

# Evaluation of lymph node status in patients with urothelial carcinoma – still in search of the perfect imaging modality: a systematic review

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**Abstract:** While accurate lymph node status evaluation in urothelial carcinoma patients is essential for the correct disease staging and, hence, establishing the most beneficial treatment strategy, the diagnostic performance of routine imaging in regards to this issue is not satisfactory. For the purpose of this article, we systematically reviewed the contemporary literature on the sensitivity and specificity of particular imaging modalities which have been studied for detecting lymph node metastases in patients diagnosed with urothelial carcinoma. The evidence reviewed shows that computed tomography (CT), although recognized as the imaging modality of choice, is associated with marked limitations, resulting in its low sensitivity for lymph node involvement detection in urothelial carcinoma patients, with no study reporting a value higher than 46% using standard cut-off values. Markedly higher sensitivity rates may be achieved with magnetic resonance imaging (MRI), especially when using ultrasmall superparamagnetic iron oxide as the contrast agent, however, no uniform protocol has been systematically studied up to date. The vast majority of recent evidence concerns positron emission tomography (PET), which is being reported to improve the diagnostic performance of CT alone, as has been demonstrated in multiple articles, which investigated the accuracy of PET/CT at primary or post-treatment staging of urothelial carcinoma patients. However, there has been substantial heterogeneity in terms of methodology and results between those studies, making it premature to draw any definitive conclusions. The results of this review lead to a conclusion, that while CT, despite being not fully satisfactory, still remains the gold-standard method of imaging for staging purposes in urothelial carcinoma, other imaging modalities are under investigation, with promising results.

**Keywords:** Urothelial carcinoma; bladder cancer; lymph node involvement; magnetic resonance imaging (MRI); positron emission tomography (PET)

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## Introduction

Urothelial carcinoma, or transitional cell carcinoma (TCC), comprises a group of heterogeneous malignant diseases typically involving the urinary system. Bladder cancer (BC), being the most common urinary malignancy worldwide, with the urothelial type accounting for 90 percent of cases diagnosed in the United States and Europe, is the ninth leading cause of cancer death in the United States (1,2). With the exception of non-muscle invasive bladder cancer (NMIBC), relatively indolent but still capable of progressing into muscle invasive and metastatic disease (3-5), urothelial carcinomas are known for its rapid metastatic ability (6,7). While the risk of metastatic lymph node involvement (LNI) reaches 10–30% in patients with organ-confined muscle-invasive bladder cancer (MIBC), it increases to 50% in cases when the tumor extends into perivesical fatty tissue (8). It is estimated that 10–15% of eventually metastatic BC patients are metastatic at the time of diagnosis (9).

While cure can be achieved in as much as 75–80% of patients with organ-confined disease, this number drops to about 60% in T3, node-negative disease, and is estimated to be as low as 30% with positive lymph node status (10-14). In patients with LNI the 5-year recurrence-free survival rates are 35% regardless of the T stage (12,15). Due to short survival expectancies metastatic and node-positive patients are generally not suitable for radical treatment (6,7) and have historically been managed as with metastatic disease and included into chemotherapy clinical trials (16). Interestingly, recent studies indicate that lymph node involvement may not inevitably impair the oncologic outcome, and several treatment modalities, including radical cystectomy with or without neoadjuvant chemotherapy, are being used with promising results for clinically node-positive disease (17-19).

Given the fact that LNI has a significant impact on the prognosis and hence alters treatment selection (20,21), accurate staging of the disease with imaging studies is vital in terms of establishing the right management plan. Several different imaging modalities, including computed tomography urography (CTU), magnetic resonance (MR), or positron emission tomography (PET), are being used for the purpose of determining disease stage with variable results. Our objective was to systematically review the up to date literature concerning the role of particular imaging modalities in evaluating lymph node status in urothelial cancer patients.

## Materials and methods

The authors of this systematic review adhered to a predefined protocol developed according to PRISMA guidelines. A systematic search of literature using electronic databases was performed in order to review current evidence-based data relating to the topic of this article.

We combined searches from the Medline and Scopus electronic databases. A detailed search query developed for use in PubMed (Medline) was as follows: (bladder cancer[MeSH Terms] OR transitional cell carcinoma[MeSH Terms]) AND “english”[Language] AND (“2003/01/01”[Date, Publication] : “2018/05/30”[Date, Publication]) AND (MRI[Title/Abstract] OR MR[Title/Abstract] OR magnetic resonance[Title/Abstract] OR CT[Title/Abstract] OR computed tomography[Title/Abstract] OR PET-CT[Title/Abstract] OR PET[Title/Abstract] OR positron[Title/Abstract] OR imaging[Title/Abstract] OR uspio[Title/Abstract]). For the purpose or Scopus search we developed a query as follows: TITLE-ABS-KEY(“bladder” OR “transitional” OR “urothelial”) AND TITLE-ABS-KEY(“cancer” OR “carcinoma”) AND TITLE-ABS-KEY(MR\* OR “imaging” OR “resonance” OR “CT” OR “tomography” OR “PET” OR “positron” OR “USPIO”), and the search results were restricted to English language papers published between 2003/01/01 and 2018/05/30.

Articles were considered for this review if they: (I) were published in a peer-reviewed English language journal; (II) were either meta-analyses, reviews, clinical trials, cohort studies, case-control studies or cross-sectional studies; (IIIa) reported either sensitivity or specificity of an imaging modality in detecting urothelial carcinoma metastases or (IIIb) reported data on imaging-related understaging or overstaging of urothelial cancer disease. The eligibility of all full-text studies listed in the search results was independently assessed by two reviewers.

Each article meeting the eligibility criteria underwent a quality assessment by the co-authors, in order to exclude studies of relatively small statistical power. Eventually, data from the studies included into this review was abstracted and analyzed.

### Computed tomography (CT) (Table 1)

Multiphase contrast-enhanced CT with urinary excretory phase, or computed tomography urography (CTU), is the imaging modality of choice for the purpose of urinary

**Table 1** Computed tomography in preoperative lymph node status assessment of bladder cancer patients

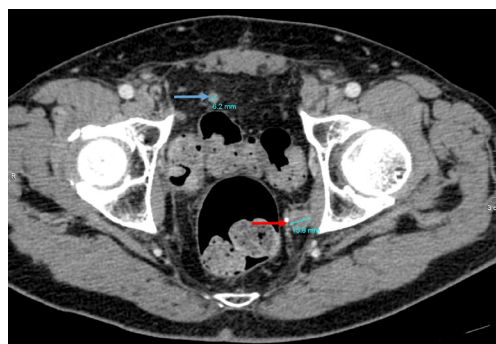
Author	Modality	Year	No. of patients	Study type	Cutoff	Additional morphologic assessment	Accuracy (%)	Overstaging (%)	Understaging (%)	Sensitivity (%)	Specificity (%)	Comments
Li <i>et al.</i> (22)	CT, MRI	2018	191	Retrospective	6.8 mm	-	-	-	-	83.0	64.3	Size, shape, presence of fat in the nodal hilum were assessed in this study but results were calculated for lymph node short axis only
Pichler <i>et al.</i> (23)	FDG-PET/ CT	2017	70	Retrospective	8 mm, 10 mm	-	84.3 (8 mm); 85.7 (10 mm)	-	-	45.5 (8 mm); 27.3 (10 mm)	91.5 (8 mm); 96.6 (10 mm)	Increase of cutoff value to 10 mm does not importantly increase specificity but decreases sensitivity nearly twofold
Horn <i>et al.</i> (24)	CT	2016	231	Retrospective	10 mm	Size, shape, presence of fat in the nodal hilum, extracapsular extension, regional clustering of LN	83.4-93.3	-	-	30.2-52.6	93.6-98	CT not useful in detecting small (<1 cm) lymph nodes with microscopic tumors
Jeong <i>et al.</i> (25)	FDG-PET/ CT	2015	61	Prospective	10 mm	Necrosis, independently of size	-	6.6	21.3	29.4	97.7	CT contributes to understaging of cancers with small foci of metastases
Aljabery <i>et al.</i> (26)	FDG-PET/ CT	2015	54	Prospective	10 mm	-	-	-	-	41	89	-
Goodfellow <i>et al.</i> (27)	FDG-PET/ CT	2014	233	Retrospective	8 mm	-	83	-	-	46	98	-
Brunocilla <i>et al.</i> (28)	11C Choline- PET/CT, CECT	2014	26	Prospective	10 mm	-	6	-	-	14	89	Very low sensitivity and accuracy for CECT
Hittier- Berhault <i>et al.</i> (29)	FDG-PET/ CT	2013	52	Prospective	10mm in a long axis	-	55.7	-	-	9.1	90	Assessment of long axis is largely insensitive for lymph node assessment
Tritschler <i>et al.</i> (30)	CT	2012	276	Retrospective	10 mm	-	54	8.3	29.4	-	-	CT contributes to understaging of cancers with small foci of metastases

**Table 1** (continued)

Table 1 (continued)

Author	Modality	Year	No. of patients	Study type	Cutoff	Additional morphologic assessment	Accuracy (%)	Overstaging (%)	Understaging (%)	Sensitivity (%)	Specificity (%)	Comments
Apolo et al. (31)	FDG-PET/CT	2010	57	Prospective	-	-	-	-	-	40.7	91.5	-
Lodde et al. (32)	FDG-PET/CT	2010	44	Prospective	10 mm	<10 mm if defined as suspicious by radiologist	-	-	-	33	100	-
Swinnen et al. (33)	FDG-PET/CT	2010	51	Prospective	-	-	80	-	-	46	92	-

CT, computed tomography; CECT, contrast enhanced computed tomography; MRI, magnetic resonance imaging; FDG-PET/CT, <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography/computed tomography.



**Figure 1** Contrast-enhanced computed tomography of the pelvis of a patient with bladder cancer (venous phase, axial section). Left-sided inferior gluteal lymph node (red arrow): its short axis diameter of 13.8 mm, as well as the round, polycyclic shape are the features of malignant involvement. Right-sided superior vesical lymph node (blue arrow): although its short axis diameter of 6.2 mm does not exceed threshold values, the round shape may be suggestive of metastatic involvement. In fact, both lymph nodes were confirmed metastatic in the postoperative pathology report.

tract cancer staging (6,7). The recognition of CT as the gold standard clinical staging method is reflected by CT being most commonly compared to in studies that evaluate the utility of other imaging modalities, as revealed in this review.

The assessment of the status of a potentially metastatic lymph node is based primarily on the measurement of its diameter, making this approach susceptible to understaging in case of small-size metastatic foci, or overstaging in case of marked nodal inflammatory response. The dimension universally used for measuring the size of a lymph node is its short axis diameter (*Figure 1*). In one study, Hitier-Berthault *et al.* (29) demonstrated a remarkably low sensitivity (9.1%) when using the long axis for this purpose. The sensitivity and specificity of CT regarding lymph node status evaluation are greatly dependent on the diameter cut-off values adopted, which may be additionally complicated by the fact that optimal short axis of a lymph node is influenced by its shape (34). The universally recognized threshold value of a lymph node short-axis diameter indicative of metastatic involvement is 8 mm for urothelial carcinoma (6,34). However, both 8 and 10 mm cut-off values were adopted in the studies included in this review, as shown in *Table 1*. Moreover, Li *et al.*, who retrospectively analyzed data collected from 191 bladder cancer patients, suggested a threshold value of 6.8 mm, as this was associated with the area under receiver operating characteristic (ROC)

curve of 0.815, with the increased sensitivity (83.0%) being accompanied by relatively low specificity (64.3%). Apart from the short axis size, the shape of a lymph node may be revealing of its status, with a round shape indicative of metastasis and an oval shape characteristic of an inflammatory response. Hence, the long-to-short axis ratio has been proposed as a measurable indicator of LNI (22). Yet, this parameter has not been shown to improve the diagnostic performance compared to short axis diameter alone (22).

A short-axis diameter cut-off value of 8 mm, while decreasing the false-positive rate, makes it virtually impossible to detect smaller metastases, which may be of dramatic significance at the early stage of metastatic spread. This is reflected by non-satisfactory, low sensitivity values of CT used for the purpose of LN status evaluation in BC patients, which, in studies included into this review, ranged from 14% in a study by Brunocilla (28), to 46% (23,27), with the majority of the values falling between 30% and 40%, as presented in *Table 1*. On the other hand, CT is characterized by relatively high specificity in regard to the nodal staging of BC, which, according to prospective studies included in this review, demonstrated values between 89% and 100% (23-27,29-33). Among other studies, summarized in *Table 1*, a retrospective analysis by Horn *et al.* (24), based on data collected from 231 patients, reported sensitivity values of 30.2% on patient-based level and 52.6% on a field basis, and specificity values of 98.0% and 93.6%, respectively.

The clinical significance of sensitivity and specificity of an imaging modality in regard to LN status evaluation is reflected in the under and overstaging rates. Tritschler *et al.* (30), demonstrated in a retrospective study on 276 patients diagnosed with bladder cancer and treated with radical cystectomy with pelvic lymph node dissection, that a preoperative CT scan was associated with LN evaluation-related under and overstaging rates of 29.4% and 8.3%, respectively. Similarly, according to the results of a prospective study by Jeong *et al.* (25), preoperative LN status assessment using a CT scan led to under and overstaging in 21.3% and 6.6% of cases, respectively.

### **Magnetic resonance imaging (MRI) (Tables 2,3)**

Although magnetic resonance (MR) appears to be an excellent imaging modality in terms of local staging of bladder cancer, mainly due to its high soft-tissue contrast resolution, its role in the process of nodal staging of

urothelial carcinoma is not definitely established (45-51). While the application of diffusion-weighted (DW) MR imaging (DW-MRI) for the purpose of detecting LN metastases has been shown to be useful in several other malignancies (52-56), the number of studies demonstrating similar clinical significance of MR in urothelial carcinoma patients is limited.

The main imaging-related advantage of MR over CT in terms of LN status evaluation is that MR provides an opportunity to assess several features other than the size or shape of a lymph node, namely, the presence of fatty hilum (as loss of fatty hilum is characteristic of metastatic involvement) and diffusion parameters (quantified with the apparent diffusion coefficient, or ADC) (*Figure 2*), as well as it enables true dynamic contrast enhanced (DCE) imaging in multiple phases without using ionized radiation. As shown in a study by Mir *et al.* (57), a fusion of high b-value ( $750 \text{ s/mm}^2$ ) DW-MRI with conventional T2-weighted images could improve lymph node identification. In the study by Li *et al.* (22) the presence of fatty hilum was indicative of non-metastatic character of a lymph node in bladder cancer patients. Papalia *et al.* (40) have stated that DW imaging sequences could increase the sensitivity of MR in detecting lymph node metastases to 76%, with the optimal ADC cut-off value of  $0.86 \times 10^{-3} \text{ mm}^3/\text{s}$ . The role of DCE-MR with gadolinium used as the contrast agent has been studied by Daneshmand *et al.* (39), who prospectively analyzed data from 122 bladder cancer patients, reported the sensitivity, specificity, and accuracy values of preoperative gadolinium DCE-MR imaging for the evaluation of nodal status of 40.7%, 91.5% and 80.3%, respectively.

A distinct method of imaging using MR is using ultra-small superparamagnetic iron oxide (USPIO) as a contrast agent. Following an injection of ferumoxtran-10 solution, a significant drop of signal intensity on T1- and T2-weighted images is observed in non-metastatic lymph nodes, as the contrast is absorbed by local macrophages. On the other hand, the presence of bright signal is indicative of a metastatic tumor growing in the lymph node, as the macrophages have been replaced by metastatic cells and therefore ferumoxtran-10 particles are not cleared (58,59). Following the development of USPIO-enhanced MR, it has been adopted for use in a variety of pelvic malignancies (60), as well as it has been studied in bladder cancer. However, a high rate of adverse events with USPIO remain an important issue (46).

According to a study by Deserno *et al.* (44), who prospectively evaluated the effectiveness of USPIO-

**Table 2** Magnetic resonance imaging in lymph node status assessment in bladder cancer patients

Author	Modality	Analyzed sequences	Magnet strength	Year	No. of patients	Study type	Accuracy	Overstaging (%)	Understaging (%)	Sensitivity (%)	Specificity (%)	Comments
Woo et al. (35)	MRI, USPIO	DWI, DCE	1.5–3 T	2018	2,928	Meta-analysis	-	-	-	56	94	Heterogeneity of studies – both prostate and bladder cancer studies included, with most regarding to prostate cancer
Li et al. (22)	MRI, CT	DWI, DCE	3 T	2018	191	Retrospective	-	-	-	83	64.3	6.8 mm – the optimal threshold to diagnose metastatic lymph node involvement; low specificity
Lin et al. (36)	MRI	DWI	1.5–3 T	2015	-	Review	Unsatisfactory	-	-	76–79	79–89	DWI better than CT or MR without DWI in assessing for lymph node metastases; failure to identify small metastatic lymph nodes due to the limited spatial resolution of DWI
Wollin et al. (37)	MRI	DWI, DCE	-	2014	36	Retrospective	-	-	-	88 (SA >5 mm), 88 (LA >6 mm)	75 (SA <5 mm), 71 (LA >6 mm)	Lymph node short axis >5 mm showed highest accuracy; ADC showed lower sensitivity, specificity and accuracy
Liedberg et al. (38)	MRI, CT	DCE	3 T	2013	53	Prospective	-	50	10	86 <sup>b</sup>	31 <sup>b</sup>	Assessment for organ and non-organ confined disease
Daneshmand et al. (39)	MRI	T2W, DCE	1.5 T	2012	122	Prospective	80.3%	-	-	40.7	91.5	Despite high accuracy in detecting positive nodes DCE-MRI shows low sensitivity in determining positive nodal disease
Papalia et al. (40)	MRI, CT	T2W, DWI	1.5 T	2012	36	Prospective	DW-MRI do not seem to be accurate	-	-	76.4	89.4	ADC improves sensitivity of MRI for lymph node metastasis, but a substantial clinical-pathologic discordance persists

MRI, magnetic resonance imaging; CT, computed tomography; USPIO, ultrasmall superparamagnetic iron oxide; T, Tesla; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast enhancement; T2W, T2-weighted; SA, short axis; LA, long axis.

enhanced MR in preoperative nodal staging of 58 bladder cancer patients, it demonstrated accuracy, sensitivity, specificity and positive and negative predictive values (PPV and NPV) of 95%, 96%, 95%, 89% and 98% respectively, compared to precontrast values of 92%, 76%, 99%, 97%, and 91%, respectively. A clinical trial has been conducted by Thoeny *et al.* (61) in order to assess the value of combined USPIO-enhanced- and DW-MR (USPIO-DW-MR) imaging in the process of preoperative pelvic lymph node metastases detection, with both prostate cancer and bladder cancer patients being enrolled into the trial. The results of the trial have been published in three separate papers. In the early report by Thoeny *et al.* (43), imaging with USPIO-DW-MR was associated with a 92% rate of correct diagnosis (24 out of 26 lymph nodes assessed), with the only two LNs missed being micrometastatic. Later, after 2,993 lymph nodes of 75 patients have been analyzed, Triantafyllou *et al.* (42) reported USPIO-DW-MR imaging to demonstrate sensitivity, specificity, PPV, NPV and diagnostic accuracy of 55.0–58.3%, 85.5–83.0%, 57.9–58.0%, 83.9–84.4% and 77.3–76.4%, respectively, with the majority of missed metastases being smaller than 5 mm in short axis diameter. Based on the same trial, Birkhäuser *et al.* (41) reported a per-patient sensitivity and specificity for detection of LNI of 65–75% and 93–96%, respectively, and sensitivity and specificity per pelvic side 58–67% and 94–97% respectively.

**Positron-emission tomography (PET)**

*Preoperative staging (Table 4)*

<sup>18</sup>F-fludeoxyglucose-PET (FDG-PET) has been long proposed as a possible imaging modality for preoperative staging of patients in whom radical cystectomy for bladder cancer is considered (Figure 3). This has been, however, confronted with conflicting viewpoints in the reviewed literature.

An early [2005] prospective study by Drieskens *et al.* (68) on 55 patients showed high concordance between FDG-PET/CT and CT alone results regarding sensitivity for lymph node metastasis detection, which was later confirmed by Swinnen *et al.* (33) who in 2010 reported similar results of a prospective study on 51 patients and concluded that FDG-PET/CT provides no real advantage in locoregional lymph node staging in bladder cancer. However, a similar prospective study by Lodde *et al.* (32), published later that year, revealed that FDG-PET/CT may be in fact more

Table 3 USPIO in preoperative lymph node status assessment of bladder cancer patients

Author	Cancer origin	Modality	Magnet strength	Year	No. of patients	Study type	Accuracy MRI per patient (%)	Accuracy DW-USPIO per patient (%)	Accuracy MRI per patient (%)	Sensitivity DW-USPIO per patient (%)	Sensitivity MRI per patient (%)	Specificity DW-USPIO per patient (%)	Specificity MRI per patient (%)	Comments
Birkhäuser (41)	Prostate and bladder	USPIO, DW-USPIO	3 T	2013	75	Prospective	-	65-75	-	-	-	93-96	-	No metastasis with a long-axis diameter of >5 mm was missed by combined USPIO-DW MRI

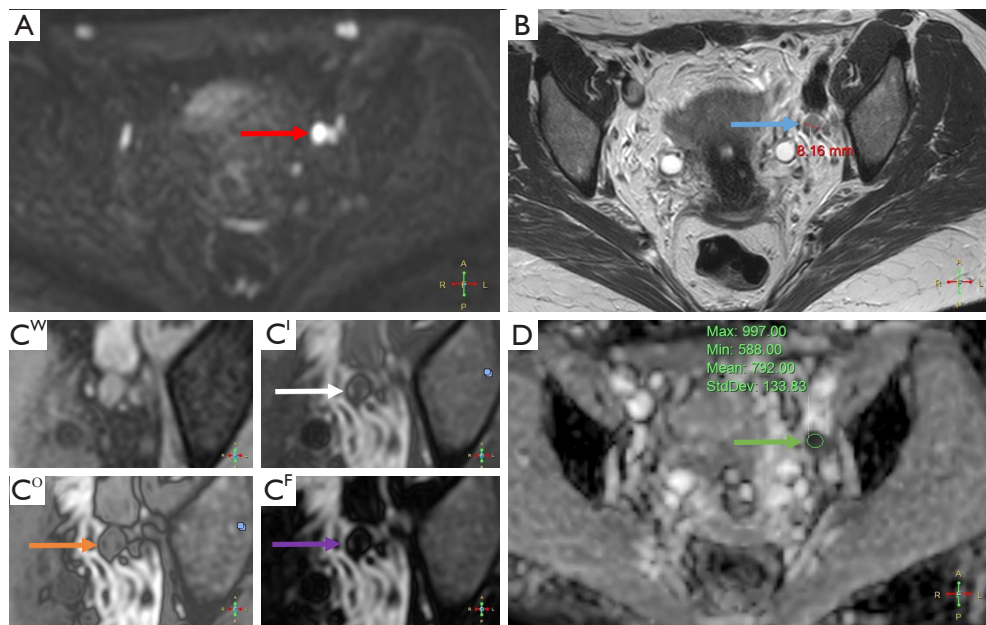
Table 3 (continued)

Table 3 (continued)

Author	Cancer origin	Modality	Magnet strength	Year	No. of patients	Study type	Accuracy		Sensitivity		Specificity		Comments	
							Accuracy MRI per patient (%)	Accuracy DW-USPIO per patient (%)	Sensitivity MRI per patient (%)	Sensitivity DW-USPIO per patient (%)	Specificity MRI per patient (%)	Specificity DW-USPIO per patient (%)		
Triantafyllou (42)	Prostate and bladder	USPIO	3 T	2013	75	Prospective	77	–	55	–	85.5	–	Accurate in detecting metastases in normal-sized lymph nodes; the majority of metastases with a short axis diameter <3 mm were still missed	
Thoeny (43)	Prostate and bladder	USPIO, DW-USPIO	3 T	2009	21	Prospective	90	90	80	–	73	87	–	
Deserno (44)	Bladder	MRI, USPIO	1.5 T	2004	58	Prospective	95	–	96	76	99	95	–	Largest study on bladder cancer patients up to date. Detection of metastases even in normal-sized lymph nodes

USPIO, ultrasmall superparamagnetic iron oxide imaging; DW-USPIO, ultrasmall superparamagnetic iron oxide-enhanced diffusion-weighted imaging; MRI, magnetic resonance imaging; T, Tesla.





**Figure 2** Multiparametric magnetic resonance imaging of the pelvis of a bladder cancer patient, performed using a 3 T scanner (axial sections). A left-sided external iliac lymph node is clearly identified on diffusion-weighted imaging with the b value of  $1,500 \text{ mm}^2/\text{s}^2$ . (A, red arrow), as demonstrated by Mir *et al.* (57) It may be considered borderline, given its short axis diameter of 8.16 mm, as seen on T2-weighted turbo spin echo imaging (B, blue arrow). (C<sup>W</sup>) DIXON water only image. The lymph node is then evaluated for a loss of fatty hilum, which would be considered a hallmark of metastatic involvement. The hilum appears visibly hypointense on fat-only imaging (C<sup>F</sup>, purple arrow) and does not exhibit signal drop-out on out-of-phase images (C<sup>O</sup>, orange arrow) as compared to in-phase images (C<sup>I</sup>, white arrow), which is indicative of no detectable fat in the hilum and therefore suggestive of malignancy. The apparent diffusion coefficient of the lymph node is  $0.79 \times 10^{-3} \text{ mm}^2/\text{s}$  (D, green arrow), which is lower than the threshold adopted by Papalia *et al.* (40) ( $0.86 \times 10^{-3} \text{ mm}^2/\text{s}$ ). This lymph node was later confirmed metastatic at the postoperative pathology report.

sensitive than CT in detecting lymph node metastases (sensitivity 57% *vs.* 33%). Other studies, published between 2009 and 2014, argued in favor of using FDG-PET/CT as a preoperative staging tool in bladder cancer patients. Kibel *et al.* (67), as well as Apolo *et al.* (31), who prospectively studied 43 and 57 (respectively) patients, reported both high sensitivity and specificity of FDG-PET/CT in detecting LNI (70% and 94% respectively for Kibel *et al.* and 92% and 81% for Apolo *et al.*). Hitier-Berhoul *et al.* (29) prospectively compared FDG-PET/CT and CT alone in 52 patients and reported significantly higher sensitivity of FDG-PET/CT in evaluating LN status for staging purposes, concluding that FDG-PET/CT is more reliable than CT alone. A bigger (n=102) study by Rouanne *et al.* (65) also showed high sensitivity and specificity values for FDG-PET/CT, which led to a conclusion pointing out improved diagnostic efficacy of FDG-PET/CT for lymph node staging.

However, later studies, which compared FDG-PET with CT showed less favorable results. Goodfellow *et al.* (27) in their study on 233 bladder cancer patients, published in 2014, showed only a small benefit in detecting lymph node metastases outside the pelvis when compared to CT (sensitivity 69% *vs.* 41% respectively), which the authors considered not to be enough to justify the use of preoperative FDG-PET outside of a proposed selected group of patients. Recently, Aljabery *et al.* (26) [2015] and Pichler *et al.* (23) [2017], based on the results of their studies both concluded that FDG-PET provided no advantage over CT in detection of metastatic lymph nodes in bladder cancer.

A novel study by Vind-Kezunovic *et al.* (63) was published in 2017, in which the authors evaluated the maximum standard uptake value (SUVmax) on FDG-PET scans. Based on data prospectively collected from 131 patients, the authors revealed that at SUVmax >2 FDG-PET

**Table 4** <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography in preoperative lymph node status assessment in bladder cancer patients

Author	Modality	Year	No. of patients	Study type	Accuracy (per patient)	Sensitivity (per patient)	Specificity (per patient)	Comments
Ha et al. (62)	FDG-PET/CT	2018	785	Meta-analysis	-	57%	92%	Low sensitivity and high specificity for the detection of metastatic LNs in patients with newly diagnosed BC. Heterogeneity between studies
Vind-Kezunovic et al. (63)	FDG-PET/CT	2017	131	Prospective	-	91.3% (SUVmax >2); 77.8% (SUVmax >4)	75.3% (SUVmax >2); 91.1% (SUVmax >4)	A higher SUVmax (e.g., SUVmax >4) can be of clinical importance aiding in differentiation between patients with a poor prognosis
Pichler et al. (23)	FDG-PET/CT	2017	70	Retrospective	CT 84%, PET 85, PET/CT 83%	CT 46%, PET 55%, PET/CT 64%	CT 92%, PET 90%, PET/CT 86%	-
Soubra et al. (64)	FDG-PET/CT	2016	78	Retrospective	PET/CT 89.7%	PET/CT 56.3%	PET/CT 98.4%	No comparison with CT
Jeong et al. (25)	FDG-PET/CT	2015	61	Prospective	-	PET/CT 47.1%, CT 29.4%	PET/CT 93.2%, CT 97.7%	-
Aljabery et al. (26)	FDG-PET/CT	2015	54	Prospective	-	PET/CT 41%, CT 41%	PET/CT 86%, CT 89%	-
Goodfellow et al. (27)	FDG-PET/CT	2014	233	Retrospective	PET 82%, CT 83%, PET/CT 87%	PET 46%, CT 46%, PET/CT 69%	PET 97%, CT 98%, PET/CT 95%	PET scan may be useful in selected patients with enlarged pelvic LNs and a small primary bladder tumor, suspected metastases in LNs outside of the pelvic lymphadenectomy window and patients with indeterminate metastases
Rouanne et al. (65)	FDG-PET/CT	2014	102	Prospective	PET/CT 85.3%	PET/CT 50%	PET/CT 97.4%	Improved diagnostic efficacy of PET/CT for lymph node staging in patients staged N0 with conventional cross-sectional imaging
Hittier-Berthault et al. (29)	FDG-PET/CT	2013	52	Prospective	CT 55.7%, PET/CT 65.4%	CT 9.1%, PET/CT 36.4%	CT 90%, PET/CT 86.7%	-
Jensen et al. (66)	FDG-PET/CT MRI	2011	18	Retrospective	-	MRI 0%, PET/CT 33%	MRI 80%, PET/CT 93.3%	-
Apolo et al. (31)	FDG-PET/CT, CT, MRI	2010	57	Prospective	-	PET/CT 92%	PET/CT 81%	FDG-PET/CT compared with conventional MRI or CT alone, detected more lesions detected in 40% of patients
Lodde et al. (32)	FDG-PET/CT	2010	44	Prospective	-	CT 33%, PET/CT 57%	CT 100%, PET/CT 100%	-
Swinnen et al. (33)	FDG-PET/CT	2010	51	Prospective	CT 80%, PET-CT 84%	PET-CT 46%, PET/CT 46%	CT 92%, PET/CT 97%	-

**Table 4** (continued)

Table 4 (continued)

Author	Modality	Year	No. of patients	Study type	Accuracy (per patient)	Sensitivity (per patient)	Specificity (per patient)	Comments
Kibel <i>et al.</i> (67)	FDG-PET/CT	2009	43	Prospective	-	PET/CT 70%	PET/CT 94%	FDG-PET/CT detected occult metastatic disease in seven of 42 patients with negative conventional preoperative evaluations. PET findings were strongly correlated with survival
Driessens <i>et al.</i> (68)	FDG-PET/CT	2005	55	Prospective	PET 65%, PET/CT 78%	PET 53%, PET/CT 60%	PET 72%, PET/CT 88%	-

FDG-PET-CT, 18F-fluorodeoxyglucose positron-emission tomography/computed tomography; PET-CT, positron-emission tomography/computed tomography; PET, positron-emission tomography; CT, computed tomography; SUVmax, maximum standard uptake value; MRI, magnetic resonance imaging; BC, bladder cancer; LNs, lymph nodes.

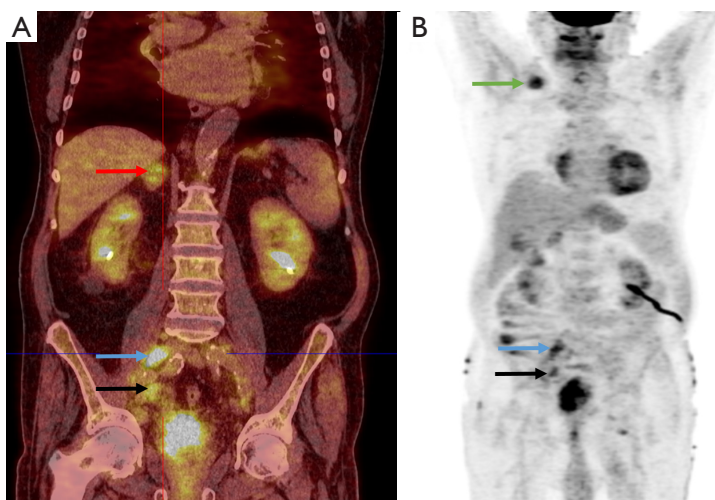
scan sensitivity and specificity values in detecting metastatic LNs were 79.4% and 66.5%, respectively, while at SUVmax >4 FDG-PET showed sensitivity of 61.8% and specificity of 84.5%. The authors concluded that at higher SUVmax (>4) FDG-PET scans can aid in differentiation between patients with a poor prognosis.

The data regarding the use of FDG-PET/CT for the purpose of preoperative bladder cancer staging was recently meta-analyzed by Ha *et al.* (62) The meta-analysis included 14 studies, all of which are reviewed in this article (62,63,67-78); and revealed a relatively low pooled sensitivity of 57% and high pooled specificity of 92% of FDG-PET in preoperative detection of metastatic LNs. The authors pointed out the substantial heterogeneity of the studies in terms of the estimates of sensitivity and specificity, which, according to their analysis, could be explained both by diverse methodology between different studies and major baseline differences between patients.

**Postoperative staging (Table 5)**

Postoperative nodal recurrence of urothelial carcinoma is associated with a poor prognosis (69). Although no therapy has been proven to significantly prolong survival in these patients, early and precise detection of disease recurrence may be of substantial significance in terms of selecting the right management strategy.

The number of studies evaluating the role of PET/CT in postoperative restaging of urothelial carcinoma patients is scant. However, the literature available suggests that this modality may be of significant value in terms of detecting nodal recurrence in bladder cancer. In an early [2008] study by Jadvar *et al.* (70), who retrospectively analyzed data from 35 patients, PET/CT was reported to be two times more sensitive than CT in detecting metastatic lymph nodes. Moreover, the information provided with PET/CT affected the clinical management in 6 patients (17% of-total), mainly by prompting additional therapy. This data is consistent with the conclusions of Apolo *et al.* (31), who also stated that according to their study results PET/CT scans changed the postoperative management of 68% BC patients. In a study by Yang *et al.* (71) PET/CT demonstrated sensitivity of 87.1% and specificity of 89.7% regarding the detection of LN metastases in BC recurrence, by which it outperformed CT, MRI, and ultrasound, and was noted to affect management plans. Recently [2015] Öztürk *et al.* (72) reported good outcomes of using PET/CT in identifying post-cystectomy



**Figure 3**  $^{18}\text{F}$ -fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) scan of a patient with urothelial bladder cancer. The fusion image (A) shows a high uptake of FDG in a right-sided common iliac lymph node (blue arrow) and in a right-sided external iliac lymph node (black arrow), as well as in the right adrenal gland (red arrow), which is consistent with metastatic involvement. The minimum intensity projection (MIP) image (B) additionally depicts an increased FDG uptake in a right-sided supraclavicular lymph node (green arrow).

**Table 5**  $^{18}\text{F}$ -fluorodeoxyglucose positron-emission tomography in post-treatment assessment of lymph node status in bladder cancer patients

Author	Modality	Year	No. of patients	Study type	Accuracy (per patient)	Sensitivity (per patient)	Specificity (per patient)	Comments
Öztürk <i>et al.</i> (72)	FDG-PET/CT	2015	51	Retrospective	90%	92%	83%	–
Chakraborty <i>et al.</i> (64)	FDG-PET/CT	2014	43	Retrospective	CT 58%, FDG-PET/CT 70%	CT 80%, FDG-PET/CT 85%	CT 50%, FDG-PET/CT 60%	–
Lu (79)	FDG-PET/CT	2012	236	Metaanalysis	–	82%	89%	–
Yang <i>et al.</i> (71)	FDG-PET/CT, CT, MRI, US	2012	60	Retrospective	–	87.1%	89.7%	PET/CT outperformed CT, ultrasound, and MRI in changing management and correctly restaging UC after surgery
Apolo <i>et al.</i> (31)	FDG-PET/CT	2010	25	Prospective	–	75%	92%	PET-CT change management decisions in 68% of patients undergoing PET scans for restaging
Jadvar <i>et al.</i> (70)	FDG-PET/CT	2008	35	Retrospective	–	–	–	PET-CT affected the clinical management in 6 patients

FDG-PET-CT,  $^{18}\text{F}$ -fluorodeoxyglucose positron-emission tomography/computed tomography; PET/CT, positron-emission tomography/computed tomography; PET, positron-emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound; UC, urothelial carcinoma.

metastases of BC, with sensitivity, specificity, PPV and NPV of 92%, 83%, 94%, 77%, respectively.

Apart from the above, according to the study by Giannatempo *et al.* (73), FDG-PET may be useful in the assessment of treatment response in metastatic urothelial carcinoma treated with chemotherapy alone, with a survival advantage reported in those with favorable response on FDG-PET imaging after two cycles of first-line chemotherapy.

### Novel radiotracers (Table 6)

For the purpose of cancer staging, <sup>18</sup>F-fludeoxyglucose (FDG) has been traditionally used as the radiotracer of choice. Besides, several other compounds have been employed for use in oncology, yielding varying results, with <sup>11</sup>C-methionine, <sup>11</sup>C-acetate, and <sup>11</sup>C-choline being most widely used.

We found no essential research data regarding the use of <sup>11</sup>C-methionine for the purpose of metastases detection in urothelial carcinoma patients among the results of our database search queries. This could be explained by the fact that the low specificity of <sup>11</sup>C-methionine and increased background uptake make this radiotracer of very limited value in terms of precise urothelial cancer staging (74,75).

The value of the radiotracer <sup>11</sup>C-choline in detecting metastases in cases of urothelial carcinoma has been assessed in several small studies on patients diagnosed with urothelial BC and referred for radical cystectomy with pelvic LN. In a prospective study on 27 patients by Picchio *et al.* (76), <sup>11</sup>C-choline-PET/CT demonstrated 62% sensitivity and 100% specificity regarding the preoperative LN metastases detection. In a study by Brunocilla *et al.* (28), who compared preoperative <sup>11</sup>C-choline-PET/CT to contrast-enhanced CT in 26 BC patients, <sup>11</sup>C-choline-PET/CT was shown to have much greater sensitivity than CT, while demonstrating similar specificity. On the other hand, in a prospective study on 44 patients by Maurer *et al.* (77), <sup>11</sup>C-choline PET/CT was found not to be able to improve preoperative diagnostic efficacy compared with conventional CT alone. Ceci *et al.* (78), who retrospectively analyzed data from 59 patients diagnosed with BC, making it the largest study on the utility of <sup>11</sup>C-choline-PET up to date, reported sensitivity of 59%, specificity of 90%, positive predictive value of 71%, negative predictive value 84% and accuracy of 81% for nodal staging with <sup>11</sup>C-choline-PET/CT.

Two studies concerning the use of <sup>11</sup>C-acetate were included into this review, both being conducted in the

same institution. Schöder *et al.* (83), in a study on 17 patients, reported results indicating 100% sensitivity and 87% specificity of <sup>11</sup>C-acetate-PET/CT regarding correct identification of metastatic LN, with a significant rate of false positive uptake in LNs being secondary to inflammatory response due to prior intravesical chemotherapy. In a study by Vargas *et al.* (82), who prospectively collected data from 16 patients referred for radical cystectomy with pelvic lymph node dissection, <sup>11</sup>C-acetate-PET/CT, while demonstrating 100% sensitivity and 71% specificity for nodal staging, was concluded to display similar levels of accuracy with MRI and CT.

### PET/MRI

PET/MR is a hybrid imaging modality that combines the ability of PET to delineate biochemical or physiologic phenomena with the high anatomic resolution of MR imaging. An inestimable advantage of PET/MR over PET/CT is the much lower dose of radiation (84). Yet, the evidence-based literature regarding the utility of PET/MR in nodal or metastatic staging of urothelial carcinoma is very scant. The only article we included into the review was a recent prospective pilot study by Rosenkrantz *et al.* (85), who prospectively compared the diagnostic performance of FDG-simultaneous PET/MRI and MRI alone. According to the study results, PET/MRI exhibited greater accuracy for detection of metastatic pelvic LNs (95% *vs.* 76% of MRI) and non-nodal pelvic malignancy (100% *vs.* 91%), and was concluded to have helped to appropriately determine the level of suspicion for equivocal findings on MRI alone.

### Discussion

Increasing the accuracy of imaging studies for lymph node status evaluation in urothelial carcinoma patients is essential for establishing appropriate treatment strategies. While low sensitivity for detection of metastatic lymph nodes is associated with understaging of the disease, a decrease in specificity leads to an increased rate of overstaging. This is of clinical significance both at primary staging, where an understaged patient may be unnecessarily exposed to severe complications of surgical management or an overstaged patient may be wrongly disqualified from potentially curative treatment, and at posttreatment staging, or evaluation of treatment response, where overstaging may lead to further purposeless management or understaging

**Table 6** Performance of novel radiotracers in PET/CT in lymph node status assessment of bladder cancer patients

Author	Modality	Year	No. of patients	Study type	Accuracy (per patient)	Sensitivity (per patient)	Specificity (per patient)	Comments
Kim et al. (80)	<sup>11</sup> C Choline PET/CT <sup>11</sup> C acetate PET-CT	2018	282	Meta-analysis	-	PET/CT 66%	PET/CT 89%	Heterogeneity of the studies - prospective and retrospective studies included
Ceci et al. (78)	<sup>11</sup> C Choline PET/CT	2015	59	Retrospective	PET/CT 81%	PET/CT 59%	PET/CT 90%	-
Brunocilla et al. (28)	<sup>11</sup> C Choline- PET/CT	2014	26	Prospective	CT 6%, PET/CT 73%	CT 14%, PET/CT 42%	CT 89%, PET/CT 84%	-
Maurer et al. (77)	<sup>11</sup> C Choline PET/CT	2012	44	Prospective	CT 90%, PET/CT 91%	CT 39%, PET/CT 28%	CT 92%, PET/CT 95%	-
Golan et al. (81)	<sup>11</sup> C Choline PET/CT, FDG-PET/CT	2011	20	Prospective	-	-	-	The only study comparing <sup>11</sup> C-Choline PET/CT and FDG-PET/CT. Only the PPV reported. Only 4 patients had pathology reports. PPV: 79.4% for Choline PET/CT and 90.7% for FDG-PET/CT
Picchio et al. (76)	<sup>11</sup> C Choline PET/CT	2006	27	Prospective	CT 63%, PET/CT 88.9%	CT 50%, PET/CT 62%	CT 68.4%, PET/CT 100%	-
Vargas et al. (82)	<sup>11</sup> C acetate PET/CT, MRI	2012	16	Prospective	MRI 56%, PET/CT 63%	CT 50%, MRI 50%, PET/CT 100%	CT 79%, MRI 71%, PET/CT 71%	-

<sup>11</sup>C Choline PET/CT, <sup>11</sup>C Choline positron-emission tomography/computed tomography; <sup>11</sup>C acetate PET-CT, <sup>11</sup>C acetate positron-emission tomography/computed tomography; FDG-PET-CT, <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography/computed tomography; PET-CT, positron-emission tomography/computed tomography; PET, positron-emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; PPV, positive predictive value.

may result in not applying necessary salvage treatment.

As previously mentioned in this article, CT is still recognized as the gold-standard imaging modality for nodal staging of urothelial carcinoma patients. However, given its low accuracy and sensitivity values for detecting lymph node metastases, this may be considered controversial. As shown in this review, despite relatively high specificity values of CT scans, usually exceeding 90%, no study reported its sensitivity to be greater than 46% (on a per-patient analysis and using standard cut-off values). Invasive urothelial carcinoma is a malignant disease associated with a high metastatic potential and thus an already clinically significant metastatic tumor in a lymph node may not be large enough to make the LN short-axis diameter exceed the cut-off value (23,30,31). Unfortunately, CT is not able to evaluate other lymph node features than its size or shape. Thus, in order to decrease the rate of false-negative rates in cases of small LN metastases, the only option would be to lower the short-axis diameter threshold, at the expense of specificity. However, apart from the article by Li *et al.*, who actually suggested such an approach, no other study regarding this issue has been included into this review. In light of the above mentioned limitations of CT in regards to nodal status evaluation in urothelial cancer, the simplicity, cost-effectiveness and easy accessibility of this method appear to be its only main advantages (86,87). The rush towards developing or establishing a more accurate imaging modality is reflected by the fact that for the purpose of this review almost all of the available data regarding the diagnostic performance of CT has been abstracted from studies evaluating other modalities, with CT being used for comparison purposes only.

Magnetic resonance, which due to its increased accuracy has been adopted as the diagnostic modality of choice for nodal status evaluation in several other malignancies (52-56), is a method of imaging characterized with more diverse capabilities. As previously mentioned in this article, MR is able not only to measure the size and shape of a lymph node, but also to evaluate for detailed changes in its anatomy suggestive of metastatic involvement, as well as to assess the precise density of a tissue, or to dynamically visualize its function. *Table 2* shows that the sensitivity value of MR regarding the detection of metastatic lymph nodes in urothelial cancer may be even as high as 88% (with concomitant specificity of 75%), but also as low as 40.7% (with concomitant specificity of 91.5%), the latter being similar to the diagnostic performance of CT. The marked variations between the results of different studies may be

explained by their significant heterogeneity, regarding not only the character of the specific method studied, i.e., DW-MR or DCE-MR, but also to the strength of the magnetic field used. However, the results of the studies included into this review tend to suggest that the use of DW-MR for urothelial carcinoma nodal staging may yield relatively high sensitivity values, with no significant deterioration in terms specificity, and thus its use may result in lower rates of understaging compared to the golden-standard of CT. Yet, the amount of clinical evidence that would suggest this conclusion is scant and more research involving a precise imaging protocol is needed. Moreover, reproducibility of study results could be hindered by the marked heterogeneity between different MR scanners used in health-care facilities (35).

The diagnostic performance of MRI in detection of lymph node metastases in urothelial carcinoma patients can be further improved by the use of USPIO as the contrast agent. The results of the studies quoted in this review demonstrate impressively high sensitivity and specificity values of USPIO-MRI in regard to lymph node status evaluation. However, in our opinion, a study on 58 patients and a clinical trial with 75 patients do not serve as sufficient evidence to justify routine use of USPIO-MRI in urothelial carcinoma patients, especially given the significant risk of possible adverse effects associated with the use of this method (41,44). Moreover, the above studies demonstrated interestingly high diagnostic performance of pre-contrast DW-MRI alone. Although the influence of contrast enhancement appeared to be significant, the high sensitivity and specificity values of USPIO-MRI reported by those studies might be also explained by the accuracy of DW-MRI alone, which could serve as another evidence of the high potential of DW-MRI in terms of accurate nodal staging of urothelial carcinoma patients.

The ability of PET to evaluate the metabolic activity of investigated regions makes it a considerably distinct imaging modality in regard to nodal staging of malignant diseases. As the tridimensional map of highly-metabolic areas requires precise anatomic imaging for guiding purposes, a PET study is most commonly performed concomitantly with a CT scan (PET/CT). Thus PET imaging may be considered an essential adjunct to organ morphology assessment provided by CT, given the potential capability of PET to increase the sensitivity of CT by pointing out highly-metabolic metastatic LNs, otherwise not large enough to exceed the short-axis diameter cut-off value. Although the sensitivity of PET/CT is in fact negatively

affected by small metastatic lesions not being able to reach threshold metabolic activity and there are studies presented in this review that based on their results doubt the potential of PET to increase the sensitivity of CT for primary lymph node staging of urothelial carcinoma, yet a substantial portion of the articles, including the recent meta-analysis by Li *et al.*, may be considered suggestive of an actually high diagnostic performance of PET/CT compared to CT alone. However, as pointed out by the meta-analysis, there has been marked heterogeneity between the studies reviewed and thus further research using a uniform protocol is warranted in order to evaluate or establish a possibly superior role of PET/CT in the process of preoperative staging of urothelial carcinoma patients.

Apart from primary staging, the evidence-based literature, as presented in this review, also suggests a significant role of PET/CT at posttreatment staging, or evaluation of treatment response. An important advantage of PET is the ability to accurately differentiate between viable recurrences and treatment-induced changes of the LN morphology (88). Kollberg *et al.* (89), who investigated the results of PET/CT scans performed before and after neoadjuvant chemotherapy in 50 bladder cancer patients, reported PET/CT to demonstrate an 86% rate of correct prediction of the histological nodal chemotherapy response (9). As shown in this review, the few studies which evaluated the role of PET/CT in the process of nodal restaging, have shown relatively high sensitivity and specificity values of posttreatment PET/CT, as well as demonstrated its ability to influence the clinical decision making process and to change individual treatment plans. Thus, the authors of this article would like to emphasize the need for further research regarding this issue, given the promising character of the up-to-date reports.

While the majority of studies which evaluated the diagnostic performance of PET/CT used FDG as the radiotracer, the role of other compounds in the process of nodal staging of urothelial carcinoma has been assessed as well. While no study reliably compared  $^{11}\text{C}$ -choline-PET/CT or  $^{11}\text{C}$ -acetate-PET/CT versus FDG-PET/CT in terms of detecting metastatic LNs in urothelial carcinoma patients, the sensitivity and specificity rates of PET/CT scans using these novel radiotracers usually did not reach the values demonstrated by FDG-PET/CT, which was particularly noticeable for sensitivity, as presented in *Table 6*. However, a shortcoming of FDG is its renal route of excretion, which results in accumulation of the radiotracer in the urinary bladder. This may cause interference with

visualization of adjacent locoregional lymph nodes, as the metabolic activity of lymph nodes is usually not high enough to make the radiotracer visible through the bladder content (90,91). While administration of diuretics may help to partially overcome these limitations, as reported by Nayak *et al.* (92), the use of  $^{11}\text{C}$ -choline or  $^{11}\text{C}$ -acetate may solve the problem entirely, as these compounds are associated with minimal urinary excretion. However, a significant issue limiting the accessibility of  $^{11}\text{C}$ -choline-PET is the radiotracer half-life of only 20 minutes, making it very difficult to perform the scan in a health-care facility without an onsite cyclotron available (90).

A relatively novel approach consists in combining PET with MRI instead of CT, which may be beneficial not only given the reduction in the dose of ionizing radiation (85), but also due to possible sensitivity boost provided by the earlier mentioned advantages of MR imaging. However, the pilot character of the only evidence-based data available so far, despite being interestingly optimistic, as presented in this review, makes it premature to draw any conclusions regarding the use of PET/MRI for the purpose of lymph node status evaluation in urothelial carcinoma patients. Moreover, the significant costs of PET/MRI (86), as well as low accessibility of the scanners (91), would definitely hinder implementation of this imaging modality into clinical practice. Obviously, the combination of advantages of PET and MR imaging could be also achieved by performing both PET/CT and MRI scans separately with subsequent cognitive fusion of results, however, we found no studies regarding this issue in the up-to-date literature.

It is worth mentioning, that the vast majority of studies listed among the results of the database search performed for the purpose of this systematic review concerned PET, which may be recognized as a reflection of current trends in clinical research. According to the authors of this article, establishment of conclusive evidence regarding the role of PET in the process of lymph node status evaluation in urothelial carcinoma patients is only a question of time.

An underinvestigated field of research in terms of metastatic lymph node detection in urothelial carcinoma is the so-called targeted imaging, which utilizes the ability of radiotracer-and-ligand complex to specifically bind to particular cancer-affected tissues. While, as an example,  $^{99\text{m}}\text{Tc}$ -TSHR analogue has been studied for its potential role in detecting metastases of poorly differentiated metastatic thyroid cancer (93), or prostate-specific membrane antigen (PSMA)-PET (94,95) has been shown to improve the accuracy of lymph node status evaluation in prostate cancer,



no method specific for urothelial carcinoma has been definitely developed up to date, despite intense ongoing efforts (96).

The authors of this review recognize that an important factor influencing the accuracy of lymph node status evaluation, namely the inter-reader variability, has not been systematically studied for urothelial carcinoma. Although few of the studies included into this review did group their results per reader, this data is insufficient to draw conclusions regarding this issue.

## Conclusions

We have presented a systematic review of recent studies that evaluate the diagnostic performance of different imaging modalities in regards to detection of lymph node metastases in urothelial carcinoma patients. An explicit trend towards replacing CT with other methods of imaging can be observed in the current literature, as the limitations of CT, resulting primarily in its low sensitivity, are widely acknowledged. Although the up-to-date literature regarding the role of PET/CT, or MR imaging, or the fusion of both, may be recognized as promising, further research involving uniform protocols is required in order to establish one of those methods as the imaging modality of choice, or at least to recommend its routine use in selected group of patients. This may be in fact achieved relatively soon, as the amount of evidence is rapidly growing. Until then, given the uniqueness of every cancer patient, the authors believe that this review may appear to be helpful in individual decision making processes.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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