in postoperative PPS between surgery groups **SHIM** *ranging from 5-25* • Overall median (n=17): 19 (IQR 6) • Skin graft (n=8): 19 (IQR 2.25) • Tissue expansion (n=5): 20 (IQR 1) • Phalloplasty (n=4): 15 (IQR 4.25)	the importance of managing expectations with routine psychological counselling.	was shorter in the tissue group, self-reported outcome assessment The authors received no specific funding for this work. The authors declare that they have no conflicts of interest.	

						no significant difference between subgroups (p=0.33) **Erectile dysfunction** (n=17) No difference (p=0.339). **MSHQ-EjD-SF** *ranging from 1-15* • Skin graft (n=10): 5 (IQR 12.5), • Tissue expansion (n=5): 15 (IQR 1) • Phalloplasty (n=6): 12 (IQR 3.5), No significant difference was seen between groups (p=0.08) **MSHQ-Bother** *ranging from 0-5* • Skin graft (n=10): 1 (IQR 1.75 • Tissue expansion (n=5): 1 (IQR 1) • Phalloplasty (n=6): 0 (IQR 0.75) Bother score was also noted to be			

						similar between groups (p=0.49) **Masturbating satisfaction** *ranging from 1-5* • Skin graft (n=14) Before: 4 (IQR 0.75) After: 4 (IQR 0.75) • Tissue expansion (n=6) Before: 4 (IQR 1.5) After: 4.5 (IQR 1.75) • Phalloplasty (n=7) Before: 4 (IQR 0.5) After: 4 (IQR 0.5) **Overall satisfaction with the final reconstruction result** *ranging from 0-3* • Skin graft (n=14): 2 (IQR 0.75) • Tissue expansion (n=6): 1.5 (IQR 1) • Phalloplasty (n=6): 1.5 (IQR 1.75) Median satisfaction			

						between reconstructive techniques was similar (p=0.88)			
Bhat, 2021 [145]	Retrospective case series Reconstruction period: 2015-2018 India Follow-up: 3-18 mo	The objective of the study was to evaluate the functional and cosmetic outcome of single-stage modified partial penile disassembly repair in isolated male epispadias.	n=15 male with epispadias • Peno-pubic variant (n=9) • Penile variant (n=6) Mean age: 11 y (4 mo-21 y)	Single-stage modified partial penile disassembly repair	• Correction of curvature (chordee/penile rotation) • Cosmesis • Patient satisfaction • Continence • Complications	**Cosmesis & correction of curvature** • 86.66 % (n=13) had excellent cosmetic outcome with complete correction of chordee/torque 13.44 % (n=2) had residual chordee but did not require surgery and were satisfied with the cosmetic result	Single-stage modified partial penile disassembly repair is an alternative to Cantwell Ransley repair with acceptable results to avoid morbidity and cost associated with multiple procedures. This technique aims to restore near-normal penile anatomy with satisfactory cosmesis and function.	Consecutive patient inclusion, method of outcome measurement unclear, no statistical analysis was performed The authors declare that they did not receive funding for this work. The authors declare that they have no conflicts of interest.	4 RoB: 12/20
Hussain, 2021 [191]	Case series Reconstruction period: 2004 – 2020 Pakistan Mean follow-up: 7.8 y (1 - 16 y)	To evaluate surgical outcomes and renal functions after cystectomy + MAINZ Pouch II and epispadias repair as a staged procedure in adult patients with exstrophy epispadias complex.	n=17 patients with exstrophy epispadias complex Mean age: 25.18 y (17-36 y) Male: 94.1 % (16/17)	Cystectomy and MAINZ Pouch II and epispadias repair as a two-staged procedure	• Renal function • Sexual function • Quality of life • Continence • Complications	**Sexuality** (n=16 male) <u>Morning erections present</u> 83 % (14/16) <u>Ejaculation night emission</u> 81 % (13/16) <u>Fertility</u> 0 % (0/16)	This study concludes that cystectomy + MAINZ Pouch II and staged epispadias repair provide good results, very high patient satisfaction, and rehabilitation back to society. Cosmetic results after genital reconstruction and epispadias repair were satisfactory.	unclear if data collection was prospective or retrospective, self-reported outcomes The authors declare that they have no conflicts of interest.	4 RoB: 16/20
Thomas, 2020 [192]	Retrospective case series 1998-2001	What procedures and operations did these patients require following	n=30 patients with primary epispadias	• Modified Cantwell-Ransley (n=22)	• Neourethroplasty and final appearance	**Sexual function** <u>Erections with Kelly procedure</u>	This study also shows high rates of erectile and ejaculatory function;	not described, if all eligible patients were	4 RoB: 12/20

	United Kingdom Median follow-up: 18.5 y (15-27 y)	their original surgery? What were their outcomes as adults in terms of continence, cosmesis, and sexual function?	• peno pubic (n=24) • midshaft (n=3) • distal (n=3)	• Tumble-Type repair (n=3) • reversed Duckett repair (n=1) no information about primry repair (n=4)	• Bladder dynamics and continence outcomes • Sexual function	• 3/4 normal erections • 1/4 poor erections: forearm flap phalloplasty as an adult, not clearly documented whether the erectile dysfunction was present before or after the Kelly procedure) **Children** 0/30	dissatisfaction with genital appearance is significant.	included, no validated instruments were used for the assessment, no statistical analysis was performed The authors declare that they have no conflicts of interest and they did not receive funding for this work.	
Reynaud, 2018 [193]	Case series 2016 France	The primary aims of this study were to report the sexuality, infertility, and urinary incontinence outcomes in a cohort of men born with bladder exstrophy-epispadias complex. The secondary aim was to highlight some predictive factors of infertility in this population.	n=38 male with bladder exstrophy-epispadias complex • n=31 classic bladder exstrophy • n=7 epispadias Mean age: 32 y (18-64 y)	• urinary diversion (cystectomy) (n=10, 26.3 %) • reconstruction (n=25, 65.8 %) • penile surgery in adulthood • (penile implant or phalloplasty) (n=9, 23.7 %)	• Sexuality • Fertility • Continence	**Sexuality** <u>IIEF-5</u> • No significant difference was between the cystectomy and reconstruction groups <u>Erection Hardness Score</u> *ranging from 1-4* • higher for patients who had reconstruction (3.88, SE=1.07) than for patients who had cystectomy (2.78, SE=1.09, p=0.02 **Fertility** • no patient from the cystectomy	Based on these data, assessment of sexuality and fertility in men with exstrophy seems highly pertinent. Early sperm storage along with genital reconstruction procedures in adulthood seem warranted interventions in the context of overall sexual medicine management of the bladder exstrophy-epispadias complex population.	Study design was not clearly defined, self-reported outcome assessment (not all instruments are validated) The authors declare that they did not receive funding for this work. The authors declare that they have no conflicts of interest.	4 RoB: 15/20

						group had tried to conceive no difference was noted between the 2 techniques regarding spermatozoa concentration or the IIEF-5 total score.			
Traceviciute, 2018 [194]	Case series 2009-2012 Germany	To investigate sexual function and QoL in adult male individuals with exstrophy epispadias complex.	n=19 male with exstrophy epispadias complex • 84 % (16/19) with classical bladder exstrophy • 16 % (3/19) with epispadias Median age: 26 y (22-38 y)	• single-stage reconstruction (31.5 %; 6/19) • staged reconstruction (37 %; 7/19) • primary urinary diversion (31.5 %; 6/19)	• Sexual function • Quality of life	**Sexual Function** • The method of penile reconstruction did not seem to influence the ability of orgasms. • Primary single-stage or staged approach and those reconstructed with primary urinary diversion with respect to potential decreased erectile function or impaired satisfaction with sexual life, no differences were found. <u>IIEF</u> • primary single-stage or staged approach and those with primary urinary diversion: no	The following are authors' recommendations to physicians: (1) Physicians should provide the best penile reconstruction possible. (2) Physicians should support male exstrophy epispadias complex patients in psychosexual education to allow an adequate and open-minded discussion during clinical consultations. (3) During consultations for sexual problems, standardized questionnaire should be used. Penile penetration and maintenance ability should be addressed, as there is a medical treatment option for confirmed erectile dysfunction.	Recruitment via German self-help support group Funds and conflict of interest: not reported.	4 RoB: 14/20

						significant differences			
Bhat, 2017 [195]	Retrospective case series Reconstruction period: 1998-2013 India Mean follow-up: 4 y (2-10 y)	To evaluate the functional and cosmetic outcome of single stage partial penile disassembly repair in isolated male epispadias.	n=50 male patients with primary epispadias repair • glanular (n=2) • penile (n=17) • peno-pubic (n=24) Mean age: 9 y (6 mo-26 y)	• Single stage partial penile disassembly repair	• Correction of curvature (chordee/penile rotation) • Cosmesis • Patient satisfaction • continence • Complica-tions	**Cosmesis** (determined by the surgeons) • 93 % with excellent cosmetic outcomes • 7 % had minimal residual chordee/torque but did not require any surgery **Patient satisfaction** None of the patients required any surgical procedure for correction of chordee/torque and were satisfied with the cosmetic result **Ejaculation** All the 12 patients in the post-pubertal group reported normal erections and successful ejaculations after the surgery.	This technique tries to restore the penile anatomy nearest to normal to achieve satisfactory cosmesis.	Consecutive patient inclusion, method of outcome measurement remains unclear, no statistical analysis was performed The authors declare that they did not receive funding for this work. The authors declare that they have no conflicts of interest.	4 RoB: 12/20
Rubenwolf, 2016 [196]	Retrospective case series Reconstruction period: 1969 - 2014	We evaluated patients with classic bladder exstrophy and a history of urinary diversion for sexual function,	n=39 men with bladder exstrophy Mean age: 36 y (19 – 59 y)	• undergone continent cutaneous (n=18) • continent anal urinary	• Sexual function • Social integration • Fertility • Paternity	**Sexual function** Sexual function as measured by IIEF was better in patients who had undergone primary continent	Importantly despite acceptable results regarding sexual function and fertility, particularly in men who have undergone primary urinary	Men who had undergone primary urinary diversion were significantly younger than those who had	4 RoB: 15/20

	Germany Mean follow-up: 23.8 y (2 - 45 y)	social integration and paternity.		diversions (n=15) • incontinent cutaneous urinary diversions (n=6)		anal diversion compared to continent cutaneous and incontinent diversion (not statistically significant) **Fertility** <u>Paternity</u> primary urinary diversion: 72 % secondary urinary diversion: 28 % p <0.05	diversion, the present study is not a plea for primary urinary diversion in patients with exstrophy. Modern reconstructive concepts should be applied whenever possible to further improve the cosmetic and functional results of exstrophy repair. Sexual function, sexual satisfaction, and fertility of males with exstrophy and a history of urinary diversion appear to be at least comparable to reported series of men in whom the bladder had been preserved. However, our findings confirm that sexual function in males with exstrophy is impaired across all dimensions, and thus followup should include assessment of sexuality and genital function. Surgical revision may be considered in men with persistent chordee, uncorrected epispadias and unacceptable cosmetic appearance of the genitalia.	undergone secondary urinary diversion, self-reported data Funding: Not reported. The authors declare that they have no conflicts of interest	
Djordjevic, 2013 [197]	Case series Reconstruction period:	Our aim was to present a radical approach for correction of all	n=13 male patients who underwent redo surgery	Patients were operated in a two-stage procedure	• Pre-/ postoperative penis	• 10/13 patients have completely straightened	Complete penile disassembly enables full correction of all deformities, primarily	Patient recruitment was not clearly described,	4 RoB: 10/20

	January 2006 and January 2011 Serbia Mean follow-up: 33 mo (12 – 60 mo)	penile deformities in patients after epispadias repair in childhood.	due to failed epispadias repair in childhood Age: 13-22 y Median number of previous repairs: 2.2 (1-5) All patients had severe dorsal curvature and short penile urethra before redo surgery	• <u>First stage:</u> included penile disassembly and grafting procedure for complete straightening and lengthening of the penis • <u>Second stage:</u> included reconstruction of the penile urethra using buccal mucosa graft and scrotal hairless skin flap	length in erection • Residual penile curvature • Sexual activity • Voiding function	and lengthened penis • 3/13 patients manifested mild curvature that did not require further treatment • 9 patients were sexually active and reported satisfactory sexual intercourse	marked dorsal curvature, and short penile shaft. Radical approach in redo epispadias repair is necessary to achieve functionally and aesthetically satisfactory result, but it should be performed only by experienced and skillful team in highly specialized surgical centers.	inclusion and exclusion criteria not clearly described, method of outcome measurement unclear, no statistical analysis was performed This article is supported by the Ministry of Science, Republic of Serbia. The authors declare that they have no conflicts of interest	
Djordjevic, 2013 [198]	Retrospective case series Reconstruction period: February 2006 to June 2011 Serbia Mean follow-up: 33 mo (14 – 78 mo)	We evaluated the results of 1-stage and multistage penile reconstruction in adults with complications after multiple failed epispadias repairs.	n=23 male who underwent penile disassembly for repeat epispadias repair • 14/23 isolated penopubic epispadias • 9/23 bladder exstrophy Mean age: 27 y (17 to 41 y)	Surgical treatment included penile disassembly with complete straightening and lengthening of the penis, followed by urethral lengthening	• Cosmesis • Quality of sexual life and satisfaction	**Cosmesis** • 19/23 patients with satisfactory cosmesis with no residual curvature • 4/23 cases mild curvature did not require additional correction **Penis length as measured during erection** • penis was lengthened in all patients by a	Complete penile disassembly enables full correction of all abnormalities, resulting in satisfactory penile lengthening and straightening. A radical approach to repeat epispadias repair is necessary to achieve functionally and esthetically satisfying outcomes, especially in terms of sensation, erection, orgasm and ejaculation.	Patient recruitment was not clearly described, inclusion and exclusion criteria not clearly described, no statistical analysis was performed Supported by the Ministry of Science, Republic of Serbia	4 RoB: 12/20

						mean of 3.9 cm (2.7 - 6.69 cm) **Erectile function** • All 21 sexually active patients reported good erectile function (IIEF score 25 or greater of 30) • Ejaculatory function was low in four patients (score 5-7 of 10) **Sexual function** • Sexual desire, and intercourse and overall satisfaction scores were adequate in all patients **Satisfaction with surgical outcome** • 87 % (20/23) were satisfied and did not regret the decision to undergo this type of surgery		Conflict of interest: not reported.	
Gobet, 2009 [185]	Case series Switzerland 1937-1968	We describe the long-term psychosocial and sexual outcomes of patients born with bladder exstrophy treated with ureterosigmoidosto	n=35 patients with bladder exstrophy Mean age: 50 y (39-67 y) Male: 21/35	Ureterosigmoi dostomy according to the Mathisen technique	• long-term psychosocial and sexual outcomes	**Andrological** • Epididymitis (1 episode): 3/21 • Recurrent epididymitis: 4/3 **Erection**	A third of the followed patients in this study experienced some fertility or sexual dysfunction. Intervention in the form of counseling may help patients to discover alternative	Partially self-reported outcomes (no information about validated instruments), no statistical analysis was performed	4 RoB: 14/16

		my at our institution.				• able to achieve erection: 20/21 • use of medication: 2/21 • normal erection until he • underwent renal replacement therapy: 1/21 **Ejaculation** • able to ecajulate: 15/21 • incomplete ejaculation: 3/21 • never experienced ejaculation: 3/21 **Masturbatory** • masturbatory activities throughout life: 20/21 • no mastrubation; 1/21 **Sexual active** • yes: 19/21 • no: 2/21 **Age at first sexual experience vs peers:** • Normal: 12/21 • Later: 4/21 • Never: 2/21 • Unknown: 3/21	ways in which to ease these problems.	Financial interest and/or other relationship with Health Vision. Funding: not reported.	

						Children Overall: 7 • After normal conception: 4/21 • Assisted reproduction: 2/21 Normal conception+ assisted reproduction: 1/21			
Ebert, 2008 [199]	Case series Germany/other European centers Mean follow-up Germany (n=16): 19 y (12.2-29.4 y) Europe (n=5): Median 1.2 y	The complications of early reconstructive surgery, however, seem to be disastrous to fertility. Therefore, we evaluated the long-term genital and reproductive function of functionally reconstructed male patients with exstrophy-epispadias complex.	n=21 male with exstrophy-epispadias complex • 85.7 % (18/21) with exstrophy • 14.3 % (3/21) with epispadias	• single-stage reconstruction (n=17) • staged approach (n=1) • primarily undergone urinary diversion (n=2) • external genital reconstruction of epispadias (n=1)	• Genital and reproductive function	**Erections** All patients reported erections **Ejaculation** 94.1 % of patients with exstrophy-epispadias complex report normal ejaculation after single-stage reconstruction with consequent placement of the colliculus seminalis in the posterior urethra	Single-stage reconstruction with consequent placement of the colliculus seminalis in the posterior urethra results in normal ejaculation in 94.1 % of patients with EEC. Because of the severely impaired sperm quality and hormonal findings, patients with exstrophy-epispadias complex should be offered adequate diagnostic and treatment options.	Recruitment via German self-help support group, no inclusion or exclusion criteria reported, less patient characteristics reported Funds and conflict of interest: not reported.	4 RoB: 11/20
Baird, 2005 [200]	Retrospective case series USA Mean follow-up: 88 mo	This is an evaluation and update of the long-term results of using the modified CantwelleRansley technique for epispadias repair.	n=129 patients with exstrophy-epispadias complex • classic bladder exstrophy (n=97) • complete epispadias (n=32)	• Cantwell-Ransley technique	• Fistula and stricture • Soft tissue infection • Cosmetic outcome and sexual function	**Cosmetic outcome and sexual function** • 120/129 cosmetically acceptable penis • 1/129 unacceptably short penis since his	The modified CantwelleRansley technique for epispadias repair produces durable functional and cosmetic results, and fewer major complications than seen with other repairs.	recruitment process and outcome measurement not clearly described, no statistical analysis was performed Funds and conflict of	4 RoB: 10/20

			Mean age • at primary repair: 19 mo • at secondary repair: 23 mo			corrective surgery **Sexually active** (n=15) all: straight erections, able to have orgasms and ejaculate without difficulty		interest: not reported.	
Stein, 1997 [187]	Case series Germany Reconstruction period: 1968 until July 1994 Mean follow-up: 16.7 y (0.2-35 y)	To determine the late outcome concerning urinary continence, late complications, sexuality, and fertility in patients with the exstrophy-epispadias complex	n=115 patients with exstrophy-epispadias complex • bladder exstrophy (n=95) • incontinent epispadias (n=20) Mean age: 20.2 y (1-48) Males: 74/115	• urinary diversion (n=88) • modified Young-Dees procedure (n=8) • sling plasty (n=3) • genital reconstruction alone (n=3)	• Renal function • Continence • Late complications • Social development • Sexual behavior • Fertility •	**Erection** • All except 1 man, who had a necrosis of the penis after primary bladder closure, achieved erection **Ejaculation** • No patient with reconstruction of the external genitalia can ejaculate normally or has fathered children • 5 who did not undergo genital reconstruction had normal ejaculation and 2 have fathered 4 children	The risk of infertility after genital reconstruction in males is extremely high.	unclear if data collection was prospective or retrospective, partially self-reported outcomes (no information about validated instruments), no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 11/20
Avolio, 1996 [201]	Case series Recruitment period: 1970 – 1995	We report our results with the long-term follow-up of cosmetic appearance, sexual function, fertility	n=29 male with bladder exstrophy and/or epispadias	Initial form of treatment in 25 bladder exstrophy patients:	• Sexual function • Social integration • Fertility	**Impression of genitalia** *Subgroup patients with bladder exstrophy (n=25)*	Our long-term review demonstrates that reconstructive surgery in patients with an epispadiac penis can result in a successful	self-reported statisfaction outcomes, no statistical analysis was performed	4 RoB: 12/20

	USA Mean follow-up: 17 y (4-24 y)	potential and social integration of 29 men with bladder exstrophy (25) and/or epispadias (4) who underwent reconstruction of the external genitalia.	• n=25 bladder exstrophy • n=4 epispadias (2 peno-pubic, 2 mid-shaft) Mean age: 25 y (18-53 y)	• bladder closure (n=7) • Ureterosiemoidostomy (n=11) • Ileal conduit (n=6) • colon conduit (n=1)		<u>Bladder closure (n = 7)</u> Poor: 2/7 Fair: 2/7 Good: 3/7 <u>Urinary Diversion (n=15)</u> Poor: 2/15 Fair: 5/15 Good: 8/15 **Sexual activity** <u>Bladder closure (n=7)</u> Present: 6/7 Absent: 1/7 <u>Urinary Diversion (n=15)</u> Present: 11/15 Absent: 4/15 **Orgasm** <u>Bladder closure (n=7)</u> Present: 7/7 <u>Urinary Diversion (n=15)</u> Present: 15/15 **Erection** <u>Bladder closure (n=7)</u> Straight: 4/7 Curved: 3/7 <u>Urinary Diversion (n=18)</u> Straight: 12/18 Curved: 6/18 **Ejaculation**	cosmetic appearance, suitable genital function and potential for preservation of fertility. An encouraging finding of our study was that men with bladder exstrophy or epispadias seem to do well despite what appears to be a severe sexual handicap. The evidence of overall successful social integration is an important consideration, since whatever the surgical outcome in a child without a normal social life overall treatment can be considered to have failed.	Funds and conflict of interest: not reported.	

						<u>Bladder closure (n=7)</u> Straight: 6/7 Curved: 1/7 <u>Urinary Diversion (n=18)</u> Straight: 16/18 Curved: 2/18 **Fertility potential** (n=8 exstrophy patients) <u>Case 1 (18 y)</u> • Urinary Diversion: Ureterosigmoidostomy • Urethral Opening: Apex • Vol. (ml): 0.7 • Sperm Count (millions/ml.): 200 • Motility and Viability: 50 % <u>Case 2 (18 y)</u> • Urinary Diversion: Ureterosigmoidostomy • Urethral Opening: Apex • Vol. (ml): 1.0 • Sperm Count (millions/ml.): 7 • Motility and Viability: 50 % <u>Case 3 (20 y)</u> • Urinary Diversion:			

						Ureterosigmoidostomy • Urethral Opening: Apex • Vol. (ml): 0.22 • Sperm Count (millions/ml.): 7 • Motility and Viability: 65 % <u>Case 4 (23 y)</u> • Urinary Diversion: Colon conduit • Urethral Opening: Apex • Vol. (ml): 0.9 • Sperm Count (millions/ml.): 16 • Motility and Viability: 20 % <u>Case 5 (24 y)</u> • Urinary Diversion: Ileal conduit • Urethral Opening: Base • Vol. (ml): 2.8 • Sperm Count (millions/ml.): 43 • Motility and Viability: 45 % <u>Case 6 (28 y)</u> • Urinary Diversion: Ureterosigmoidostomy • Urethral Opening: Base • Vol. (ml): 2.8			

						• Sperm Count (millions/ml.):45 • Motility and Viability: 65 % <u>Case 7 (29 y)</u> • Urinary Diversion: Ileal conduit • Urethral Opening: Apex • Vol. (ml): 1.0 • Sperm Count (millions/ml.): 41 • Motility and Viability: 65 % <u>Case 8 (28 y)</u> • Urinary Diversion: Ileal conduit • Urethral Opening: Anejaculatory • Vol. (ml): - • Sperm Count (millions/ml.): 40 Motility and Viability: 65 %			
Kramer, 1986 [202]	Case series Recruitment period: 1946 - January 1984 USA Follow-up: 1-30 y	We report our results with long-term follow-up of the cosmetic appearance, sexual function and fertility potential in 70 male patients with epispadias who underwent reconstruction of the external genitalia.	n=70 male patients with epispadias • 42/70 classic peno-pubic • 19/70 penile epispadias 9/70 glandular epispadias	• 1-stage or multistage urethroplasty with release of dorsal skin chordee as the only attempt to achieve penile lengthening (n=57)	• Postoperative cosmetic appearance • Postoperative genital function in postpubertal patients • Intercourse • Ejaculation • Children	**Postoperative cosmetic appearance** *% straight appearance [vs. curved]* <u>peno-pubic epispadias</u> • release of dorsal skin chordee only: 61 % (20/33)	Meticulous attention to the technical aspects of reconstructive surgery usually can result in a gratifying cosmetic appearance, normal genital function and preservation of fertility potential in most patients.	Consecutive patient inclusion and method of outcome measurement unclear, less patient characteristics reported, no statistical analysis was performed, loss to follow-up not	4 RoB: 7/20

				• V-Y elongation of the penis with partial mobilization of the curura of the laterally based rhomboid flaps to provide dorsal skin coverage (n=10) • V incision for exposure of the cura and laterally based rhomboid flaps to provide dorsal skin coverage (n=3)		• penile elongation by V-Y plasty: 86 % (6/7) • penile elongation by rhomboid flaps: 100 % (2/2) <u>penile epispadias</u> • release of dorsal skin chordee only: 47 % (7/15) • penile elongation by V-Y plasty: 67 % (2/3) • penile elongation by rhomboid flaps: 100 % (1/1) <u>glandular epispadias</u> • release of dorsal skin chordee only: 100 % (8/8) • penile elongation by V-Y plasty: 100 % (1/1) **Postoperative genital function in postpubertal patients** • **Intercourse** <u>peno-pubic epispadias</u> release of dorsal skin chordee only (n=32):	Our long-term follow-up in this large series of patients confirms those earlier observations. All 56 of our post pubertal patients have adequate erections and 41 have experienced satisfactory intercourse. 29 patients are married and 19 have fathered children.	clearly described Funds and conflict of interest: not reported.	

						• Satisfactory: 26/32 • Unsatisfactory: 4/32 • No attempt: 2/32 penile elongation by V-Y plasty (n=3): • Satisfactory: 1/3 • No attempt: 2/3 penile elongation by rhomboid flaps (n=2): • No attempt: 2/2 <u>penile epispadias</u> release of dorsal skin chordee only (n=10): • Satisfactory: 9/10 • Unsatisfactory: 1/10 penile elongation by V-Y plasty (n=3): • Satisfactory: 2/3 • No attempt: 1/3 penile elongation by rhomboid flaps (n=1): • No attempt: 1/1 <u>glandular epispadias</u>			

						release of dorsal skin chordee only: • Satisfactory: 3/5 • Unsatisfactory: 1/5 • No attempt: 1/5 **Ejaculation** <u>peno-pubic epispadias</u> release of dorsal skin chordee only (n=32): • Antegrade: 24/32 • Retrograde: 0/32 • Nonejaculatory: 8/32 penile elongation by V-Y plasty (n=3): • Antegrade: 2/3 • Retrograde: 0/3 • Nonejaculatory: 1/3 penile elongation by rhomboid flaps (n=2): • Antegrade: 1/2 • Retrograde: 0/2 • Nonejaculatory: 1/2 <u>penile epispadias</u>			

						release of dorsal skin chordee only (n=10): • Antegrade: 9/10 • Retrograde: 0/10 • Nonejaculatory: 1/10 penile elongation by V-Y plasty (n=3): • Antegrade: 2/3 • Retrograde: 1/3 • Nonejaculatory: 0/3 penile elongation by rhomboid flaps (n=1): • Antegrade: 1/1 • Retrograde: 0/1 • Nonejaculatory: 0/1 **Children** <u>peno-pubic epispadias</u> 12 had fathered children <u>penile epispadias</u> 5 had fathered children <u>glandular epispadias</u> 2 had fathered children			
Mesrobian, 1986 [203]	Case series Recruitment period: 1924 through 1984	We report our results with long-term followup of the cosmetic appearance, sexual function and fertility potential in	n=53 male with exstrophy of the bladder	• n=35/53 had urinary diversion • n=18/53 had successful primary	• Cosmetic appearance • Sexual function • Fertility	**Cosmetic appearance** <u>Straight penis</u> Urethroplasty only (n=5): 23 % Penile elongation (n=19): 86 %	It is apparent from our long-term review that surgery in boys with bladder exstrophy can result in a gratifying cosmetic appearance, normal genital function	Patient recruitment was not clearly described, no detailed information on patient	4 RoB: 7/20

	USA Mean follow-up: 19 y (1-56 y)	a group of 53 male patients with bladder exstrophy who underwent reconstructive surgery on the external genitalia.		bladder closure Surgical reconstruction of the external genitalia consisted of penile elongation, urethroplasty or a combination of both: • with single-stage or multistage urethroplasty was done, with release of dorsal skin chordee as the only attempt to achieve penile elongation (n=22) • patients with penile elongation (13/22 urethroplasty, 9/22 without uretroplasty) • patients with V-Y elongation of the penis was done with partial mobilization of the crura of the		• Penile elongation with urethroplasty: 11/19 • Penile elongation without urethroplasty: 8/19 **Genital function** (n=23 postpubertal patients) <u>Satisfactory intercourse:</u> • Release of skin chordee only: 12/20 • Penile elongation by V-Y plasty: 2/3 Potency was preserved in all patients interviewed.	and preservation of fertility potential in most patients.	characteristics , self-reported satisfaction outcomes, no statistical analysis was performed Funds and conflict of interest: not reported.	

				corpora cavernosa from the pubic rami before or at the time of urethroplasty (n=16) • penile lengthening and straightening by use of rhomboid flaps (n=6)					
Lattimer, 1978 [188]	Case series USA	Long-term followup after exstrophy closure	n=17 patients with anatomically reconstructed exstrophy Male: 65 % (11/17) <u>Age</u> Male: 17-30 y Female: 21-38 y	• later ileal conduit diversion (n=8) • non-diverted (n=9)	• Sexual experience • Marriage • Children • Work success • College attendance	**Sexual function** <u>Successful sexual experience</u> • Diverted (3/3) • Non-Diverted (4/11) <u>Children</u> • Diverted (0/3) Non-Diverted (0/11)	Most of these patients are healthy, attractive, well educated adults and have achieved emotional maturity and stability, despite their many problems.	Study aim and patient recruitment were not defined, partially self-reported outcomes, no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 8/20
Bennett, 1973 [189]	Retrospective case series Recruitment period: 1931-1963 USA Mean follow-up: 17.9 y (5-35 y)	The controversy concerning the appropriate procedure for the infant with exstrophy has prompted us to review our experience in 94 patients treated by ureterosigmoidostomies to determine survival, renal	n=94 children with exstrophy of the bladder Male: 68/94 Mean age at point of operation: 4.6 y	Ureterosigmoidostomies	• Survival • Renal function • Growth • Development • Long-term health	3 males have 5 children	The efficacy of any procedure in the treatment of a child with such a congenital anomaly must be related to the long-term results, including mortality rate, morbidity, and function.	Not described, if all eligible patients were included, outcome measurement was not clearly described, no statistical analysis was performed	4 RoB: 11/20

		function, growth and development, and long-term health of these children.						Funds and conflict of interest: not reported.	
Beide Geschlechter									
Ebert, 2005 [204]	Retrospective case series Reconstruction period: 1983 - 1994 Germany Mean follow-up: 11.1 y (6 – 18 y)	We report the psychosocial and psychosexual development of children and adolescents with the exstrophy-epispadias complex after complete functional repair using the Erlangen single stage technique.	n=100 patients with exstrophy-epispadias complex • patients with exstrophy (n=91) • patients with third degree epispadias (n=9) Mean age: 14.5 y <u>Sex</u> Exstrophy: 69/91 Epispadias: 7/9 male	complete functional repair using the Erlangen single stage technique	• Psychosocial and psychosexual development	**Psychosexual development of adolescents > 15 y (n=41)** • Expressed heterosexuality Boys: 100 % Girls: 100 % • Never undressed in front of anyone Boys: 43.8 % Girls: 33.3 % • Never showered or undressed in a gym class or athletics Boys: 90.6 % Girls: 44.4 % • Never masturbated Boys: 25 % Girls: 55.6 % • Rarely masturbated Boys: 37.5 % Girls: 33.3 % • Peer contact with opposite sex Boys: 84.4 % Girls: 88.9 %	Despite favorable surgical outcome, all clinicians should respect the distinctive concerns of patients with exstrophy-epispadias complex regarding their sexuality and fertility, and provide adequate professional information about normal sexual development. In our preliminary study nearly all patients with exstrophy-epispadias complex expressed anxiety concerning genital appearance, sexual activity, social life and the future. Discussion of anxiety and psychosexual distress during consultation with the pediatric urologist may be insufficient, and, thus, additional psychological assistance should be available during childhood and adolescence. Anatomical integrity alone may not necessarily ensure	not described, if all eligible patients were included, self-reported outcomes (no information about the use of validated instruments), no statistical analysis was performed Funds and conflict of interest: not reported.	4 RoB: 10/20

						• Dated Boys: 65.6 % Girls: 77.8 % • Girlfriend/boyfriend Boys: 56.3 % Girls: 55.6 % • Petting Boys: 50 % Girls: 77.8 % • Sexual intercourse Boys: 40.6 % Girls: 55.6 % • Anxiety concerning sexual intercourse Boys: 59.4 % Girls: 55.6 % • Anxiety concerning partnership Boys: 50 % Girls: 55.6 % • Problems in answering questionnaire (2 of 28 questions) Boys: 6.3 % Girls: 11.1 % **Genital function and appearance** <u>Boys (n=31)</u> • Erection: 96.9%	acceptable body image and self-esteem.		

						• Ejaculation: 84.4% • Pain during erection: 25.8% • Epididymitis: 31.3% • Acceptable penile appearance: 21.9% • Acceptable penile size: 6.3% <u>Girls (n=9)</u> • Menstrual period: 100% • Genital pain: 22.2% • Acceptable genital appearance: 33.3% • Desire to have children: 100% **Satisfaction with genital appearance in adolescents** Satisfaction with reconstruction • Very good: Boys: 0 % Girls: 11.1 % • Good: Boys: 15.6 % Girls: 22.2 % • Regular: Boys: 15.6 % Girls: 22.2 % • Poor:			

						Boys: 15.6 % Girls: 11.1 % • Bad: Boys: 6.3 % Girls: 0 % • Very bad: Boys: 9.4 % Girls: 11.1 % • No comment: Boys: 37.5 % Girls: 22.2 %			

7. Ergebnisse der Suche nach systematischen Übersichtsarbeiten

Referenz	Studien-charakteristika	Teilnehmer	Fragestellung	Ergebnis	Kritische Bewertung
Epidemiologie					
Toobaie, 2019 [205]	n=41 studies 21 countries 2006-2017	Patients with correctible congenital anomalies	We hypothesize that significant discrepancies exist between directly reported low-income country data and surrogate high-income country **disease burden estimates of correctible congenital anomalies**.	**Bladder exstrophy** • Mean prevalence: 2 per 10,000 children **Hypospadias/Epispadias** • Mean prevalence: 34 (SD 39) per 10,000 children • Mean incidence: 11 (SD 19) per 10,000 children	3 No information if efforts were made to minimise error in the data collection or in the risk of bias assessment
Riskofaktor: Krebs					
Husman, 2009 [206]	n=8 articles	n=21 patients that had bladder cancer or adenomatous polyps develop following augmentation for congenital anomalies n=3 patients with extrophy	To review the **incidence and risks of bladder cancer** following gastrointestinal augmentations done for congenial anomalies in childhood	**n=3 patients with extrophy** • Colon: Adenocarcinoma T3 N2 M0 after 32 y • Ileum: Adenocarcinoma T3 N2 M0 after 47 y • Ileum: Adenocarcinoma T3 N2 M0 after 22 y	4 Only one database used, no search date, no information if an additional hand search was made, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment
Ragu, 2016 [207]	n=12 articles within the last 20 years	n=23 patients (21 literature search, 2 authors institution) with bladder exstrophy patients with enteric colonic or neorectal bladder diversion n=22 adenocarcinoma patients n=1 carcinoid tumour patient	The aim of this paper is to review the published literature **on neoplasia after urinary diversion** as well as the current recommendations for follow-up and management of these patients.	• Median age at urinary diversion: 3 (range 1–13) years • Cancer diagnosis after urinary diversion still in place (n = 18): median 31 (range 5–55) years • Cancer diagnosis after • incomplete excision of ureteric stump when re-diverted (n = 5): 21 years (range 1–30) • long-term outcomes of 15 patients: 10 died, 5 were disease-free at 3 y • Patients with enteric diversion for bladder exstrophy, including those with subsequent	4 no unambigous search date, no information if an additional hand search was made, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment

				reconstruction, are at risk of adenocarcinoma during adulthood: adequate surveillance is important • If lesions suggestive of carcinoma are seen, complete excision of the receptive bowel and urinary diversion are mandatory	
Schwangere und Gebärende					
Bey, 2021 [56]	n=25 studies • 1 single-center study • 3 retrospective multiple-center study • 15 retrospective single-center studies/case series • 6 case reports 1972-2020	women with neurogenic bladder or bladder exstrophy who had undergone previous lower urinary tract reconstruction n= 229 women representing 292 pregnancies n=98 women had bladder exstrophy	The aim of this systematic review of the literature was to pool all the existing data regarding **pregnancy and delivery** in women with neurogenic bladder or bladder exstrophy who had undergone previous lower urinary tract reconstruction	• Pregnancy and vaginal delivery are possible for women with lower urinary tract reconstruction who have no obstetric or medical contraindications, except for some particular cases of bladder exstrophy. • these high-risk pregnancies and deliveries should be managed by a specialist multidisciplinary team • in case of heavily reconstructed genitals, duplicated vagina, significant genital prolapse: discuss pros and contras with the patient • Spontaneous vaginal delivery: unless obstretrical, neurological or anesthesiological contra-indication • Systematic Planned C-section at 37 weeks of gestation with Urologist	3 No detailled risk of bias assessment shown for the included studies
Psychosoziale Aspekte					
Dellenmark-Blom, 2019 [208]	n=21 studies • children and adolescents (n=5) • adults only (n=5) • integrated age populations (n=11) Median sample size: 24 cases from inception to May	Patients with BEEC	This study aimed to review the literature on generic and disease-specific life **HRQOL** in BEEC patients, and methodologies used	• Impaired physical or general health has been described (n=9 articles) • diminished mental health (n=11 articles) • restricted social health (n=10 articles) • sexual health/functioning or body perception impairments (n=13 articles) • Urinary incontinence was the most common factor related to worse HRQOL (n=12 articles) • HRQOL was better than healthy norms (n=6 articles) • the pooled estimate of the effect of BEEC indicated worse HRQOL for	4 No additional hand search, no risk of bias assessment

				children and adults (0 > effect sizes < 0.5). • Thirty-six HRQOL assessments were used, none developed and validated for BEEC	
Diseth, 1999 [209]	n= 10 studies 1968-1999	n=365 patients with BEEC (children, adolescents and adults)	We present some general **biopsychosocial aspects** along with an overview of reports published over the past three decades to elucidate the mental, psychosocial, familial, and social implications BEEC.	**Studies of somatic function** • report satisfactory longterm urinary control (67-82%) • unsatisfactory urinary control (75-100%) in children without urinary diversion • 75% of males have some form of ejaculation • High incidence of scarce or absent sperm and about 50% infertility in male patients • 50-60% of male patients are dissatisfied with their penile appearance [or bothered by their insufficient penile length and chordea **Studies of mental health, psychosocial functioning, or quality of life** Children/Adolescents: • problems were related to urinary incontinence and to the appearance of the genitalia or sexual function • more psychological problems than the average child • children tended to have more severe behavioral and developmental problems, body image distortion, and self-esteem problems than children with other anomalies Adults: • more positive picture • strikingly normal and well-adjusted	4 only one database used, no additional hand search, no information about if efforts were made to minimise error in the data collection and study selection, no risk of bias assessment
Holmdahl, 2020 [175]	n=16 articles between January 1, 2015 and December 31, 2019	n=546 patients with BEEC (children & adults)	The aim of this review is to summarize and discuss the latest 5 years of published reports on **HRQOL** in children and adults with the	**Generic HRQOL** Children • better self-reported HRQOL in children with the BEEC than among	4 No information if an additional hand search was made, no

			BEEC and its relationship to incontinence and sexual factors.	other pediatric chronic health conditions • children's self-reported HRQOL was more positive than the answers from the parent-proxy questionnaires Adults • HRQOL did not differ from that in the general population **HRQOL and Relationship to Incontinence** • it was concluded that in males, urinary leakage has a tendency to significantly reduce HRQOL • urinary incontinence was the main reason for reducing HRQOL and 84% of the incontinent women reported a moderate-to-severe impact on their sex life • females with epispadias: a low impact of incontinence on HRQOL was found • high rate of incontinence and lower urinary tract symptoms still resulted in a relatively low to some degree of bother • incontinence rate of 63%, satisfaction was still relatively high, with 46% reporting no interference by continence status on their daily life **HRQOL and Relationship to Sexual Factors** • paternity and maternity rates are lower compared with the general population, there are no reports during recent years on the impact on HRQOL **Women and Impact of Sexual Function on HRQOL** • suggests a relationship between sexual function and overall psychological wellbeing	information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment

				• females with epispadias: only one-fifth patients had a lackof self-confidence and a fear of rejection in relationships • pelvic organ prolapse causes effects on sexual function and incontinence with significant reductions in HRQOL **Men and Impact of Sexual Function on HRQOL** • no studies so far reported a significant impact of sexual function on HRQOL • sexual dysfunction is common A common concern is dissatisfaction with genital appearance and the size of the penis	
Hu, 2020 [210]	n=25 studies • 13 cohort studies • 11 cross-sectional studies • 1 case-control study Between 1995 and 2019	n=6520 patients 17 patients with bladder exstropy (n=1 retrospective cohort study)	The purpose of this review is to systematically summarize the literature evaluating the impact of multiple surgeries on **psychosocial development in** children with complex congenital birth defects and identify any existing gaps in knowledge	**Bladder exstrophy** • the global number of surgical procedures is significantly related to patient relations with family	3 No additional hand search reported, no information if efforts were made to minimise error in selection or in the risk of bias assessment
Operative Techniken					
Sarikaya, 2017 [211]	n=15 articles 2008-2016	276 patients with neophallus creation • 191 female-to-male transgender • 9 disorder of sex development/micropenis • 16 penile trauma/amputation • 9 ambigous genitalia • 40 exstrophy and/or epispadias • 11 other problems	This study was designed for reviewing the literature for **phalloplasty** articles and comparing the results and complications of this surgery.	**Exstrophy and/or epispadias** • Radial forearm free-flap (n=16) • Total phallic reconstruction with radial artery based forearm free flap phalloplasty (n=16) • Radial forearm free-flap or Anterolateral thigh flap (n=4) Massanyi et al. (n=10) • Transferred flap survived in all 10 patients Garaffa et al. (n=16) • 93% were fully satisfied with phallic cosmesisand size	4 No additional hand search, no information if efforts were made to minimise error in the study selection or data collection, no risk of bias assessment

				• patient had distal part loss due to acute thrombosis Timsit et al. (n=6) • 3 complications in the postoperative period	
Markiewicz, 2007 [212]	n=57 studies • Urethral Stricture Reconstruction (n=22) • Urethral Stricture Reconstruction+ Hypospadias/Epispadias (n=7) • Hypospadias/Epispadias (n=17) January 1966 through August 1, 2006	1,353 cases involving oral mucosa based urethroplasty for the repair of defects associated with urethral stricture and hypospadias/epispadias	We provide the reader with a critical, nonbiased, systematic review of current and precedent literature regarding the use of **oral mucosa in the reconstruction of urethral defects** associated with stricture and hypospadias/epispadias.	**The Use of Oral Mucosa in Hypospadias/Epispadias Reconstruction** • epispadias defect repair was found to only account for less than 1% of current oral mucosa graft • oral mucosa graft urethroplasties were performed for primary and secondary reconstruction. • Average success rate was 66.5% • Only tube grafts with a success rate of 52.7% (n=5) • only onlay grafts with a success rate of 80.4% (362 cases) (p<0.001) (n=5) • ventral placement of the oral mucosa graft onlay, success rate was reported to be 80.4% (n=4) • only dorsal onlay for hypospadias/ epispadias repair had a success rate of 87.3% (p= 0.234) (n=1) • Multistage urethroplasty with a success rate of 81.6% (n=2) • single stage oral mucosa graft urethroplasty the success rate was 78% (n=15) • labial harvest in 288 cases with a success rate of 71.5% (n=10) • buccal harvest with an 86.9% success rate (p <0.001) (n=7) • common recipient site complications of oral mucosa graft urethroplasty were fistula formation (9.7%), stricture (4.1%) and meatal stenosis (3.2%)	4 no information if efforts were made to minimise error in the data collection, no risk of bias assessment
Berrettini, 2021	n=7 studies • Case report (n=1) • Case series (n=5)	n=47 patients with BEEC 89.4% bladder exstrophy	To determine whether patients with bladder exstrophy-epispadias	**Free radial forearm flap** • most commonly: 89% • overall complication rate: 15%	4

[213]	• Cross-sectional (n=1) January 1st, 1990, to December 31st, 2019	10.6% cloacal exstrophy Median follow-up after substitution phalloplasty: 43.5 mo (2-135 mo)	complex might benefit from **substitution phalloplasty.**	**Urethroplasty** • performed in 47% patients • most cases (20/22) a "tube-within-the-tube" technique was performed simultaneously with the phalloplasty (20/47) • overall complication rate: 54% **Penile prosthesis** • performed in 68% patients • overall complication rate: 25% Aesthetic, sexual, and psychological outcomes were satisfactory (no use of validated instruments for assessment)	No additional hand search, no information if efforts were made to minimise errors in the study selection, data collection and risk of bias assessment
Pathak, 2020 [214]	n=11 articles 1989-2018	n=236 patients with complete primary repair of the bladder exstrophy 153 boys 72 girls 11 sex unreported Timing of the primary closure: from birth to 5.6 years	Does **complete primary repair** reduce the numbers of procedures for reconstruction of bladder exstrophy?	• Infants reported having closure beyond the first 72 h of life (34/236 patients) were most commonly managed with osteotomy and spica cast immobilization • Complications of primary closure: 63 • Most were considered minor, including superficial infections • failure of the closure (n=8), complete dehiscence (n=2), fistula (n=20, 18 required fistula closure), death (n=2) • Further reported surgical interventions: ureteral reimplantation (n=58), injection of dextranomer/hyaluronidase (n=3), hypospadias repair (n=11), bladder neck reconstruction (n=33), bladder neck bulking procedures (n=7), revision of epispadias (n=10) • Continence status not universally reported: Volitional voiding (n=34), dry with only primary bladder closure (n=11), bladder neck closure (n=7), intermittent catheterization for bladder-emptying (n=6)	4 No study overview, only one database used, no additional hand search, no information if efforts were made to minimise errors in the study selection or data collection, no risk of bias assessment
Gesundheitsprobleme/Krankheitslast					
Yousef, 2019	n=36 publications (+ 1 own retrospective study)	n=2864 surgical procedures in 13 African countries	The purpose of this study was to estimate the unmet	**Bladder exstrophy** (n=3 articles+1 own study)	4

[215]			**burden of surgically correctable congenital anomalies** in African low- and middle-income countries	Egypt Mean surgical delay: 0.99 y Surgical backlog: 84 number of cases Unmet prevalent need: 77 DALY Ethopia Mean surgical delay: 5.48 y Surgical backlog: 575 number of cases Unmet prevalent need: 529 DALY Nigeria Mean surgical delay: 0.11 y Surgical backlog: 26 number of cases Unmet prevalent need: 24 DALY	No additional hand search, no risk of bias assessment
Musleh, 2021 [216]	n=12 retrospective studies (2 multicenter, 10 monocenter) between 1960 and September 2020	n=191 patients with cloacal exstrophy Patients age: 10-34 y	This systematic review aims to define the **prevalence of long-term active medical problems** affecting cloacal exstrophy patients after the first decade of life.	**Prevalence** • urinary incontinence: 9.1% to 85% • Sexual function issues related to vaginal anomalies: 8.3% to 71.3% • uterine anomalies: 14.3% to 71% • gender identity issues: 11.1% to 66.7% • abnormality of the upper urinary tract: 14.3% to 48% • chronic kidney disease: 15% to 87.1% • vaginal anomalies: 8.3% to 71.3% • sexual activity: 17.9% (overall) • female gender assignment at bith: 44.4% to 85.7% • gender reassignment: 38.5% • Impairment of ambulatory capacity: 13.8 • no documented history of paternity • successful pregnancy: 4.1% • miscarriage: 4.1% • psychological well-being: significantly higher levels of depression among gender reassigned patients.	4 the used risk of bias assessment is not the appropriate instrument for all included studies, no information if efforts were made to minimise errors in the ris of bias assessment
Genderidentität					
Meyer-Bahlburg, 2005	1966-2004	N=77 female-raised 46,XY persons	This review addresses the **long-term gender outcome of gender**	**Cloacal Exstrophy of the Bladder** • The difference in gender outcome between female- and maleraised	4

[217]		n=16 patients with penile agenesis n=51 patients with cloacal exstrophy n=3 patients with classical bladder exstrophy n=7 patients who suffered a traumatic loss of the penis in infancy or early childhood	**assignment** of persons with intersexuality and related conditions.	patients with cloacal exstrophy is highly significant (≤ .001) **Classical Exstrophy of the Bladder** • The difference in gender outcome between the male- and female-raised groups also goes into the expected direction, but cannot be statistically tested because of the small sample size of the female-raised group. The findings clearly indicate an increased risk of later patient-initiated gender re-assignment to male after female assignment in infancy or early childhood, but are nevertheless incompatible with the notion of a full determination of core gender identity by prenatal androgens.	no information if efforts were made to minimise errors in the study selection and data collection, no risk of bias assessment

8. Ergebnisse der Studienregister

Nummer	Name	Status	Studienplan	Ergebnis
Laufende Studien				
NCT04580186	Outcome Of Classic Bladder Exstrophy Repair	Estimated Study Completion Date: December 30, 2022 Recruitment Status: Not yet recruiting	n=10 patients with bladder exstrophy prospective, observational Intervention: bladder exstrophy repair	No results available
NCT04729582	Autologous Muscle Stem Cell Therapy for Treatment of Congenital Urinary Incontinence in Epispadias Patients (MUST)	Estimated Study Completion Date: April 2025 Recruitment Status: Not yet recruiting	n=21 patients with Epispadias and Urinary Incontinence randomized placebo-controlled clinical trial Intervention: Primary human muscle stem cells (Satori-01) vs Placebo	No results available
NCT03061084	Prospective Cohort of Transitional Urology Patients	Estimated Study Completion Date: December 31, 2025 Recruitment Status: Recruiting	n=200 participants with Spina Bifida, Myelomeningocele, Meningocele, Bladder Exstrophy, Genitourinary Congenital Anomalies or Cloacal Exstrophy prospective, observational Outcome: Quality of life changes	No results available
NCT04626167	Concomitant Renal and Urinary Bladder Allograft Transplantation	Estimated Study Completion Date: January 1, 2026	n=30 participants with Chronic Kidney Diseases, Chronic Kidney Diseases, Bladder Absence, Posterior Urethral Valve, Neurogenic Bladder, Bladder	No results available

Nummer	Name	Status	Studienplan	Ergebnis
		Recruitment Status: Recruiting	Exstrophy, Bladder Outlet Obstruction, Kidney Failure or Transplant single-arm, interventional Intervention: Concomitant Renal and Urinary Bladder Allograft Transplantation	
NCT03698721	Urothelium Tissue Engineering Using Biopsies From Transurethral Resection of Prostate	Estimated Study Completion Date: October 2026 Recruitment Status: Not yet recruiting	n=365 participants with Spina Bifida, Urothelial Neoplasm, Neurogenic Bladder, Bladder Exstrophy or Hypospadias prospective, observational Intervention: Transurethral Resection of Prostate	No results available
NCT04935918	Evaluation of the safety and efficacy of adjustable continence therapy balloons in bladder extrophy and incontinent epispadias patients	Estimated Study Completion Date: April 2028 Recruitment Status: Recruiting	n=7 patients with bladder exstrophy single-arm, interventional Intervention: adjustable continence therapy	No results available
CTRI/2020/04/024590	To examine the two techniques of using curved shaped device in kids for inserting tube in windpipe	Estimated Study Completion Date: not available Recruitment Status: not available	n=76 patients with acquired deformity of musculoskeletal system, Anorectal fistula, Bilateral inguinal hernia, Congenital chordee, Congenital deformity of hip, Congenital malformation of kidney, Disease of stomach and duodenum, xstrophy of urinary bladder, Hypospadias, Undescended testicle,	No results available

Nummer	Name	Status	Studienplan	Ergebnis
			Unilateral inguinal hernia, Unspecified appendicitis or Urethral disorder randomized controlled clinical trial intubated with restricted glottic view vs. intubated with complete glottic view	
IRCT20161126855 4N2	The use of two different wraps in reducing the number and size of polyps in patients with bladder exstrophy	Estimated Study Completion Date: not available Recruitment Status: not available	n=10 patients with bladder exstrophy randomized controlled clinical trial non-adherent film (Plastic Wrap) (PVDC) vs. non-adherent film (Plastic Wrap) (LDPE)	No results available
Abgeschlossene Studien mit Resultaten				
NCT01878500	Navigation of the Pelvic Floor in Bladder Exstrophy Using Pre-operative MRI	Estimated Study Completion Date: December 31, 2020 Recruitment Status: Completed	n=48 patients with bladder exstrophy single-arm, interventional Intervention: Intraoperative stereotactic imaging with VectorVision	Success or Failure of Exstrophy Closure: 44 (3 patients did not represent bladder closures and were subsequently excluded from final analysis) Urinary Continence: data not collected Operative Time: 619 (503 to 647) min Length of Hospital Stay: 50 (45 to 54) days

Nummer	Name	Status	Studienplan	Ergebnis
				Peri-operative Complications as Assessed by the Total Number of Transfusions: 26 Subjective Improved Identification of the Pelvic Floor Anatomy During Bladder Exstrophy Closure as Reported by the Surgeon: 44 Total Number of Post-operative Complications: 10 • Grade I: 3 • Grade II 3 Grade IIIb: 4
Abgeschlossene Studien ohne Resultate				
NCT00863070	Biomechanical Assessment of Level Gait in Patient's Status Post Bladder Exstrophy	Estimated Study Completion Date: March 2013 Recruitment Status: Completed	n=6 patients with bladder exstrophy prospective Outcome: Gait Testing and Analysis, Demographic Data, Pediatric Outcomes Data Collection Instrument	No results available
NCT02192801	Kidney Function in Patients With Bladder Exstrophy	Estimated Study Completion Date: April 2016 Recruitment Status: unknown	n=30 patients with bladder exstrophy prospective cohort study Outcome: Renal function	No results available

Nummer	Name	Status	Studienplan	Ergebnis
NCT03145415	Comparison of Pudendal Nerve Block and Caudal Block for Hypospadias in Young Children	Estimated Study Completion Date: April 30, 2018 Recruitment Status: unknown	n=60 patients with Hypospadias and Epispadias randomized controlled clinical trial Intervention: Caudal block vs. Bilateral Pudendal block	No results available
NCT02075216	Transurethral Myoblast Injection for Urinary Incontinence in Children With Bladder Exstrophy	Estimated Study Completion Date: December 2016 Recruitment Status: unknown	n=50 patients with bladder exstrophy single-arm, interventional Intervention: Transurethral Myoblast Injection	No results available
NCT01011777	Muscle Derived Cell Therapy for Bladder Exstrophy Epispadias Induced Incontinence	Estimated Study Completion Date: January 23, 2020 Recruitment Status: Terminated (Due to participants withdrawal prior to anticipated end of study.)	n=30 patients with bladder exstrophy phase I study, single-arm, interventional Intervention: Muscle derived cell therapy	No results available
NCT02759705	Bladder Exstrophy (FIVES FertIlity Vesical Exstrophy Sexuality) (FIVES)	Estimated Study Completion Date: May 2018 Recruitment Status: Withdrawn (no staff available to do the research)	patients with bladder exstrophy Prospective, observational Outcome: Fertility	No results available
NCT03685955	Efficacy of Amniotic Membranes in Complex	Estimated Study Completion Date: March 2021	patients with Hypospadias, Hypospadias and Epispadias and Other Penile Anomalies, Fistula, Urinary Fistula, Bladder Exstrophy and Epispadias	No results available

Nummer	Name	Status	Studienplan	Ergebnis
	Genitourinary Reconstruction	Recruitment Status: Withdrawn (Lack of supporting staff)	Complex or Bladder and Bladder Neck Disorders (Excluding Calculi) Prospective, observational Intervention: Amniotic membranes	

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Versionsnummer: **1.0**

Erstveröffentlichung: **05/2024**

Nächste Überprüfung geplant: **04/2029**