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REVIEW PAPER

UROLOGICAL ONCOLOGY

Differential performance of imaging modalities predicting pathological response to neoadjuvant chemotherapy in urothelial bladder cancer: a systematic review and meta-analysis

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Introduction We assessed the differential performance of imaging modalities predicting pathological response to neoadjuvant chemotherapy (NAC) in urothelial bladder cancer (UBC).

Material and methods Literature search was conducted using the MEDLINE, SCOPUS, and Cochrane Library in December 2023 to identify eligible studies.

Results Twenty-two studies comprising 1085 patients were selected. The pooled diagnostic odds ratio (DOR), positive likelihood ratio (LR), and negative LR of FDG positron emission tomography–computed tomography (PET/CT) for predicting bladder tumor complete pathological response (CPR) were 17.33 (95% CI: 1.65–180.99), 2.80 (95% CI: 1.04–7.57), and 0.16 (95% CI: 0.02–0.90), respectively. The pooled DOR, positive LR, and negative LR of FDG- PET/CT for predicting lymph node CPR were 5.25 (95% CI: 2.77–9.93), 1.62 (95% CI: 1.20–2.19), and 0.30 (95% CI: 0.22–0.43), respectively. The pooled DOR, positive LR, and negative LR of contrast enhanced magnetic resonance imaging (CEMRI) for predicting bladder tumor CPR were 153 (95% CI: 26.29–890.1), 16.20 (95% CI: 4.19–62.54), and 0.10 (95% CI: 0.04–0.26), respectively. The pooled DOR, positive LR, and negative LR of CEMRI for predicting lymph node CPR were 13.33 (95% CI: 1.06–166.37), 5.62 (95% CI: 0.82–38.53), and 0.42 (95% CI: 0.16–1.06), respectively.

Conclusions We demonstrated that CEMRI (including mpMRI) helps accurate assessment of response to NAC in UBC. While CEMRI is a useful tool to detect residual tumor in lymph nodes, contrast enhanced CT scan and FDG-PET/CT are precise staging modality to identify nodal metastasis responders to NAC. Nevertheless, this differential diagnostic performance needs to be further refined with radiomics and novel tracers to help individualized clinical decision-making.

Key Words: urothelial carcinoma ‹› bladder cancer ‹› response rate ‹› chemotherapy ‹› radical cystectomy

INTRODUCTION

Neoadjuvant cisplatin-based combination chemotherapy (NAC) and radical cystectomy (RC) with lymphadenectomy are the current gold standard treatment for cisplatin-eligible patients with muscle invasive urothelial bladder carcinoma (MIBC) [1–3].

However, the absolute net benefit of only 5% overall survival (OS) benefit for patients treated with NAC of 5-years underline the importance of patient selection with an identification of MIBC patients who are most likely to benefit from NAC [4–6]. Although several clinical, pathologic, and molecular characteristics have been suggested to help identify responders to systemic therapies, their use in clinical practice is not existent [3, 7–10].

Modern imaging modalities help discern responders from non-responders by accurately staging the tumor burden and identifying imaging signatures of sensitive/resistant tumors [11, 12]. Anatomical imaging techniques including magnetic resonance imaging (MRI) and computed tomography (CT) have limitations owing to over- and understaging with a staging accuracy of only 70% [13].

However, multiparametric MRI (mpMRI) and positron emission tomography (PET)/CT offer improved sensitivity and specificity, enabling more accurate assessment of response to systemic therapy in MIBC patients [14–16]. Moreover, PET and MRI together could provide a comprehensive assessment of residual tumor both at the primary and lymph node sites after NAC [17]. Therefore, there is a need to collect reported diagnostic accuracy of current conventional and functional imaging modalities in patients who underwent NAC for MIBC to have an overview of their respective performances to help us relay on one of them for current decision-working and to set the bed for improvement.

To address this need, we performed this systematic review and meta-analysis, investigating the differential diagnostic performances of imaging modalities predicting pathological response to NAC in radical cystectomies performed for MIBC.

MATERIAL AND METHODS

Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. The protocol of this study was a priori registered in PROSPERO, and the protocol is available online (CRD42023470963).

We performed a systematic literature search through PUBMED, SCOPUS, and Cochrane Library in December 2023 to identify the eligible studies investigating the predictive value of imaging modalities for assessment of pathological response to NAC in patients with UBC. All full text papers were assessed by two reviewers and excluded with reasons when inappropriate after initial screening based on study title and abstract. Disagreements were resolved by consensus with the co-authors. The string terms used in our search strategy were ((bladder cancer OR bladder carcinoma OR bladder tumor OR urothelial) AND (imaging OR MRI OR magnetic resonance Imaging OR PET OR positron emission tomography OR computed tomography OR CT)) AND (systemic therapy OR chemotherapy).

Inclusion and exclusion criteria

We used the population, intervention, comparator, outcome, and study design (PICOS) approach to define the eligibility criteria. Studies were included when patients with UBC (P: population) who underwent NAC before RC (I: interventions) were assessed by imaging modality predicting tumor extent and location compared with pathologic report (C: comparators) in terms of pathological response to NAC (O: outcomes) in the primary (i.e., bladder) and regional lymph nodes using retrospective or prospective approaches (S: study design). We excluded abstract, replies, editorial comments, review articles, and articles published in other languages than English.

Data extraction

Two investigators independently extracted the following information from the included articles: study name, publication year, region, study design, recruitment period, number of patients, patients' characteristics, index imaging modality, time of imaging, pathological assessment, site of response assessment, chemotherapy regimen, age, sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value), and test accuracy.

Risk of bias assessment

We assessed the risk of bias of included studies according to the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [19]. Imaging modality and pathologic assessment were defined as index test and standard reference, respectively. Each bias domain and overall risk of bias were judged as 'low', 'high', or 'unclear' risk of bias.

Disagreements were resolved by consensus or consultation with other authors.

Statistical analyses

A random effect model was used to estimate pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio as well as diagnostic odds ratio for imaging modalities. We created hierarchical summary receiver operating curve (SROC) and calculated the area under the curve (AUC) to examine the differential diagnostic accuracy. We created forest plots with 95% confidence interval (CIs) for sensitivity and specificity for each study. Significant heterogeneity was indicated by $p < 0.05$ in the Cochrane's Q tests and a ratio of >50% in I^2 statistics. We performed statistical analyses using R version 4.0.3 (2020; R Foundation for Statistical Computing, Vienna, Austria) and Meta-DiSc 2.0 [20]. The statistical significance level was set at $p < 0.05$.

RESULTS

Study selection and characteristics

A total of 435 studies were identified by our initial literature search and seven duplicates were removed. Then, 374 studies were excluded after title/abstract evaluation. Full-text reviews were performed for the remaining 54 articles. Finally, 22 and 10 studies were included for qualitative and quantitative analyses (Figure 1). Eight studies were designed prospectively [15, 17, 21–26] and 14 were retrospective [14, 16, 27–38]. All studies were published between 1990 and 2023. Ten studies came from Europe, five from North America, three from Europe/North America, three from Asia, and one from Africa. Tables 1 and 2 summarize the characteristics of the studies and patients' clinical data.

Meta-analysis of imaging modalities predicting response to NAC

Primary tumor and fluorodeoxyglucose (FDG) – PET/CT

Diagnostic performance of FDG-PET/CT for predicting pathological response to NAC in the primary tumor was assessed in three studies [16, 35, 36]. In the forest plot, the pooled sensitivity and specificity were 0.89 (95% CI: 0.54–0.98) and 0.68 (95% CI: 0.34–0.90), respectively (Figure 2A). The Cochrane Q test and I^2 test revealed no significant and significant heterogeneity among studies for sensitivity and specificity, respectively. The pooled diagnostic odds ratio (DOR), positive likelihood ratio (LR), and negative LR were 17.33 (95% CI: 1.65–180.99), 2.80 (95% CI: 1.04–7.57), and 0.16 (95% CI: 0.02–0.90), respectively.

Primary tumor and un-enhanced MRI

Diagnostic performance of un-enhanced MRI for predicting pathological response to NAC in the primary tumor was assessed in two studies [15, 21]. In the forest plot, the pooled sensitivity and specificity were 0.81 (95% CI: 0.60–0.95) and 0.55 (95% CI: 0.34–0.74), respectively (Figure 2B). The Cochrane Q test and I2 test revealed no significant heterogeneity among studies for sensitivity and specificity. The DOR, positive LR, and negative LR were 4.97 (95% CI: 1.53–16.13), 1.77 (95% CI: 1.09–2.87), and 0.35 (95% CI: 0.16–0.76), respectively.

Primary tumor and contrast enhanced MRI (CEMRI)

Diagnostic performance of CEMRI (including mpMRI) for predicting pathological response to NAC in the primary tumor was assessed in four studies [15, 21, 24, 27]. In the forest plot, the

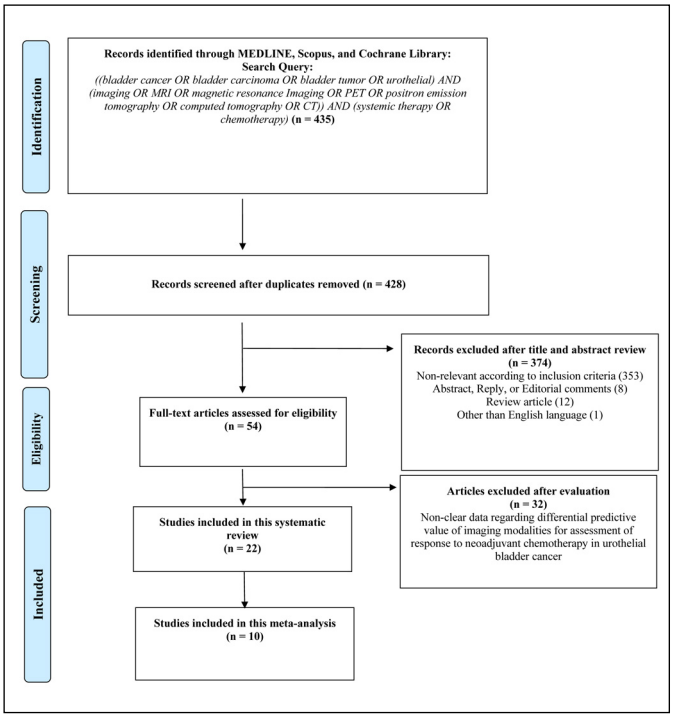

Figure 1. *PRISMA flow chart for article selection process to analyze the differential performance of imaging modalities predicting pathological response to neoadjuvant chemotherapy in urothelial bladder cancer.*

Table 1. *Study characteristics of 22 studies assessing the diagnostic accuracy of imaging modalities to predict pathological response to neoadjuvant chemotherapy in the in patients with urothelial bladder carcinoma*

Study	Year	Region	Study design	Recruitment period	Pts[a]	Pts characteristics (TNM)	Index test	Time of imaging	Reference standard	Site of response assessment	CTx regimen
Jakse et al. [30]	1990	Europe	Retrospective	NA	31	≥T2	CT-Scan + CT-cystography	After completion of CTx	Biopsy, TURBT, PC, RC	Primary tumor	Cisplatin + Doxorubicin or Epi-doxorubicin
Barentsz et al. [15]	1998	Europe	Prospective	NA	22	T1-T4bN±	DCE MRI and conventional unenhanced MRI	After 2 cycles of CTx	TURBT, RC, LND	Primary tumor, LN	MVAC
Schrier et al. [21]	2006	Europe	Prospective	NA	36	≥T2N+	DCE MRI and conventional unenhanced MRI	After 2 cycles of CTx	TURBT, RC	Primary tumor	MVAC
Nishimura et al. [27]	2009	Asia	Retrospective	NA	8	≥T2	Contrast material-enhanced MRI	After 2 cycles of CTx	PC, RC	Primary tumor	MVAC
Donaldson et al. [22]	2013	Europe	Prospective	NA	21	≥T2	DCE MRI	After completion of CTx	RC	Primary tumor	GC
Mertens et al. [28]	2013	Europe	Retrospective	2011–2012	19	≥T2N+	FDG-PET/CT and CECT	After a median of 4 cycles (range 2 to 4) of CTx	LND	LN	MVAC or GC or Carboplatin based combination CTx
Hadjiiski et al. [31]	2015	North America	Retrospective	NA	18	T1–T4	CT urograms	After 3 cycles of CTx	RC	Primary tumor	NA
Nguyen et al. [23]	2015	North America	Prospective	2009–2013	30	T1–T4	DCE-MRI	Mid-cycle	RC	Primary tumor	Cisplatin-based CTx
Kollberg et al. [29]	2017	Europe	Retrospective	2007–2015	45	T1–T4N±	FDG-PET/CT	After 3 cycles of CTx	LND	LN	dose-dense MVAC
van de Putte et al. [16]	2017	Europe	Retrospective	2010–2014	47	T1–T4N±	FDG-PET/CT	After completion of CTx	RC, LND	Primary tumor, LN	MVAC or GC or GCa
Salminen et al. [17]	2018	Europe/ North America	Prospective	NA	5	≥T2N±	PET/MRI	After completion of CTx	RC, LND	Primary tumor, LN	GC
Soubra et al. [35]	2018	North America	Retrospective	2011–2016	37	≥T2	FDG-PET/CT	After completion of CTx	RC	Primary tumor	MVAC or GC
Cha et al. [32]	2019	Europe/ North America	Retrospective	NA	123	≥T2	CT-based CDSS-T	After 3 cycles of CTx	RC	Primary tumor	MVAC or carboplatin, paclitaxel, gemcitabine, and etoposide
Wu et al. [34]	2019	North America	Retrospective	NA	123	NA	CT-Scan with DL-CNN models	After completion of CTx	RC	Primary tumor	NA
Choi et al. [33]	2020	Asia	Retrospective	2017–2019	73	≥T2	Urothelial phase CT-Scan	After completion of CTx	PC, RC	Primary tumor	MVAC or GC or GCa
Hadjiiski et al. [38]	2020	Europe/ North America	Retrospective	NA	123	≥T2	CT-Scan with DL-CNN models	After completion of CTx	RC	Primary tumor	MVAC or carboplatin, paclitaxel, gemcitabine, and etoposide

Figure 1. *Continued*

Study	Year	Region	Study design	Recruitment period	Pts[a]	Pts characteristics (TNM)	Index test	Time of imaging	Reference standard	Site of response assessment	CTx regimen
Ahmed et al. [26]	2021	Africa	Prospective	2017–2019	90	≥T2N-	DCE and diffusion-weighted MRI	After completion of CTx	PC, RC	Primary tumor	MVAC or GC or GCa
Ghodoussipour et al. [36]	2021	North America	Retrospective	NA	29	T1-4N+	CT-Scan	After completion of CTx	LND	LN	MVAC or GC
Bertolaso et al. [14]	2022	Europe	Retrospective	2005–2017	39	≥T2N+	FDG-PET/CT and CT-Scan	After completion of CTx	LND	LN	NA
Pecoraro et al. [24]	2022	Europe	Prospective	2019–2020	10	NA	Multiparametric MRI	After completion of CTx	RC	Primary tumor	GC or CMV
Yang et al. [25]	2022	Asia	Prospective	2018–2020	21	≥T2	Multiparametric MRI	After 1 cycle of CTx	RC	Primary tumor	GC
Fitoussi et al. [37]	2023	Europe	Retrospective	2016–2021	45	≥T2N+	FDG-PET/CT	After completion of CTx	RC, LND	Primary tumor, LN	MVAC or GC or GCa

NA – not available; CTx – chemotherapy; CT – computerized tomography; TURBT – transurethral resection of bladder tumor; PC: partial cystectomy; RC – radical cystectomy; DCE – dynamic contrast material-enhanced; LN – lymph node; MVAC – methotrexate, vinblastine, adriamycin, and cisplatin; GC – gemcitabine + cisplatin; GCa – gemcitabine + carboplatin; FDG-PET/CT – FDG-positron emission tomography/Computerized Tomography; CECT – Contrast enhanced computerized tomography; LND – lymph node dissection; CDSS-T – computerized decision-support system for muscle invasive bladder cancer treatment response assessment; DL-CNN – deep learning-convolutional neural network; CMV – cisplatin, methotrexate, and vinblastine
[a]patients with available survival data

pooled sensitivity and specificity were 0.90 (95% CI: 0.76–0.96) and 0.94 (95% CI: 0.80–0.99), respectively (Figure 2C). The Cochrane Q test and I^2 test revealed no significant heterogeneity among studies for sensitivity and specificity. The DOR, positive LR, and negative LR were 153 (95% CI: 26.29–890.1), 16.20 (95% CI: 4.19–62.54), and 0.10 (95% CI: 0.04–0.26), respectively.

PET/CT (MRI) vs CEMRI in primary tumor

Diagnosis performance of CEMRI (including mpMRI) was compared with PET/CT (MRI) in predicting pathological response to NAC in primary tumor using metaregression. Relative sensitivity and specificity levels for PET/CT (MRI) vs CEMRI were 0.97 (95% CI: 0.79–1.20; p-value: 0.8), and 0.72 (95% CI: 0.52–0.99; p-value: 0.03), respectively. SROC curve shows differential diagnostic performance of PET/CT (MRI) and CEMRI (Figure 3-A). The Cochrane Q test and I2 test revealed no significant heterogeneity among studies [15–17, 21, 24, 27, 35, 37].

Lymph node metastasis and contrast enhanced CT scan

Diagnostic performance of contrast enhanced CT scan for predicting pathological response to NAC in the lymph node metastasis was assessed in two studies [14, 28]. In the forest plot, the pooled sensitivity and specificity were 0.96 (95% CI: 0.15–1.00) and 0.28 (95% CI: 0.06–0.72), respectively (Figure 4A). The Cochrane Q test and I^2 test revealed no significant and significant heterogeneity among studies for sensitivity and specificity, respectively. The DOR, positive LR, and negative LR were 9.81 (95% CI: 0.03–2,860.40), 1.33 (95% CI: 0.77–2.29), and 0.72 (95% CI: 0.29–0.94), respectively.

Lymph node metastasis and CEMRI

Diagnostic performance of CEMRI for predicting pathological response to NAC in the lymph node metastasis was assessed in two studies [15, 27]. In the forest plot, the pooled sensitivity and specificity were 0.62 (95% CI: 0.28–0.87) and 0.89 (95% CI: 0.50–0.98), respectively (Figure 4B). The Cochrane Q test and I^2 test revealed no significant heterogeneity among studies for sensitivity and specificity. The DOR, positive LR, and negative LR were 13.33 (95% CI: 1.06–166.37), 5.62 (95% CI: 0.82–38.53), and 0.42 (95% CI: 0.16–1.06), respectively.

Table 2. *Diagnostic accuracy of imaging modalities in 22 studies predicting pathological response to neoadjuvant chemotherapy in patients with urothelial bladder carcinoma[#]*

Study	Age, year	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		Accuracy (%)	
		Bladder tumor	LN	Bladder tumor	LN	Bladder tumor	LN	Bladder tumor	LN	Bladder tumor	LN
Jakse et al. [30]	Mean: 65.1	65	NA	100	NA	100	NA	71	NA	81	NA
Barentsz et al. [15]	Mean: 54	93[a] (79)[b]	71[a] (71)[b]	100[a] (62.5)[b]	100[a] (50)[b]	100[a] (78)[b]	100[a] (83)[b]	89[a] (62.5)[b]	50[a] (33)[b]	95[a] (73)[b]	78[a] (75)[b]
Schrier et al. [21]	Mean: 56	91[a] (82)[b]	NA	93[a] (50)[b]	NA	95[a] (72)[b]	NA	87[a] (64)[b]	NA	92[a] (69)[b]	NA
Nishimura et al. [27]	Mean: 67.5	0	NA	86	NA	0	NA	86	NA	75	NA
Donaldson et al. [22]	Mean: 63	75	NA	100	NA	NA	NA	NA	NA	NA	NA
Mertens et al. [28]	Mean: 64	NA	71[c] (64)[d]	NA	60[c] (60)[d]	NA	83[c] (82)[d]	NA	43[c] (38)[d]	NA	68[c] (63)[d]
Hadjiiski et al. [31]	Mean: 60.1	NA	NA	NA	NA	NA	NA	NA	NA	NA[e]	NA
Nguyen et al. [23]	Median: 66	96[f]	NA	100[f]	NA	NA	NA	NA	NA	97[f]	NA
Kollberg et al. [29]	Mean: 66	NA	100[f]	NA	17[f]	NA	88[f]	NA	100[f]	NA	88[f]
van de Putte et al. [16]	Median: 67	70	67	71	46	78	70	63	43	80	59
Salminen et al. [17]	Mean: 65	100	67	67	50	67	67	100	50	80	60
Soubra et al. [35]	Median: 63	75	NA	90	NA	67	NA	93	NA	86	NA
Cha et al. [32]	Mean: 63	NA	NA	NA	NA	NA	NA	NA	NA	NA[g]	NA
Wu et al. [34]	NA	41.7–75	NA	NA	NA	NA	NA	NA	NA	64.1–78.9	NA
Choi et al. [33]	Mean: 65.8	74.1–81.5	NA	80.4–84.8	NA	71.0–74.1	NA	84.8–88.1	NA	NA	NA
Hadjiiski et al. [38]	Mean: 63	NA	NA	NA	NA	NA	NA	NA	NA	NA[h]	NA
Ahmed et al. [26]	Mean: 52.4	95.4–96	NA	97–97.7	NA	NA	NA	NA	NA	88-92	NA
Ghodoussipour et al. [36]	Median: 67.4	NA	72	NA	80	NA	87	NA	62	NA	NA
Bertolaso et al. [14]	Median: 65	NA	90[i] (100)[j]	NA	60[i] (10)[j]	NA	87[i] (76)[j]	NA	67[i] (100)[j]	NA	82[i] (77)[j]
Pecoraro et al. [24]	Mean: 68.3	100	NA	100	NA	100	NA	100	NA	100	NA
Yang et al. [25]	Median: 66	87.5–100	NA	25–50	NA	NA	NA	NA	NA	NA	NA
Fitoussi et al. [37]	Mean: 66	100	83	36	30	62	83	100	75	69	82

NA – not available; PPV – positive predictive value; NPV – negative predictive value; LN – lymph node
[#]results for complete pathological response
[a]DCE MRI
[b]Conventional unenhanced MRI
[c]FDG-positron emission tomography/Computerized Tomography
[d]Contrast enhanced computerized tomography
[e]The AUC for prediction of pT0 disease at cystectomy was 0.78 ± 0.11 for auto initialized cascaded level set compared with 0.82 ± 0.10 for manual segmentation
[f]Pathological complete or partial response
[g]The mean AUCs for assessment of pathologic T0 disease were 0.80 for CDSS-T
[h]The mean areas under the curves for assessment of pathologic T0 disease were 0.85 for CDSS-T
[i]FDG-positron emission tomography/Computerized Tomography
[j]Computerized Tomography Scan

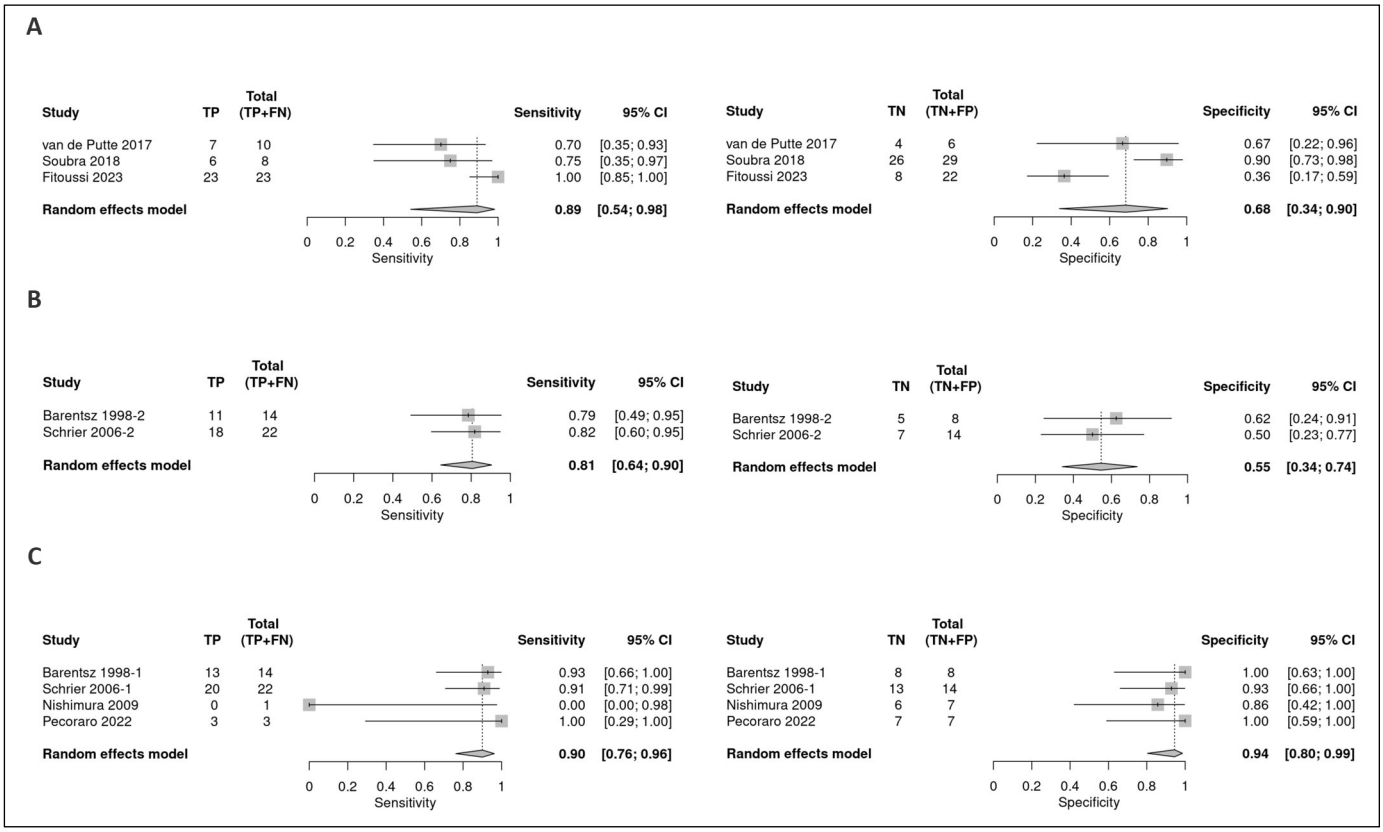

Figure 2. *Forest plots showing the pooled sensitivity and specificity for the diagnostic performance of imaging modalities to predict complete pathological response to neoadjuvant chemotherapy in the bladder tumor in patients with urothelial bladder carcinoma:* **A)** *FDG-PET/CT,* **B)** *un-enhanced MRI,* **C)** *contrast enhanced MRI.*

FDG-PET/CT – FDG-positron emission tomography/Computerized Tomography; MRI – magnetic resonance imaging

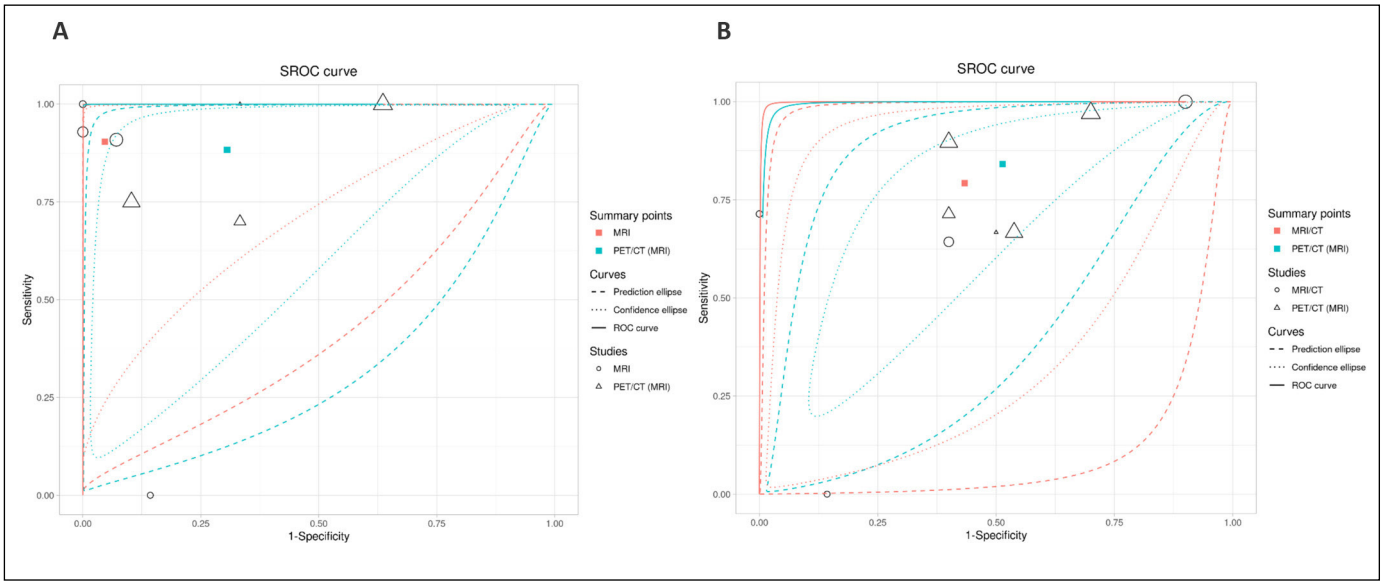

Figure 3. *Summary receiver operating characteristic curves for the diagnostic performance of imaging modalities to predict complete pathological response to neoadjuvant chemotherapy in patients with urothelial bladder carcinoma.* **A)** *Contrast enhanced MRI versus PET/CT (or PET/MRI) in Bladder tumor.* **B)** *Contrast enhanced CT (or MRI) vs PET/CT (or PET/MRI) in lymph node metastasis.*

PET/CT – FDG-positron emission tomography/Computerized Tomography; MRI – magnetic resonance imaging

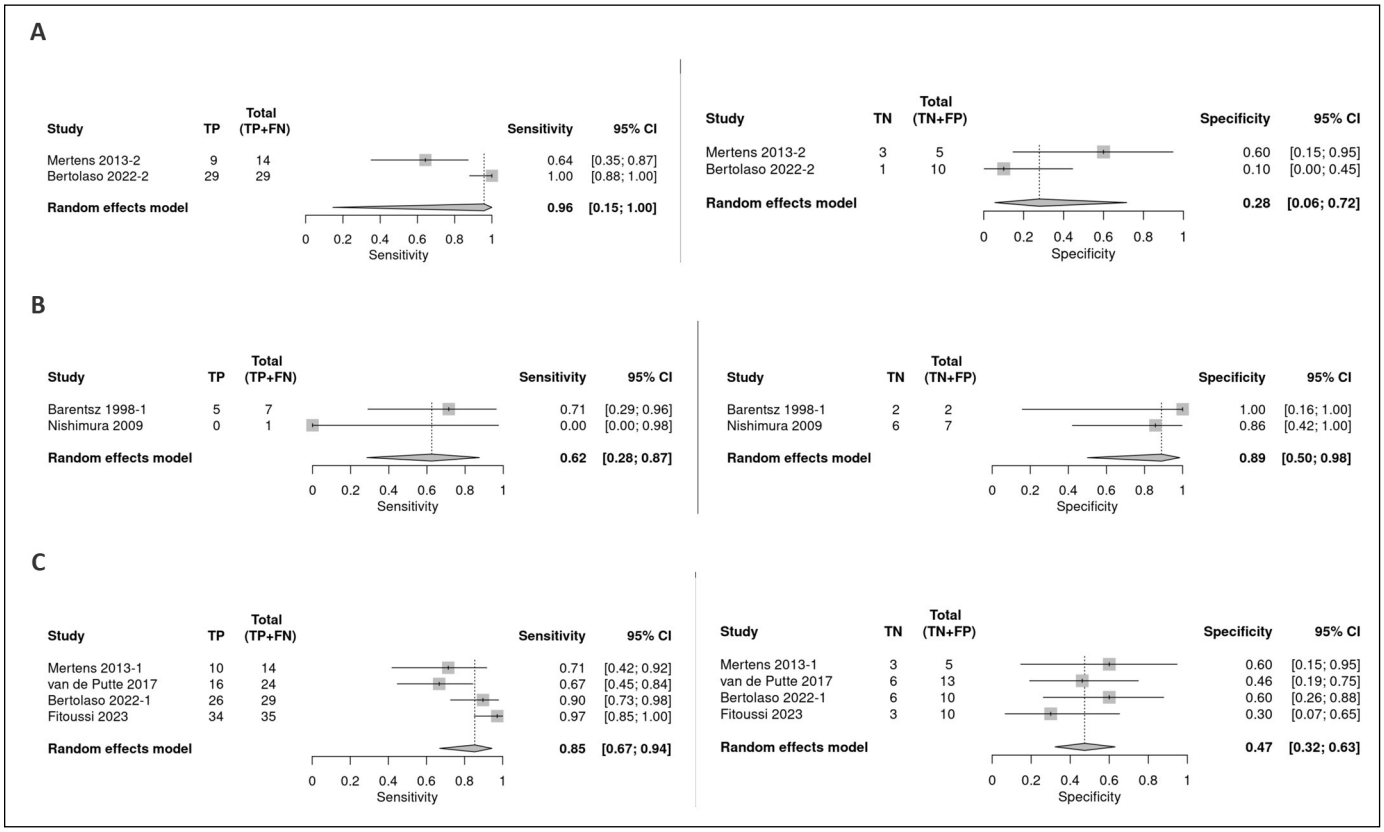

Figure 4. *Forest plots showing the pooled sensitivity and specificity for the diagnostic performance of imaging modalities to predict complete pathological response to neoadjuvant chemotherapy in lymph nodes metastasis in patients with urothelial bladder carcinoma :* **A)** *contrast enhanced CT scan;* **B)** *contrast enhanced MRI;* **C)** *FDG-PET/CT.*

CT – computerized tomography; FDG-PET/CT – FDG-positron emission tomography/computerized tomography; MRI – magnetic resonance imaging

Lymph node metastasis and FDG-PET/CT

Diagnostic performance of FDG-PET/CT for predicting pathological response to NAC in the lymph node metastasis was assessed in four studies [14, 16, 28, 37]. In the forest plot, the pooled sensitivity and specificity were 0.85 (95% CI: 0.67–0.94) and 0.47 (95% CI: 0.32–0.63), respectively (Figure 4C). The Cochrane Q test and I^2 test revealed significant and no significant heterogeneity among studies for sensitivity and specificity, respectively. The DOR, positive LR, and negative LR were 5.25 (95% CI: 2.77–9.93), 1.62 (95% CI: 1.20–2.19), and 0.30 (95% CI: 0.22–0.43), respectively.

PET/CT (MRI) vs MRI (CT) in lymph node metastasis

Diagnosis performance of PET/CT (MRI) was compared with MRI (CT) in predicting pathological response to NAC in lymph node metastasis using metaregression. Relative sensitivity and specificity levels for PET/CT (MRI) vs MRI (CT) were 1.06 (95% CI: 0.7–1.60; p-value: 0.8), and 0.85 (95% CI: 0.40–1.80; p-value: 0.7), respectively. Summary receiver operating characteristic (SROC) curve shows differential diagnostic performance of PET/CT (MRI) and CEMRI (Figure 3B). The Cochrane Q test and I^2 test revealed no significant heterogeneity among studies [14–17, 27, 28, 37].

Risk of bias assessment

The RoB assessment indicated a low to intermediate level of bias across the studies and intermediate level of bias for applicability concerns (Table 3).

DISCUSSION

We analyzed and compared the performance of imaging modalities predicting pathological response to NAC in UBC. We found a high pooled sensitivity and specificity for CEMRI suggesting it to be a useful tool for prediction of pathological response to NAC in the primary tumor. In addition, FDG-PET/CT, has a highly favourable pooled diagnostic

Table 3. *Risk of bias assessment using Quality Assessment of Diagnostic Accuracy Studies-2 (Quadas-2)*

Study, Year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Jakse et al. [30]	Unclear	Low	High	High	Low	High	Low
Barentsz et al. [15]	Low	Low	High	Low	Low	High	Low
Schrier et al. [21]	High	Low	High	Low	High	High	Unclear
Nishimura et al. [27]	Low	Low	Low	Unclear	Low	Low	Low
Donaldson et al. [22]	Low	Low	Low	Unclear	Low	Unclear	Low
Mertens et al. [28]	Low	Low	Low	Low	Low	Low	Low
Hadjiiski et al. [31]	Low	Unclear	Low	Low	Low	Unclear	Low
Nguyen et al. [23]	Low	Low	Low	Unclear	Low	Low	High
Kollberg et al. [29]	Low	Low	Low	Low	Low	Low	High
van de Putte et al. [16]	Low	Low	Low	Low	Low	Low	Low
Salminen et al. [17]	Low	Low	High	Low	Low	Low	High
Soubra et al. [35]	Low	Low	Low	Low	Low	Unclear	Low
Cha et al. [32]	Low	Low	Low	Low	Low	High	Low
Wu et al. [34]	Unclear	Low	Low	Low	High	High	Low
Choi et al. [33]	Low	Low	Low	Low	Unclear	High	Low
Hadjiiski et al. [38]	Unclear	Unclear	Low	Unclear	High	High	Low
Ahmed et al. [26]	Low	Low	Low	Unclear	Low	Low	Low
Ghodoussipour et al. [36]	Low	Low	Low	Low	Low	Low	Low
Bertolaso et al. [14]	Low	Low	Low	Low	Low	Low	Low
Pecoraro et al. [24]	Low	Low	Low	Low	Low	Low	Low
Yang et al. [25]	Low	Unclear	Low	Unclear	Low	High	Low
Fitoussi et al. [37]	Low	Low	Low	Low	Low	Unclear	Low

sensitivity, but is not accurate enough to find residual primary tumor in non-responder patients to NAC. Indeed, we demonstrated that PET/CT (MRI) has a significant lower specificity than CEMRI in predicting pathological response to NAC in the primary tumor.

While limited accuracy of PET/CT has been attributed to the FDG accumulation from the bladder exhibiting similar FDG uptake as tumors, the implementation of deep learning-based image segmentation approach of the bladder on PET/CT seems to be a promising strategy removing FDG physiological background noise [39]. In addition, the introduction of prostate-specific membrane antigen (PSMA) as a potential biomarker of neo-angiogenesis in UBC has put substantial effort into investigating of PSMA and other tracers such as nectin-4 and Her-2 as targets for PET imaging enhancing the diagnostic performance of PET/CT in T and N staging of patients with UBC [40, 41]. Despite the ability of PET/CT with novel tracers to better characterize response to NAC in the primary tumor of UBC patients, remains still unreliable for clinical decision-making at this time.

Implementation of mpMRI, which combines anatomical sequences of T1and T2-weighted imaging and functional sequences of dynamic contrast-enhanced (DCE) MRI and diffusion- weighted imaging, plays an important role enhancing test accuracy for post-chemotherapy T staging in UBC [21, 23]. Pecoraro et al. demonstrated a sensitivity and a specificity of 100% for vesical imaging-reporting and data system in setting of mpMRI to assess response to NAC in UBC patients [24]. Nevertheless, no consistent recommendation can be made owing to the limited data.

We found that contrast enhanced CT scan and FDG-PET/CT are strong rule-out tests for the assessment of residual tumor in lymph nodes after NAC in UBC patients. Indeed, high test sensitivity allows with high certainty to identify patients with pN0 after NAC. Therefore, negative lymph nodes on contrast enhanced CT scan and FDG-PET/CT means a high probability of response to NAC in the lymph node metastatic site. These findings might drive the decision to complete chemotherapy schedule in responders prior to RC and/or to proceed

to surgery as response already happened with a window of opportunity for surgery.

Our analyses demonstrated that the specificity of CEMRI was high (89%) compared to contrast enhanced CT scan and PET/CT indicating the clinical relevance of MRI use for ruling in nodal involvement after chemotherapy in UBC patients. However, owning to moderate sensitivity (62%) for detection of post-chemotherapy locoregional lymph node involvement, using CEMRI might increase the risk of underestimating the metastatic burden, potentially leading to suboptimal treatment.

While early suspicion and timely surgical intervention are crucial for successful treatment in non-responder UBC to NAC, the appropriate timing of imaging modality during chemotherapy is unclear for maximum diagnostic accuracy. Indeed, so early post-chemotherapy imaging might lead to false-positive results denying potential responder patients a chance of benefit from chemotherapy [25]. In the absence of strong evidence on optimal timing of imaging, some studies have specifically addressed the diagnostic accuracy of imaging modality to predict response to NAC after two cycles of chemotherapy [15, 21, 27]. Despite the promising results on diagnostic accuracy of post-two cycles chemotherapy DCE MRI, designing larger prospective studies to confirm the reported high sensitivity and specificity rates of CEMRI protocols is of paramount importance for guiding post-chemotherapy imaging with reliable diagnostic performance [15, 21].

The study has several limitations. First, the vast majority of the included studies were limited by their retrospective design and small sample sizes. There is significant study heterogeneity, and the wide CIs which can lead to potential confounding and bias. Third, discrepancy across the included studies in the time period between first course of chemotherapy and imaging, as well as in the imaging protocols and reporting criteria, might contribute to heterogeneity among the studies. Further well-designed prospective studies are necessary to demonstrate the clinical benefit of different imaging modalities assessing response to NAC in patients with UBC.

CONCLUSIONS

Our analysis suggests that CEMRI (including mpMRI) helps accurate assessment of response to NAC in primary tumor for UBC patients. While contrast enhanced CT scan and FDG-PET/CT are precise staging modality to identify nodal metastasis responders to NAC, CEMRI is a useful tool to detect residual tumor in lymph nodes. However, their relative roles in patients with UBC are yet to be fully defined, and Well-designed, powered, multicenter studies are needed to compare the performance of different imaging modalities for the assessment of response to chemotherapy across UBC patients selected for NAC and RC.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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