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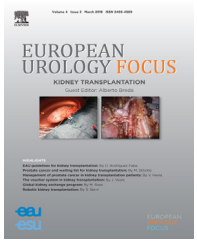

Review – Bladder Cancer

Accuracy of Frozen Section Analysis of Urethral and Ureteral Margins During Radical Cystectomy for Bladder Cancer: A Systematic Review and Diagnostic Meta-Analysis

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Abstract

Context: The question of the ability of frozen section analysis (FSA) to accurately detect malignant pathology intraoperatively has been discussed for many decades.
Objective: We aimed to conduct a systematic review and meta-analysis assessing the diagnostic estimates of FSA of the urethral and ureteral margins in patients treated with radical cystectomy (RC) for bladder cancer (BCa).
Evidence acquisition: The MEDLINE and EMBASE databases were searched in February 2021 for studies analyzing the association between FSA and the final urethral and ureteral margin status in patients treated with RC for BCa. The primary endpoint was the value of pathologic detection of urethral and ureteral malignant involvement with FSA during RC compared with the final margin status. We included studies that provided true

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Keywords:
Urothelial carcinoma
Bladder cancer
Radical cystectomy
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Accuracy

positive, true negative, false positive, and false negative values for FSA, which allowed us to calculate the diagnostic estimates.

Evidence synthesis: Fourteen studies, comprising 8208 patients, were included in the quantitative synthesis. Forest plots revealed that the pooled sensitivity and specificity for FSA of urethral margins during RC were 0.83 (95% confidence interval [CI] 0.38–0.97) and 0.95 (95% CI 0.91–0.97), respectively. While for the FSA of ureteral margins, the pooled sensitivity and specificity were 0.77 (95% CI 0.67–0.84) and 0.97 (95% CI 0.95–0.98), respectively. Calculated diagnostic odds ratios indicated high FSA effectiveness, and patients with a positive urethral or ureteral margin at final pathology are over 100 times more likely to have positive FSA than patients without margin involvement at final pathology. Area under the curves of 96.6% and 96.7% were reached for FSA detection of urethral and ureteral tumor involvement, respectively.

Conclusions: Intraoperative FSA demonstrated high diagnostic performance in detecting both urethral and ureteral malignant involvement at the time of RC for BCa. FSA of both urethral and ureteral margins during RC is accurate enough to be of great value in the routine management of BCa patients treated with RC. While its specificity was great to guide intraoperative decision-making, its sensitivity remains suboptimal yet.

Patient summary: We believe that the frozen section analysis of both urethral and ureteral margins during radical cystectomy should be considered more often in urologic practice, until quality of life–based cost-effectiveness studies can identify patients within each institution who are unlikely to benefit from it.

1. Introduction

Disease recurrence with the remnant urothelium after radical cystectomy (RC) for bladder cancer (BCa) is not uncommon due to the panurothelial nature of urothelial carcinoma [1,2]. Indeed, the incidences of urethral and ureteral recurrences after RC range from 1% to 8% and from 4% to 10%, respectively [1,3,4]. To identify malignant involvement of urethral and ureteral margins, intraoperative frozen section analysis (FSA) might be performed. Studies have reported that both positive urethral and ureteral FSAs are associated with an increased risk of urothelial carcinoma recurrence as well as worse overall survival [5–7]. The American Urological Association guidelines recommend intraoperative verification of a negative urethral margin using FSA before offering an orthotopic urinary diversion, especially in patients with risk factors of urethral recurrence [8]. While the current European Association of Urology (EAU) guidelines have not provided any recommendations regarding the role of intraoperative FSA, its potential usefulness is discussed only in men undergoing radical cystoprostatectomy who harbor carcinoma in situ (CIS) or an extension of the tumor in the prostatic urethra [9]. Neither of these guidelines made any recommendations regarding FSA of ureteral margins. Thereby, there is no clear evidence on the necessity of performing FSA during RC [10,11].

The question of FSA's ability to accurately detect malignant pathology intraoperatively has been discussed for many decades [12–14]. However, according to the currently available literature, the accuracy and prognostic benefit of FSA during RC remains controversial [11,15,16]. A systematic review reported FSA of ureteral margins to have sensitivity of 69–77% and specificity of 83–96%, while for urethral margins, the sensitivity varied from 33% to 93% and specificity from 99% to 100% [17]. Such a wide range of FSA diagnostic accuracy continues to feed the debate, limiting precise recommendations on this potentially important surgical step during RC for BCa. A specific analysis of the test accuracy of FSA using pooled diagnostic test accuracy assessment has not yet been done and has been shown to improve the evidence regarding test accuracy evaluation [18].

Therefore, we aimed to conduct a systematic review and diagnostic meta-analysis assessing the estimates from FSA of urethral and ureteral margins during RC in BCa patients.

2. Evidence acquisition

2.1. Protocol

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [19]. The study protocol was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO; registration ID CRD42021243035).

2.2. Literature search

The MEDLINE and EMBASE databases were searched in February 2021 to identify studies addressing the predictive role of FSA at RC for BCa. A comprehensive systematic literature search was performed independently by two authors. Terms and keywords such as "bladder cancer", "radical cystectomy", "urethra", "ureter", and "frozen section" were used to perform the search. The primary endpoint was the value of pathologic detection of urethral and ureteral malignant involvement with FSA during RC. Studies were eligible if FSA was used to detect ureteral and urethral malignant involvement and they reported data on two or

more of the following: true positive (TP), true negative (TN), false positive (FP), and false negative (FN), or the sensitivity, specificity, accuracy, positive predictive value (PPV), or negative predictive value (NPV).

After removing duplicates, two independent reviewers screened the titles and abstracts. Any citation that either reviewer thought should be included or unclear for inclusion was identified for full-text screening. Subsequently, full texts of eligible articles were reviewed for final inclusion and data extraction. Any discrepancies during the primary and secondary literature screenings were resolved by referring to the senior author.

2.3. Inclusion and exclusion criteria

We included studies analyzing the association between FSA and the final margin status during RC for BCa. The population, intervention, control, and outcome (PICO) criterion in this study was the following: patients who underwent FSA during RC for BCa and with detected ureter and urethral malignant involvement at the final margin analysis compared with patients without malignant involvement. We analyzed diagnostic differences for the value of pathologic detection of urethral and ureteral malignant involvement. Final urethral and ureteral margin status was defined as the margin at the cystectomy specimen reviewed for a permanent pathologic analysis.

We excluded reviews, letters to editors, editorials, animal studies, study protocols, case reports, meeting abstracts, replies from authors, brief correspondence, and articles not published in English. References of all papers included were scanned for additional studies of interest.

2.4. Data extraction

Two investigators independently extracted the following information from the included articles: first baseline study and patients' characteristics such as author's name, number of the patients, number of positive FSAs, positive final margin status, and urethral or ureteral recurrence rates, as well as sensitivity, specificity, and the number of TP, FP, FN, and TN for the main outcome (the value of pathologic detection of urethral and ureteral malignant involvement). All discrepancies regarding data extraction were resolved by consensus with the committee of investigators.

2.5. Risk of bias assessment

The risk of bias of included studies was evaluated according to the risk of bias with the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [20]. The index test was defined as the value of pathologic detection of urethral and ureteral malignant involvement with FSA. The final margin analysis was used as a reference.

2.6. Statistical analyses

Pooled sensitivity, specificity, PPV, NPV, and diagnostic odds ratio (DOR) were calculated. We developed a hierarchical summary receiver operating curve (SROC) and calculated the area under the curve (AUC) to examine the diagnostic accuracy of pathologic detection of urethra and ureter malignant involvement using FSA. Forest plots with 95% confidence interval (CI) were calculated and depicted [18]. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane's Q test and the I^2 statistic. Significant heterogeneity was indicated by $p < 0.05$ in Cochrane's Q tests and a ratio of >50% in I^2 statistics. All statistical analyses were performed using R version 4.0 (2020; R Foundation for Statistical Computing, Vienna, Austria) and Cochrane Collaboration Review Manager software (RevMan v.5.4; Cochrane Collaboration, Oxford, UK). The statistical significance level was set at $p < 0.05$.

3. Evidence synthesis

3.1. Study selection and characteristics

The literature search identified 189 unique references. Among them, 52 records were removed due to duplication, and 99 articles were excluded due to unrelated outcomes during the screening process (Supplementary Fig. 1). Of the 38 full-text articles assessed for eligibility, 20 were excluded based on the selection criteria.

Eighteen studies were included in the qualitative synthesis [7,13,21–36]. Table 1 summarizes the characteristics of included studies. Fourteen studies, comprising 8208 patients, were included in the quantitative synthesis [7,13,21–36].

The summary of the risk of bias and applicability concerns is presented in Supplementary Figure 2. Overall, the risk of bias of the index test was high. There was an unclear risk of bias as to reference standards because included studies did not specify whether pathologists were blinded to FSA results during final margin analyses.

3.2. Meta-analysis

3.2.1. Urethral margins

Five studies provided data on the value of pathologic detection of malignant involvement of the urethra on FSA during RC [7,33–36]. The prevalence of urethral malignant involvement in FSA varied from 0.8% [34] to 7.8% [7], and the final positive urethral margin was reported to range from 1.1% [34] to 15% [36]. The diagnostic variables of the included studies are presented in Table 2. The forest plots revealed that the pooled sensitivity, specificity, PPV, and NPV were 0.83 (95% CI 0.38–0.98), 0.95 (95% CI 0.91–0.97), 0.62 (95% CI 0.53–0.71), and 0.99 (95% CI 0.92–0.99), respectively (Fig. 1). The Cochrane's Q tests ($p \leq 0.05$) and I^2 tests ($I^2 > 50\%$) revealed significant heterogeneity among studies in terms of sensitivity, specificity, and NPV, while the Cochrane's Q tests ($p = 0.49$) and I^2 tests ($I^2 = 0\%$) revealed no significant heterogeneity among studies in terms of PPV. The pooled DOR was 169.23 (95% CI 31.57–907.24). We constructed an SROC curve with the following parameters: theta –2.98, lambda 7.41, beta –1.55, sigma2theta 0.71, and sigma2alpha

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Table 1 – Characteristics of included studies reporting the diagnostic estimates of frozen section analysis (FSA) of urethral and ureteral margin status in patients treated with radical cystectomy for bladder cancer

Author (publication year)	Study design	Number of patients	Positive margin on FSA, *n*/*N* (%)	Positive final margin, *n*/*N* (%)	Sensitivity (%)	Specificity (%)	Recurrence rate
Urethral margin status							
Gaya (2014) [29]	R	234	1 (3%)	NR	100	78.9	2/182 (1%) of the patients with an intact urethra
Gordetsky (2014) [33]	R	822	48/366 specimens	39 specimens	NR	NR	NR
Kassouf (2008) [34]	R	1006	1/118 (0.8%)	3/252 (1.1%)	NR	NR	2/252 (0.7%)
Kates (2016) [7]	R	298	28 (7.8%)	15 (5%)	100	99.3	4 (26.6%) patients with positive final urethral margins
Osman (2012) [36]	P	100	6%	15%	33.3	98.8	None of the 10 patients with false-negative results developed late urethral recurrence at 5 yr
Reder (2015) [30]	R	364	NR	NR	71	99	NR
von Rundstedt (2016) [35]	R	272/2498	5/26	6/272 (2.2%)	66.7	90.9	NR
Ureteral margin status							
Gakis (2011) [28]	P	218	17/425 specimens (4%)	23/425 specimens (5.4%)	73.9	99.8	In 3/5 patients, recurrence was located proximally to the ureterointestinal anastomosis and in 2 at the anastomosis
Gordetsky (2014) [33]	R	822	207/1222 specimens	182 specimens	NR	NR	NR
Hakozaki (2017) [27]	R	458	30/356	28/356	94.7	98.0	NR
Hoang (2014) [26]	R	660	95/1346 specimens	30/1346 specimens	80	95	1 ureteroenteric anastomotic recurrence
Kim (2015) [25]	R	402	46 (11.2%)	35 (8.7%)	75	96	11 patients (2.7%)
Loeser (2014) [32]	P	243	1/117 patients (0.85%) without CIS and 21/59 patients (35.6%) with CIS	NR	NR	NR	2 patients (1.1%)
Moschini (2016) [31]	R	1447	368 (25%)	190 (13%)	69	83	26 (7.1%) in patients with positive FSA and 28 (2.6%) in patients with negative FSA
Osman (2007) [21]	P	193	14 patients: 16 ureters (8.3%)	24 patients: 29 (15%) specimens	45	98	NR
Raj (2006) [22]	R	1330	9% of ureters (13% of patients)	9% of ureters	75	99	13 (91%)
Reder (2015) [30]	R	364	NR	NR	86	99	NR
Satkunasivam (2016) [23]	R	2047	460	335	77	88	15/28 patients (54%) with UTUC recurrence had benign ureteric FSA
Schoenberg (1996) [13]	R	101	8	12	NR	NR	0
Touma (2010) [24]	R	301	36	32	71.9	96.1	6 patients (2%) with more proximal than ureteral-intestinal anastomoses

CIS = carcinoma in situ; NR = not reported; P = prospective; R = retrospective; UTUC = upper tract urothelial carcinoma.

0.00. FSA of urethral margins during RC reached an AUC of 96.6% for pathologic detection of malignant involvement of the urethra (Fig. 2A).

3.2.2. *Ureteral margins*

Ten studies provided data on the value of pathologic detection of malignant involvement of the ureter on FSA during RC [13,21–28,33]. The prevalence of ureteral malignant involvement on FSA and final margin analysis varied from 0.85% (in patients without concomitant CIS) [32] to 35.6% (in patients with concomitant CIS) [32] and from 5.4% [28] to 15% [21], respectively. The diagnostic variables of these studies are presented in Table 2. The forest plots revealed that the pooled sensitivity, specificity, PPV, and NPV were 0.77 (95% CI 0.67–0.84), 0.97 (95% CI 0.95–0.98), 0.73 (95% CI 0.57–0.84), and 0.98 (95% CI 0.96–0.99), respectively (Fig. 3). The Cochrane's Q tests ($p \leq 0.05$) and I^2 tests ($I^2 > 50\%$) revealed significant heterogeneity among studies. The pooled DOR was 131.75 (95% CI 51.88–334.59). We constructed an SROC curve with the following parameters: theta –1.34, lambda 4.94, beta –0.15, sigma2theta 0.43, and sigma2alpha 1.42. FSA of ureter margins during RC reached an AUC of 96.7% for pathologic detection of malignant involvement of the ureter (Fig. 2B).

3.3. *Discussion*

To the best of our knowledge, we conducted the first systematic review and diagnostic meta-analysis analyzing the diagnostic estimates of FSA at urethral and ureteral margins during RC for BCa. This approach led to several important findings of interest.

Our analyses support the role of FSA as an appropriate diagnostic tool for the detection of both urethral and ureteral malignant involvement during RC for BCa. Indeed, FSA had high accuracy (at 96%) and specificity for both urethral and ureteral margins. However, the sensitivity (83% and 77% for urethral and ureteral margins, respectively) was lower,

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Table 2 – Diagnostic performance of frozen section of urethra and ureter across included studies

Author	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Urethral margin FSA								
Gordetsky [33]	39	9	0	301	100	93.2	66.2	100
Kassouf [34]	1	0	0	117	100	100	100	100
Kates [7]	26	2	0	270	100	95.4	53.6	100
Osman [21,36]	5	1	10	84	33.3	98.8	83.3	89.4
von Rundstedt [35]	2	3	1	30	66.7	90.9	40	96.8
Ureteral margin FSA								
Gakis [1,28]	17	1	6	401	73.9	99.8	94.4	98.5
Gordetsky [33]	178	29	4	930	97.8	97	86	99.6
Hakozaki [27]	25	5	3	323	89.3	98.5	83.3	99.1
Hoang [26]	24	71	6	1340	80	95	25.3	99.6
Kim [25]	30	24	10	581	75	96	55.6	98.3
Osman [21,36]	13	3	16	161	44.8	98.2	81.2	91
Raj [22]	112	12	40	1053	73.7	98.9	90.3	96.3
Satkunasivam [23]	258	202	77	1501	77	88.1	56.1	95.1
Schoenberg [13]	6	2	6	83	50	97.6	75.0	93.3
Touma [24]	23	13	9	317	71.9	96.1	63.9	97.2

FN = false negative; FP = false positive; FSA = frozen section analysis; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

potentially leading to the reduced ability of FSA to identify patients with malignant involvement intraoperatively. Notably, the highest sensitivity of intraoperative FSA (up to 98–100%) was reported by Gordetsky et al [33]; in their study, most of the patients had CIS in the analyzed margins. Similarly, Loeser et al [32] reported higher rates of positive ureter FSA in patients with solitary or concomitant CIS of the bladder as compared with patients without CIS (35.6% vs 0.85%). Despite the lack of data available to perform a subgroup analysis in the CIS population, in patients with CIS, intraoperative FSA of the urethra and ureter might be proposed to reduce the risk of a positive surgical margin. Accurate identification of patients at a higher risk of urothelial recurrence after RC is of importance in order to improve the oncologic outcomes. Thus, for example, in case of positive urethral FSA, a prophylactic urethrectomy in case of ileal conduit might be considered for those patients who are most likely to benefit from it.

With an NPV of over 97%, performing FSA for the urethra and the ureters might be very helpful intraoperatively to avoid positive surgical margins, especially when an orthotopic neobladder is considered. On the contrary, the low PPV (both <72%) could be attributed to the high FP rate of suspected malignant involvement. However, both NPV and PPV are associated with disease prevalence and, therefore, could not be directly transferable/applicable to all clinical scenarios. We believe that a DOR is the most appropriate diagnostic estimate for FSA due to its stable diagnostic performance and high variability of positive margin prevalence. In our study, pooled DORs suggest that patients with positive final urethral and ureteral margins are over a hundred times more likely to have positive FSA than patients with negative margins at final pathology.

Nevertheless, unawareness about the number and level of frozen sections taken might lead to controversial results, especially for ureteral margins. In the previously published

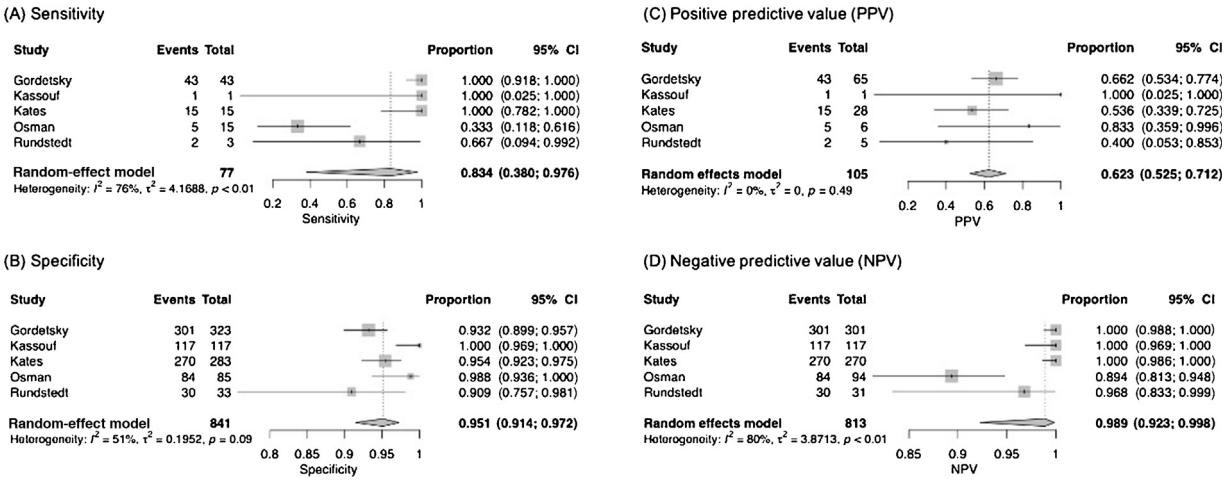

Fig. 1 – Forest plots for pooled (A) sensitivity, (B) specificity, (C) positive predictive value (PPV), and (D) negative predictive value (NPV) of frozen section analysis of a urethral margin during radical cystectomy for bladder cancer. CI = confidence interval.

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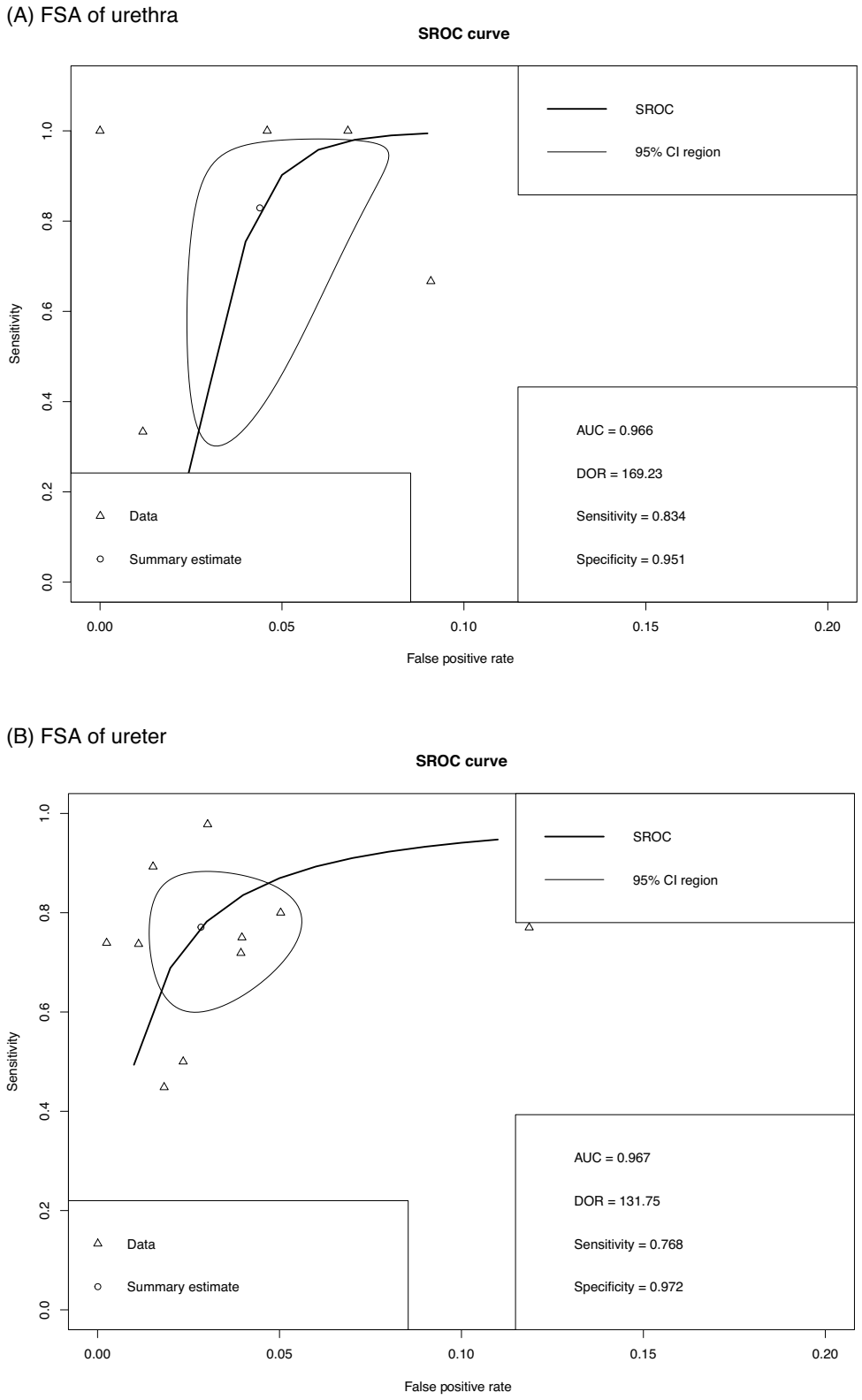

Fig. 2 – Summary receiver operating characteristic (SROC) curve for the diagnostic estimates of frozen section analysis (FSA) of (A) urethral and (B) ureteral margin status in patients treated with radical cystectomy for bladder cancer. AUC = area under the curve; CI = confidence interval; DOR = diagnostic odds ratio.

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systematic review, Soliman et al [15] reported no clear evidence on the optimal number of ureter sections: one section may be sufficient, while two or more may be needed to reach benign pathology. Thus, Raj et al [22] proposed the "serial step sectioning" strategy to achieve uninvolved anastomotic margins if an involved ureter was found intraoperatively. Tollefson et al [5] suggested that patients who undergo conversion to a negative ureteral final margin with sequential sectioning are at a decreased risk of recurrence of upper tract urothelial carcinoma. In terms of section level, it has been suggested that a more proximal ureteral segment can be excised to assure a tumor-free anastomosis because the incidence of urothelial malignancies in the upper urinary tract is highest in the distal ureter [37,38]. Interestingly, Tang et al [6] reported that FSA of the distal ureters was unlikely to be positive unless BCa is of ≥T2 stage. Hence, in some patients, including those treated with RC for non–muscle-invasive BCa, the routine ureteral FSA might be omitted. Moreover, we believe that even in case of the achievement of an uninvolved anastomotic margin, patients with known preoperative risk factors for urothelial carcinoma recurrence should be counseled accordingly.

Another disputable question in the context of FSA is its predictive value for recurrence rate and survival outcomes. Lebret et al [39] reported no urethral recurrence in patients with negative urethral FSA after a 10-yr follow-up. Moreover, two studies reported worse overall survival when positive FSAs were found intraoperatively [6,7]. In contrast to these results, Reder et al [30] failed to find the associations between carcinoma of urethra or ureter on FSA and overall survival or disease-free survival. Thereby, FSA may help ensure a cancer-free anastomosis in patients planned for orthotopic urinary diversion, supposedly leading to reduced urothelial carcinoma recurrence rates after RC for BCa, while its association with survival outcomes remains insufficiently investigated.

Unfortunately, data regarding the experience of pathologists performing FSA and its association with the final margin are limited. We believe that implementation of a standardized reporting scheme can minimalize an association between the quality of pathology analysis and pathologists' experience. Additionally, the fusion of digitalized pathology and artificial intelligence (pathomics) might change the landscape of the pathologic workflow and improve the diagnostic and predictive abilities of current models [40]. Nevertheless, further studies should shed light on this "dark spot" of the balance between patients' oncologic and survival outcomes and the quality of life–driven cost effectiveness of routine FSA compared with the rarely available salvage treatment with radical extirpation in case of urothelial carcinoma recurrence.

There are several potential limitations of this study. The main limitation was the retrospective design of the included studies that resulted in a potential selection bias due to surgeon selection of the urethras and ureters chosen for FSAs. Additionally, most of the included studies did not report the number and level of frozen sections as well as surgical technique of RC; although that might be questionable, we were unable to perform subgroup analyses in that regard. Among other limitations of observational studies, there is heterogeneity of patient populations in terms of inclusion criteria and clinicopathologic features. Moreover, most of the studies do not report any information on the characteristics of the patients with positive FSA as well as prostate biopsies taken and whether patients were not subjected to surgery on the basis of these biopsies. Hence, it was not possible to assess specifically the potential factors of positive FSA. Second, the significant heterogeneity across

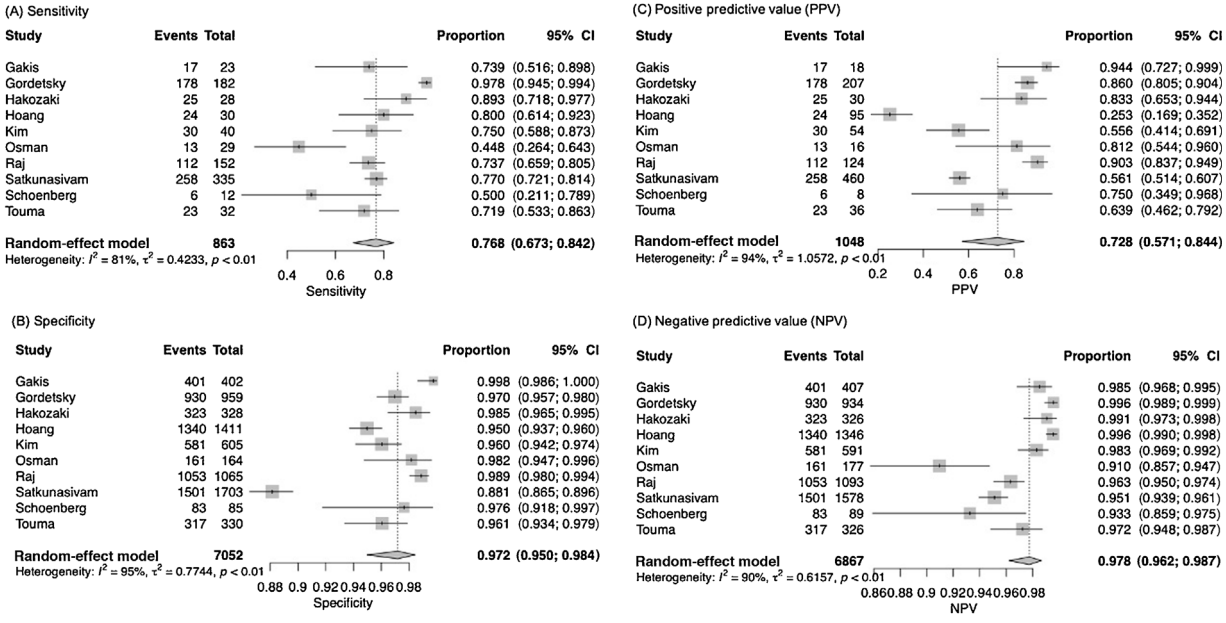

Fig. 3 – Forest plots for pooled (A) sensitivity, (B) specificity, (C) positive predictive value (PPV), and (D) negative predictive value (NPV) of frozen section analysis of a ureteral margin during radical cystectomy for bladder cancer. CI = confidence interval.

the studies was detected in almost all analyses, thereby limiting the value of the findings. Although the random-effect model was used to address heterogeneity among studies, our conclusions should still be interpreted with caution. Third, there was a high risk of bias among the included studies, as illustrated in the QUADAS-2 assessment. Different patient populations in the studies are likely to be the main reason behind the high risk of bias. Therefore, well-designed large-scale trials with a centralized review of pathologic slides are required to confirm the findings of the present study.

4. Conclusions

Intraoperative FSA demonstrated very high diagnostic performance in detecting suspicious urethral and ureteral malignant involvement at the time of RC for BCa. A negative margin on FSA can lead to a decreased likelihood of recurrence after RC. Therefore, we believe that the FSA of both urethral and ureteral margins during RC should be considered more often in our practice, until quality of life–based cost-effectiveness studies can identify patients within each institution who are unlikely to benefit from it.

Author contributions: Ekaterina Laukhtina had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shariat, Pradere, Laukhtina.
Acquisition of data: Laukhtina, Pradere.
Analysis and interpretation of data: Laukhtina, Pradere, Rajwa.
Drafting of the manuscript: Laukhtina, Pradere.
Critical revision of the manuscript for important intellectual content: Rajwa, Mori, Moschini, D'Andrea, Abufaraj, Soria, Mari, Krajewski, Albisinni, Teoh, Quhal, Motlagh, Mostafaei, Katayama, Grossmann, Enikeev, Zimmermann, Fajkovic, Shariat.
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Appendix A. Supplementary data

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