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UNINVITED REVIEW

Comparative sensitivity and specificity of imaging modalities in staging bladder cancer prior to radical cystectomy: a systematic review and meta-analysis

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Abstract

Purpose The detection of lymph node metastases in bladder cancer has a significant impact on treatment decisions. Multiple imaging modalities are available to clinicians including magnetic resonance imaging, computed tomography and positron emission tomography. We aimed to investigate the utility of alternate imaging modalities on pre-cystectomy imaging in bladder cancer for the detection of lymph node metastases.

Methods We performed systematic search of Web of Science (including MEDLINE), EMBASE and Cochrane libraries in accordance with the PRISMA statement. Studies comparing lymph node imaging findings with final histopathology were included in our analysis. Sensitivity and specificity data were quantified using patient-based analysis. A true positive was defined as a node-positive patient on imaging and node positive on histopathology. Meta-analysis of studies was performed using a mixed-effects, hierarchical logistic regression model.

Results Our systematic search identified 35 articles suitable for inclusion. MRI and PET have a higher sensitivity than CT while the specificity of all modalities was similar. The summary MRI sensitivity = 0.60 (95% CI 0.44–0.74) and specificity = 0.91 (95% CI 0.82–0.96). Summary PET/CT sensitivity = 0.56 (95% CI 0.49–0.63) and specificity = 0.92 (95% CI 0.86–0.95). Summary CT sensitivity = 0.40 (95% CI 0.33–0.49) and specificity = 0.92 (95% CI 0.86–0.95).

Conclusion MRI and PET/CT provides superior sensitivity compared to CT for detection of positive lymph nodes in bladder cancer prior to cystectomy. There is variability in the accuracy that current imaging modalities achieve across different studies. A number of other factors impact on detection accuracy and these must be considered.

Keyword Bladder cancer · Transitional cell carcinoma · Positron emission tomography · Magnetic resonance imaging · Computed tomography

Introduction

Detection of lymph node-positive disease when staging bladder cancer has a significant impact on disease prognosis [1]. The overall survival for all patients undergoing curative intent radical cystectomy and bilateral lymphadenectomy is 66% at 5 years [2]. Subgroup analysis based on lymph node positivity shows the 5-year disease-specific survival for lymph node-positive bladder cancer is 31.2% compared to 66.7% for node-negative disease [3]. The same findings are observed at 10 years with a DSS of 27.7% in node-positive patients compared to 61.7% in node negative [3]. Node positivity is an important consideration when making treatment decisions.

In patients considered candidates for radical treatment, guidelines recommend using computed tomography (CT) or magnetic resonance imaging MRI to stage locally advanced or metastatic disease [1]. CT and MRI are considered equivalent in diagnosing local disease and distant metastases of the abdomen [1]. They are anatomy-based imaging modalities that assess lymph node positivity based on lymph node

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size and morphology [4]. This compares to positron emission topography (PET), which detects positive nodes based on tracer uptake [4]. One of the benefits of PET is that it can potentially identify metastases in normal sized lymph nodes [4]. This is an area of growing interest and emerging evidence suggests non-standard imaging modalities are useful in detection of pelvic lymph node metastases [5–7]. We aimed to assess the ability of preoperative imaging to identify positive regional lymph nodes in bladder cancer patients subsequently treated by radical cystectomy and pelvic lymphadenectomy.

Materials and methods

Search strategy and selection criteria

A systematic review was performed in accordance with Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [8, 9]. Scientific literature databases including: Web of Science (including MEDLINE), EMBASE, and Cochrane Libraries were systematically searched in April 2017. Several keywords were utilized, including: ("bladder" or "bladder cancer" or "bladder neoplasm" or "bladder malignancy" or "transitional cell carcinoma") and ("computed tomography" or "computerized tomography" or "CT" or "magnetic resonance imaging" or "MRI" or "positron emission tomography" or "PET") and ("lymph node"). Search strategy and article selection was performed by three independent evaluators (JC, NP, MP) and any discrepancies were resolved. After screening based on study title and abstract, the remaining articles were assessed based on full text and excluded with reasons when appropriate. Case reports, conference proceeding, editorial comments and letters to the editor were excluded, as study quality was unable to be assessed. The reference lists of the included articles were examined for any further studies that could be included.

Studies comparing radiographic pelvic staging for primary bladder cancer treated by radical cystectomy with final lymphadenectomy pathology were included for analysis. Study designs considered for inclusion included clinical trials, prospective studies and retrospective cohorts or comparative series. The respective sensitivity and specificity data must have been compared against the reference gold standard of lymph node dissection pathology. Only studies that included routine imaging prior to pre-planned lymph node dissection were included. Inclusion of series that performed nodal biopsy at clinical discretion does not provide meaningful false-negative data and thus does not provide accurate specificity values. Sensitivity and specificity data must be reported in a per-patient-based manner. Studies were excluded if they were not assessing primary bladder cancer or lymphadenectomy was performed on selective patients.

Quality assessment

Studies were quality assessed based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [10]. The QUADAS-2 tool primarily assesses four domains; risk of bias in patient selection, index test, reference standard and the timing of reference test. The degree of applicability of the patient selection, index test and reference standard are also assessed. Each paper was scored independently by two evaluators (JC, BN) and any discrepancies were resolved.

Data extraction and analysis

From the included studies, data extracted included: cohort size, indication for staging, procedural type, extent of nodal dissection, mean nodal yield from lymphadenectomy, number of true positive, number of true negatives, number of false positives and number of false negatives. Data regarding pre-operative imaging modality and associated enhancements were recorded. Where a study reported per-patient and per-lesion-based sensitivity and specificity data, only per-patient-based data were collected. Where a study reported results from individual reporters and the consensus opinion, the latter was selected for analysis. Where a paper described variants in the precise imaging procedure data from the process that provided the highest accuracy was included. Data were collected by two investigators (JC, NP) and any discrepancies were resolved. The primary outcome was determining the pooled sensitivity and specificity of various imaging modalities utilized in pre-operative pelvic staging for advanced bladder cancer.

Extracted data were collated in Excel 2007 (Microsoft Corporation, Redmond, CA) and analysis was performed using Stata v.13.0SE (College Station, TX, USA). Summary sensitivity, specificity and hierarchical ROC curves were created using the user-written metandi command. Briefly, this method fits a two-level mixed logistic regression model. This accounts for correlation between sensitivity and specificity. Full details of the method of analysis are provided at this reference [11].

Results

Using the systematic search strategy outlined in the methods, 35 unique studies were identified for inclusion. 581 articles were identified by the search strategy, of which 11

were duplicate records and excluded. Of the remaining 570 records, 496 were not relevant to the research question. Of the remaining 74 articles, 39 were excluded as they did not meet the inclusion criteria as outlined in the methodology. The findings from the search strategy are summarised in Fig. 1 and the quality appraisal summarised in Fig. 2.

20 studies reported upon CT imaging, 10 on MRI and 20 on PET/CT imaging. The characteristics of these are summarised in Table 1. The percentage of patients with histology confirmed lymph node metastasis was slightly lower in the MRI studies (22%) than the CT and PET/CT studies (both 29%) (Table 2). This percentage was also variable between studies with the range being 10 to 53.5%. The accuracy of CT imaging ranged from 56 to 90%, the range for MRI being 67 to 95% and for PET/CT 64 to 94%. The summary sensitivity of CT was found to be 40% (95% CI 33–49%) (Fig. 3). Both MRI and PET/CT demonstrated a summary sensitivity point estimate superior to CT; MRI 60% (95% CI 44–74%) and PET/CT 56% (95% CI 49–63%) (Figs. 4, 5). The estimate for MRI is higher than PET/CT, though the confidence interval is wider and overlaps that of CT. Pooled specificity point estimates were similar for all modalities (92% for CT and PET/CT, 91% for MRI).

Discussion

Accurate clinical staging of pelvic lymph nodes in bladder cancer is an ongoing challenge. Conventional staging methods including CT and MRI have well-recognized benefits and limitations. Parameters defining lymph node metastases in anatomical imaging modalities are largely based on size parameters. These imaging modalities fail to detect metastases in normal size lymph nodes. This inability to detect metastases that fulfil normal size parameters may explain the high-false-negative rates (40%) found in conventional CT imaging [12]. Equally, false-positive assessment can result from inability to differentiate between cancer and inflammatory enlargement that may occur for example following transurethral resection of a bladder tumour [13]. Research has shown that post-lymphadenectomy, occult lymph node metastases are detected in 28% of patients originally staged N0 [4]. Despite these failures, CT and MRI continue to be the most commonly used clinical staging methods in clinical practice.

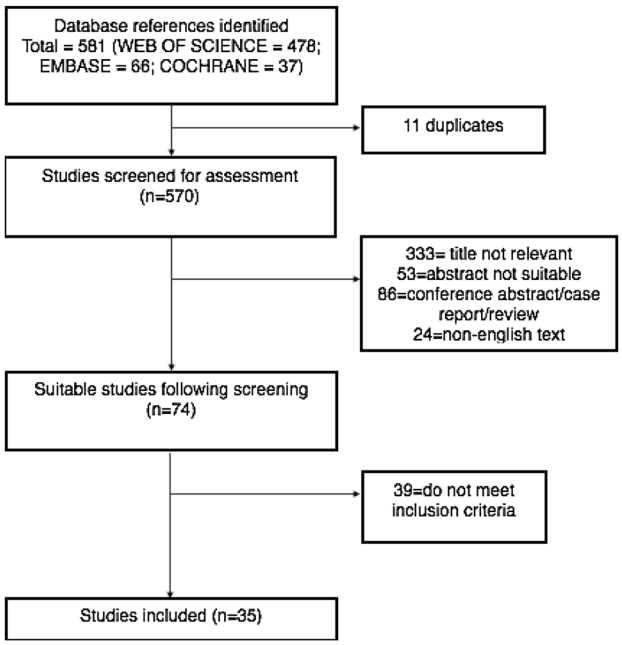

Fig. 1 PRISMA search strategy and results

Currently, there are no consensus recommendations on the routine use of positron emission tomography (PET) in the nodal staging of bladder cancer [1]. FDG-PET is commonly employed to assess a wide variety of cancers. FDG uptake serves as a measure of tissue metabolic activity, which is relatively higher in malignant tissue [13]. To aid localization of lesions, PET imaging is typically combined with anatomy-based CT imaging. One of the main limitations of FDG-PET imaging is that FDG is excreted into the urine which interferes with accurate assessment of bladder and perivesical structures [13]. This has led to a number of initiatives that aim to improve FDG imaging and limit the degree to which urinary tracer obscures urinary structures. For example, pre-hydration before the study can dilute the urinary tracer, bladder catheterization may limit urinary tracer accumulation and forced diuresis may aid in discrimination of physiologic from pathologic tracer activity [13, 14]. Alternatively, surgeons have the option of using substitute tracers such as 11C-choline, 11C-acetate and 11C-methionine, which have significantly lower rates of urinary excretion [6, 13, 15–18].

Our findings indicate that PET/CT and MRI have a higher sensitivity than CT alone. While these findings are encouraging, it is unlikely to change the current status quo. CT will continue to be the modality of choice when staging bladder cancer as it still has the advantages of being widely available, low cost and with a short acquisition time. The clinical utility of all these tests is still limited by the high number of false negatives they generate.

European guidelines only recommend the use of neoadjuvant chemotherapy in T2–T4a cN0 M0 bladder cancer [1]. Accurate detection of nodal status is then important for appropriate selection of candidates for neoadjuvant chemotherapy. Previous research has shown that patients with locally advanced bladder cancer have a 33% reduction in the risk of death if they receive combination neoadjuvant chemotherapy and cystectomy compared to cystectomy alone [19]. But utilization is low and depending on

Reference	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Aljabery[12]	+	+	-	-	+	+	+
Amendola[22]	+	+	+	+	+	+	+
Baltaci[24]	+	+	-	-	+	+	+
Barentsz[25]	+	+	-	-	+	+	+
Brunocilla[18]	+	+	-	+	+	+	+
Ceci[17]	+	+	-	+	+	+	+
Chakraborty[26]	+	-	-	-	+	+	+
Chen[27]	+	+	+	-	+	+	+
Daneshmand[28]	+	+	-	-	+	+	+
Ficarra[29]	+	-	-	-	+	+	+
Gofrit[30]	+	+	-	-	+	+	+
Goodfellow[31]	+	+	-	+	+	+	+
Heicappell[32]	+	+	-	+	+	+	+
Hitier-Berthault[33]	+	+	+	-	+	+	+
Horn[34]	-	+	-	-	-	+	+
Jensen[35]	+	-	-	-	+	+	+
Jeong[36]	+	+	-	-	+	+	+
Kibel[37]	-	+	+	-	-	+	+
Li[38]	+	+	+	+	+	+	+
Liedberg[39]	-	+	-	-	+	+	+
Lista[40]	+	+	+	+	+	+	+
Lodde[41]	-	-	-	-	+	+	+
Maurer[6]	+	-	-	-	+	+	+
Orevi[16]	+	+	-	+	+	+	+
Paik[42]	+	+	-	-	+	+	+
Persad[43]	+	-	-	-	+	+	+
Picchio[44]	+	+	-	+	+	+	+
Rouanne[45]	+	-	-	+	+	+	+
Soubra[14]	+	+	-	-	+	+	+
Swinnen[46]	+	-	-	+	+	+	+
Thoeny[7]	+	-	-	-	+	+	+
Tritschler[47]	+	-	-	-	+	+	+
Uttam[48]	+	+	+	-	+	+	+
Vargas[15]	+	+	-	+	+	+	+
Wollin[49]	+	+	-	-	+	+	+

Fig. 2 Quality appraisal for included studies using the QUADAS-2 tool. Green = low i.e. risk of bias low or concerns about applicability low. Red = high or uncertain i.e. risk of bias high/uncertain or concerns about applicability high/uncertain

the study as few as 12% of muscle-invasive bladder cancer patients undergoing cystectomy are considered for neoadjuvant chemotherapy [20]. Factors associated with low neoadjuvant treatment rates are uncertain clinical benefit, time delay of cystectomy and patient refusal [20]. Inaccurate preoperative staging may represent another barrier to achieving high rates of neoadjuvant treatment.

In practice, patients with muscle-invasive bladder cancer who are considered eligible for radical surgery are often offered neoadjuvant chemotherapy irrespective of nodal status. The candidacy for surgery does not specifically consider

Table 1 Summary of included studies

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
1.	Aljabery et al. [12]	2015	54	47:7 (87.0:13.0%)	Mean 68	Retrospective	Urinary bladder cancer scheduled for RC and PLND	No RC (distant metastases, high surgical risk, preferred radiation therapy) or PLND performed	From the level of the ureteric crossing of common iliac vein, immediately cranial to the confluence of the external and internal iliac veins, with extension to the aortic bifurcation	Mean 28	Independent review by two radiologists specialised and/or with extensive clinical experience in PET/CT, unaware of operative or post-operative data	CT FDG-PET/CT	LN diameter ≥ 10 mm (CT) SUV-max ≥ 2.5 (PET)
2.	Amendola et al. [22]	1986	11	11:0 (100:0%)	Mean 63	Prospective	Males with bladder TCC deemed suitable for RC	Non-surgical candidates (patients with gross pelvic adenopathy on imaging)	Bilateral PLND	Not reported	Consensus of two independent observers	CT MRI	LN diameter > 15 mm (Both modalities)
3.	Baltaci et al. [24]	2008	100	89:11 (89:11%)	Mean 62.7	Retrospective	Invasive bladder cancer on TURBT for RC and bilateral iliacoobturator LN dissection	None reported	Bilateral iliacoobturator lymphadenectomy	Not reported	Re-interpretation of prior imaging by one uroradiologist, unaware of final pathological results	CT	LN diameter > 10 mm
4.	Barentsz et al. [25]	1998	28	Not reported	Not reported	Prospective	Consecutive patients with biopsy-proven urinary bladder carcinoma referred for local and regional preoperative staging prior to cystectomy	None reported	Not reported	Not reported	Independently by two reviewers unaware of clinical/surgical findings or other MRI findings	MRI	Index calculated = shortest axis of node/long axis. Pathologic if index > 0.8 and minimal axis size > 8 mm OR when index < 0.8 and minimal axis size ≥ 10 mm OR asymmetric cluster of small lymph nodes

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
5.	Brunocilla et al. [18]	2014	26	25:1 (96:4%)	Mean 69.5	Retrospective	Histologically proven bladder TCC for RC and PLND	None reported	Paravesical, internal, external and common iliac, as well as obturator, presacral, preaortic, and precaval LNs dissected up to the origin of the inferior mesenteric artery	Mean 32.5	Consensus of two experienced nuclear medicine physicians with > 5 years in 11C-choline PET/CT reading, aware of clinical data	CT 11C-Choline-PET/CT	LN diameter > 10 mm (CT) Increased tracer uptake, even if LN short axis < 10 mm. (PET)
6.	Ceci et al. [17]	2015	59	53:6 (89.8:10.2%)	Mean 70.1	Retrospective	Staging cohort: histologically proven bladder TCC for RC and extended PLND, Re-staging cohort: past treatment with RC and extended PLND for suspicion of nodal relapse	Restaging cohort was excluded from analysis because these patients had salvage PLND or ultrasound-guided percutaneous LN biopsy only	Paravesical, internal, external and common iliac nodes, as well as obturator, presacral, preaortic, and precaval LNs dissected up to the level of the inferior mesenteric artery	Not reported	Consensus of two experienced nuclear medicine physicians with > 5 years in 11C-choline PET/CT reading, aware of clinical data	11C-Choline-PET/CT	Qualitative tracer uptake
7.	Chakraborty et al. [26]	2014	77	72:5 (93.5:6.5%)	Mean 60	Retrospective	Histologically confirmed bladder cancer for initial staging or re-staging	None reported	Not done	Not applicable	Two experienced nuclear medicine physicians	FDG-PET/CT	Focal accumulation and SUV-max. No defined cut-off
8.	Chen et al. [27]	2016	115	115 no gender breakdown	Not reported	Retrospective	Bladder TCC for laparoscopic RC and PLND	None reported	The cranial, lateral and caudal borders were the level of the inferior mesenteric artery, genitofemoral nerve and pelvic floor, respectively	Not reported	Urologists and uroradiologists, unaware of the pathology	CT	LN diameter > 10 mm

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
9.	Daneshmand et al. [28]	2012	122	72:50 (59.0:41.0%)	Mean 67.8	Prospective	Clinical muscle-invasive bladder cancer on TURBT and histological findings of TCC	Distant metastases on pre-operative assessment by conventional CT	Extended pelvic/iliac LN dissection	Not reported	Independent review by two radiologists with special training in MRI, unaware of the pathologic stage	MRI	LN long axis ≥ 10 mm
10.	Ficarra et al. [29]	2005	156	141:15	65.6	Retrospective	Underwent radical cystectomy and bilateral iliaco-obturator lymphadenectomy for bladder cancer between 1995 and 2001 at study institution	Not reported	Bilateral iliaco-obturator lymphadenectomy	Not reported	Not reported	CT	Not reported
11.	Gofrit et al. [30]	2006	18	13:5 (72.2:27.8%)	Mean 74	Prospective	Advanced bladder cancer (stage T2 or CIS refractory to intravesical immuno- or chemotherapy) on TURBT, or extensive upper tract TCC (diameter > 3 cm) on retrograde pyelography	Not reported	Not reported	Mean 6.5 per hemipelvis	One radiologist	11C-Choline PET/CT	LN > 10 mm
12.	Goodfellow et al. [31]	2014	233	175:58 (75.1:24.9%)	Mean 69	Retrospective	Muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer for RC	No RC performed, follow-up at another hospital, death from causes other than bladder cancer, inadequate lymphadenectomy or neoadjuvant treatment	PLND up to the bifurcation of the aorta	Mean 17	Two radiologists, one reporting at time of scan and the other confirming initial findings	CT FDG-PET/CT	LN short axis > 8 mm (CT) Qualitative tracer uptake (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
13.	Heicappell et al. [32]	1999	8	4:4 (50%:50%)	Mean 65.8	Retrospective	Histopathological diagnosis of bladder cancer and a given indication for radical surgery	Not reported	All iliac and obturator LNs. Cranial limit was the common iliac artery and caudal limit was inguinal ligament. Ventrally, resection started between the iliac artery and vein and extended to the obturator nerve	Not reported	Two experienced investigators unaware of the histopathological findings	FDG-PET/CT	Malignant if spots/regions with FDG uptake > 2.5 SUV, SUV significantly greater than surrounding tissue and continuously increasing SUV FDG uptake
14.	Hitier-Berthault et al. [33]	2013	52	44:8 (84.6:15.4%)	Mean 63.7	Prospective	Histologically documented bladder cancer on TURBT, with indication for RC and LN dissection	Neoadjuvant chemotherapy or radiotherapy	Bilateral ilio-obturator, external, internal and common iliac LNs (40 cases). Bilateral ilio-obturator LN dissection only (12 cases)	Mean 16.5	Radiologists blinded to prior 18F-FDG PET/CT results	CT FDG-PET/CT	LN long axis > 10 mm (CT) Qualitative tracer uptake (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
15.	Horn et al. [34]	2016	229	Not reported	68	Retrospective	Patients who underwent radical cystectomy between 2006 and 2012. Had to have a digital dataset of a state-of-the-art contrast-enhanced CT	Patients with native imaging only or low-dose CT OR had no lymphadenectomy performed OR who received neoadjuvant chemotherapy	Standard lymphadenectomy including obturator fossa and tissue surrounding the external and internal iliac arteries. Extended lymphadenectomy up to the origin of the lower mesenteric artery was performed in patients with suspicious LN in these regions on preoperative imaging	Median 25	All scans re-evaluated by two independent radiologists who needed to come to a consensus agreement and were blinded to histopathology	CT	Scored likelihood of metastasis according to a 5-step model (1: benign;2 probably benign;3 equivocal; 4 probably tumor manifestations; 5 tumor manifestations). Score based on size, shape, presence of fat in the nodal hilum, extracapsular extension as well as regional clustering of LN All LN with a short axis diameter of > 10 mm were classified as malignant (Score 4 or 5). The exception was if they had a fatty hilum (Scored 3)
16.	Jensen et al. [35]	2011	48	Not reported	Mean 65.4	Retrospective	Invasive bladder cancer on histopathology, with ≥ pT1 disease, with pre-operative PET/CT and subsequent radical cystoprostatectomy with LN dissection	No radical cystoprostatectomy performed (distant metastases, low-grade pT1 tumour or preference for chemotherapy)	Bilateral removal of fossa obturatoria, internal and external iliac LNs below the level of the common iliac bifurcation. The boundaries were laterally the genitofemoral nerve, inferiorly at the endopelvic fascia and posteromedially the obturator nerve	Not reported	PET/CT: two nuclear medicine physicians and a radiologist in consensus MRI: review protocol not reported	MRI FDG-PET/CT	LN long axis > 10 mm (MRI) Qualitative tracer uptake (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
17.	Jeong et al. [36]	2015	61	46:15 (75.4:24.6%)	Mean 63.7	Prospective	Histologically proven high-grade T1 or muscle-invasive bladder cancer for RC and extended PLND	Non-urothelial carcinoma, withdrawn consent, no extended PLND performed (three cases), distant metastases, concomitant malignancy or neoadjuvant chemotherapy	Extended PLND including distal common and external iliac, hypogastric, obturator and presacral LNs, and regions at the level of the proximal common iliac, distal aorta, and vena cava to the level of the inferior mesenteric artery	Mean 42.3	One genitourinary imaging specialist, unaware patient clinical characteristics	CT FDG-PET/CT	LN short axis > 10 mm (CT) SUV-max ≥ 2.5 (PET)
18.	Kibel et al. [37]	2009	43	32:11 (74.4:25.6%)	Mean 68	Prospective	T2-3 N0 M0 bladder cancer (squamous or glandular) for RC and PLND	Other histological subtypes, previous chemotherapy, pending neoadjuvant chemotherapy, poorly controlled diabetes, inability to tolerate PET or prior history of malignancy within 5 years	Bilateral dissection from the bifurcation of the common iliac artery to the genitofemoral nerve, laterally to the obturator nerve, medially and carried down to the angle between Cooper's ligament and the inferior aspect of the iliac vein. Additional presacral nodes lying medial to internal iliac artery were also removed	Not reported	Consensus of one of two experienced nuclear radiologists and one diagnostic radiologist specialising in genitourinary radiology	FDG-PET/CT	Qualitative tracer uptake

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
19.	Li et al. [38]	2010	127	Not reported	Median 57	Retrospective	Bladder TCC RC for and PLND	Lack of tumour cells in RC specimen	From distal common iliac artery to inguinal ligament, and from bladder wall to genitofemoral nerve including: the common iliac artery, external iliac artery, obturator muscle and internal iliac artery LNs	Not reported	Uroradiologists and radiologists, unaware of final pathological result	CT	LN > 10 mm
20.	Liedberg et al. [39]	2013	53	34:16 (68.0:32.0%) NB: Does not sum to 53	Not reported	Prospective	Locally advanced or recurrent multifocal non-muscle-invasive urothelial carcinoma on TURBT for RC and bilateral extended PLND	Distant metastases	Not reported	Not reported	One blinded uroradiologist	MRI	"RECIST" criteria
21.	Lista et al. [40]	2013	20	19:1	Mean 69	Prospective	20 consecutive patients with high-grade muscle-invasive TCC who were candidates to receive cystectomy who had TURBT within a month	None reported	Extended lymphadenectomy in all cases, with removal of all LN defined borders including aortic, and common iliac bifurcation, the genitofemoral nerve, the circumflex vein, the Cloquet's ganglion and the hypogastric vessels	Not reported	Reviewed by experienced radiologists blinded to histopathology of cystectomy specimen	MRI	Not reported

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
22.	Lodde et al. [41]	2010	70	57:13 (81.4:18.6%)	Mean 67	Prospective	Group 1: muscle-invasive urothelial carcinoma of the bladder for RC without previous neoadjuvant chemotherapy, Group 2: follow-up after RC and urinary diversion, Group 3: re-staging after chemotherapy for locally advanced and metastatic urothelial carcinoma of the bladder	None reported	From the common iliac artery down to Cooper's ligament, with the genitofemoral nerve as the lateral boundary and the presacral and internal iliac nodes as the medial margin, extending to para-aortic and paracaval regions in cases of suspicious LN at imaging outside the pelvis	Not reported	Independent review by diagnostic radiologist and/or one of two nuclear medicine physicians	CT FDG-PET/CT	LN diameter > 10 mm or if LN < 10 mm and multiple (CT) + qualitative assessment (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
23.	Maurer et al. [6]	2012	44	34:10 (77.3:22.7%)	Median 66.5	Prospective	Histologically proven high-grade or muscle-invasive localised urothelial carcinoma of the bladder for RC	Preoperatively sufficient staging, unwillingness for further examination before RC, concomitant cancer, previous neoadjuvant chemotherapy, distant metastases. Also due to limited availability of PET, not all RC cases could be included	From the internal and external iliac arteries up to the origin of the inferior mesentery artery according to a template of 14 predefined anatomic fields. Standard PLND including anatomic fields 7-14 was performed (all cases). Extended PLND up to the origin of the inferior mesentery artery, including anatomic fields 1–6 was performed if suspicion of locally advanced disease or LN involvement (20 cases)	Mean 29.8	Independent review by two board-certified, dually trained nuclear medicine physicians/radiologists	CT 11C-Choline PET/CT	Qualitative assessment

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
24.	Orevi et al. [16]	2012	14	13:1 (92.9:7.1%)	Not reported	Prospective	Biopsy-proven urothelial carcinoma of the bladder (muscle-invaded (T2) bladder cancer, T1 disease refractory to treatment)	No surgery due to extensive omental involvement (one of the initial 14 cases)	Removal of obturator fossa and internal, external and common iliac LNs. The dissection boundaries were superiorly the bifurcation of the common iliac artery, inferiorly the inguinal ligament, laterally the genitofemoral nerve, and medially the obturator nerve	Not reported	Consensus of one board-certified nuclear medicine physician and one board-certified dually trained nuclear medicine physician/radiologist, both unaware of surgical findings at the time of reading	11C-Choline PET/CT	Qualitative tracer uptake
25.	Paik et al. [42]	2000	82	58:24 (70.7:29.3%)	Mean 64.8	Retrospective	Invasive bladder tumours for radical surgery at initial evaluation	Distant metastases	Not reported	Not reported	Routine preoperative CT reports	CT	Not defined
26	Persad et al. [43]	1993	55	Not reported	Not reported	Retrospective	Bladder TCC on TURBT or cystectomy	Not reported	Not reported	Not reported	Not reported	MRI	Not defined

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
27.	Picchio et al. [44]	2006	27	Not reported	Median 69.1	Retrospective	Histologically proven bladder cancer for RC and PLND	Distant metastases, neoadjuvant chemotherapy for bladder cancer, previous radiation therapy of the pelvis, and other secondary malignancies	PLND boundaries were 2 cm above the aortic bifurcation proximally, the genitofemoral nerve laterally, the circumflex iliac vein and lymph node of Cloquet distally, the hypogastric vessels posteriorly, including the obturator fossa, the presciatic nodes bilaterally and presacral LNs	Mean 14.4	Consensus of two experienced radiologists and two nuclear medicine physicians, unaware of results of other investigations	CT 11C-Choline PET	LN long axis > 10 mm (CT) Qualitative tracer uptake (PET)
28.	Rouanne et al. [45]	2014	102	80:22 (78.4:11.6%)	Median 69	Prospective	Histologically proven muscle-invasive bladder carcinoma for RC and extended PLND	Prior chemotherapy or radiotherapy in the pelvic area, distant metastases, enlarged pelvic LNs on conventional CT, prior PLND, upper urinary tract tumour, non-surgical candidate or no consent given	PLND along the ilio-obturator region and from the internal and external iliac arteries up to the common iliac vessels and the aortic bifurcation, according to the template defined by the European Urology Association	Mean 11.8	Two board-certified nuclear medicine physicians	FDG PET/CT	Qualitative tracer uptake (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
29.	Soubra et al. [14]	2016	78	(80:20%)	Median 68	Retrospective	All patients treated at a single centre by a single urologist from January 2011 –Feb 2015 for histologically confirmed MIBC or NMI refractory to to intravesical treatment, were identified and offered FDG-PET/CT. Patients who underwent radical cystectomy and extended PLND with or without neoadjuvant chemotherapy were included	Patients with distant metastases Patients with prior chemoradiation	Extended PLND	Not reported	Two radiologists blinded to pathology results	18F-FDG-PET/CT	Increased uptake of tracer [with a standardized uptake value (SUVmax) of 2.5 and above], with or without any change in size. Pelvic LN > 8 mm size Retroperitoneal LN > 10 mm
30.	Swinnen et al. [46]	2010	51	43:8 (84.3:15.7%)	Mean 66	Prospective	Histopathological diagnosis of endoscopically resected invasive TCC (≥ T2) or recurrent high-risk superficial TCC (T1G3 with or without Tis)	Distant metastases, neoadjuvant chemotherapy	From the para-aortic, paracaval and pelvic LNs including external and internal iliac LNs, obturator fossa and presacral region, as well as perivesical tissue attached to cystectomy specimen	Mean 16.3	Consensus of one experienced nuclear medicine physician and one radiologist	CT FDG-PET/CT	Not defined (CT) Qualitative tracer uptake (PET)

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
31.	Thoeny et al. [7]	2009	21	17: 4 (81.0:19.0%)	Median 63	Prospective	Bladder cancer, prostate cancer, or both, with MRI before and after administration of USPIO prior to surgical resection of primary tumours and extended PLND	Distant metastases	Bilateral common, external and internal iliac LNs	Mean 38.2	Consensus of two readers ('classic' reading method) or two board-certified radiologists and one-third-year resident ('new' reading method)	USPIO and DW MRI	Malignant if ≥ 1 of 3 criteria present: 1. Decrease in signal intensity of < 30% on T2-weighted fast spin-echo or gradient-echo sequences after administration of lymphotropic superparamagnetic nanoparticles, 2. Heterogenous signal, discrete focal defects, or both, 3. Nodes with a central area of hyperintensity but a peripheral decrease in signal intensity
32.	Tritschler et al. [47]	2012	276	201:75 (72.8:27.2%)	Mean 68.2	Retrospective	RC after preoperative staging by CT	None reported	Not defined	Median 10	One independent board-certified abdominal radiologist with special training in urogenital radiology	CT	LN short axis ≥ 10 mm
33.	Uttam et al. [48]	2016	15	14:1 (93.3:6.7%)	Mean 53.4	Prospective	Muscle-invasive bladder TCC for RC	High blood sugar, distant metastases, urinary tract infection, previous chemotherapy or radiotherapy, partial cystectomy or acute cystitis	Standard PLND (exact boundaries not defined)	Mean 10	Nuclear medicine physicians with > 5 years of experience	CT FDG- PET/CT	LN diameter > 10 mm (CT) SUV-max > 2.5

Table 1 (continued)

No.	Author	Year	Total number of patients in study	Male:Female (%)	Age	Study type	Inclusion criteria	Participants excluded in individual studies	Extent of PLND	Nodes per patient	Imaging reviewers	Imaging modality	Radiological definition of Malignant vs. Benign
34.	Vargas et al. [15]	2012	16	16: 0 (100:0%)	Mean 59	Prospective	Histologically confirmed bladder cancer for RC and extended PLND	Withdrawn consent (missing ≥ 1 imaging study or did not undergo surgery)	From the aortic bifurcation superiorly to the node of Cloquet inferiorly. The lateral limit of dissection was the genitofemoral nerve. Bilaterally included were external, internal and common iliac, obturator and presacral LNs	Not reported	One fellowship-trained genitourinary radiologist (MRI), one other fellowship-trained genitourinary radiologist (contrast-enhanced CT), one-third dually trained nuclear medicine physician/radiologist (11C-acetate PET/CT)	CT MRI 11C-acetate PET/CT	Qualitative assessment involving size, shape, margin, presence of fatty hilum, enhancement (CT/MRI) Qualitative tracer uptake (PET)
35.	Wollin et al. [49]	2014	36	30:6 (83.3:16.7%)	Mean 71	Retrospective	Bladder cancer, with preoperative MRI (including DWI) for RC	Interval treatment between imaging and surgery or non-diagnostic DWI MRI due to severe artefact	PLND including up to aortic bifurcation, genitofemoral nerve, bladder wall, inguinal ligament and hypogastric vessels	Mean 17.6	One fellowship-trained radiologist with expertise in urologic MRI interpretation, unaware of final pathologic diagnosis	MRI	Malignant if LN short axis > 5 mm

Table 2 Sensitivity and specificity data for each included study, stratified by imaging modality

	Years	Number of patients	% LN positive	% Sensitivity	% Specificity	% Accuracy	% PPV	% NPV
CT studies								
Amendola et al. [22]	1986	10	10.0	0.0	100.0	90.0	N/A	90.0
Heicappell et al. [32]	1999	8	37.5	33.3	100.0	75.0	100.0	71.4
Paik et al. [42]	2000	82	25.6	19.0	96.7	76.8	66.7	77.6
Ficarra et al. [29]	2005	156	31.4	42.2	100.0	83.3	100.0	81.0
Picchio et al. [44]	2006	27	29.6	50.0	68.4	63.0	40.0	76.5
Baltaci et al. [24]	2008	100	13.0	30.8	94.3	86.0	44.4	90.1
Li et al. [38]	2010	127	36.2	47.8	80.2	68.5	57.9	73.0
Lodde et al. [41]	2010	33	45.5	33.3	100.0	69.7	100.0	64.3
Swinnen et al. [46]	2010	51	25.5	46.2	92.1	80.4	66.7	83.3
Maurer et al. [6]	2012	44	27.3	75.0	56.3	61.4	39.1	85.7
Tritschler et al. [47]	2012	219	31.5	30.4	90.0	71.2	58.3	73.8
Vargas et al. [15]	2012	16	12.5	50.0	78.6	75.0	25.0	91.7
Hitier-Berthault et al. [33]	2013	52	42.3	9.1	90.0	55.8	40.0	57.4
Brunocilla et al. [18]	2014	26	26.9	14.3	89.5	69.2	33.3	73.9
Goodfellow et al. [31]	2014	93	30.1	46.4	98.5	82.8	92.9	81.0
Aljabery et al. [12]	2015	54	31.5	41.2	89.2	74.1	63.6	76.7
Horn et al. [34]	2015	229	24.9	52.6	93.6	83.4	73.2	85.6
Jeong et al. [36]	2015	61	27.9	29.4	97.7	78.7	83.3	78.2
Chen et al. [27]	2016	115	36.5	52.4	79.5	69.6	59.5	74.4
Uttam et al. [48]	2016	15	20.0	100.0	50.0	60.0	33.3	100.0
MRI Studies								
Amendola et al. [22]	1986	11	18.2	50.0	100.0	90.9	100.0	90.0
Persad et al. [43]	1993	24	33.3	62.5	100.0	87.5	100.0	84.2
Barentsz et al. [25]	1995	28	21.4	50	95.4	92.9	100.0	91.7
Thoeny et al. [7]	2009	20	25.0	80.0	86.7	66.7	66.7	92.9
Jensen et al. [35]	2011	18	16.7	0.0	80.0	80.7	0.0	80.0
Daneshmand et al. [28]	2012	122	22.1	40.7	92.1	68.8	59.5	84.5
Vargas et al. [15]	2012	16	12.5	50.0	71.4	83.0	20.0	90.9
Liedberg et al. [39]	2013	47	17.0	50.0	89.7	95.0	50.0	89.7
Lista et al. [40]	2013	20	35.0	85.7	100	77.8	100.0	92.9
Wollin et al. [49]	2014	36	22.2	87.5	75.0	90.9	50.0	95.5
PET Studies								
Heicappell et al. [32]	1999	8	37.5	66.7	100.0	87.5	100.0	83.3
Gofrit et al. [30]	2006	16	18.8	100.0	92.3	93.8	75.0	100.0
Picchio et al. [44]	2006	27	29.6	62.5	100.0	88.9	100.0	86.4
Kibel et al. [37]	2009	42	23.8	70.0	93.8	88.1	77.8	90.9
Lodde et al. [41]	2010	43	53.5	56.5	100.0	76.7	100.0	66.7
Swinnen et al. [46]	2010	51	25.5	46.2	97.4	84.3	85.7	84.1
Jensen et al. [35]	2011	18	16.7	33.3	93.3	83.3	50.0	87.5
Maurer et al. [6]	2012	44	27.3	58.3	65.6	63.6	38.9	80.8
Orevi et al. [16]	2012	13	15.4	100.0	81.8	84.6	50.0	100.0
Vargas et al. [15]	2012	16	12.5	100.0	71.4	75.0	33.3	100.0
Hitier-Berthault et al. [33]	2013	52	42.3	36.4	86.7	65.4	66.7	65.0
Brunocilla et al. [18]	2014	26	26.9	42.9	84.2	73.1	50.0	80.0
Chakraborty et al. [26]	2014	23	34.8	87.5	80.0	82.6	70.0	92.3
Goodfellow et al. [31]	2014	93	30.1	67.9	95.4	87.1	86.4	87.3
Rouanne et al. [45]	2014	102	25.5	50.0	97.4	85.3	86.7	85.1
Aljabery et al. [12]	2015	54	31.5	41.2	86.5	72.2	58.3	76.2

Table 2 (continued)

	Years	Number of patients	% LN positive	% Sensitivity	% Specificity	% Accuracy	% PPV	% NPV
Ceci et al. [17]	2015	39	30.8	50.0	88.9	76.9	66.7	80.0
Jeong et al. [36]	2015	61	27.9	47.1	93.2	80.3	72.7	82.0
Soubra et al. [14]	2016	78	20.5	56.3	98.4	89.7	90.0	89.7
Uttam et al. [48]	2016	15	20.0	100.0	58.3	66.7	37.5	100.0

nodal status. Instead radical cystectomy and bilateral lymphadenectomy is recommended if patients are appropriately fit for surgery and the disease is surgically resectable non-metastatic muscle-invasive bladder cancer [21]. Therefore, the main determination a surgeon makes on imaging is whether the cancer is surgically resectable and metastatic. Once the decision is made to operate, determination of nodal status only appears to influence when and whether chemotherapy is offered. If patients do not receive neoadjuvant chemotherapy prior to surgery, it is recommended they have adjuvant cisplatin-based combination chemotherapy if they are found to be node positive on histopathology [1].

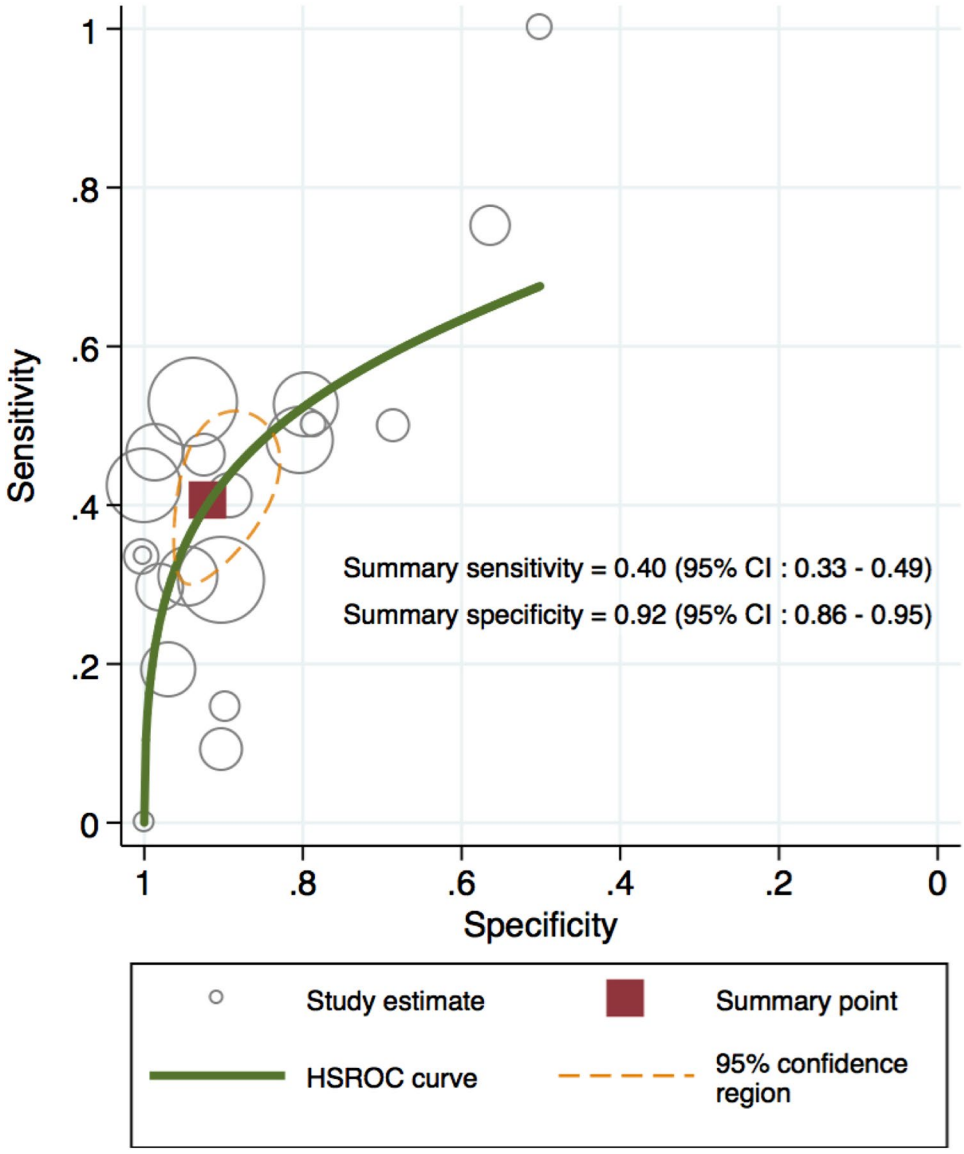

Fig. 3 Summary pooled sensitivity, specificity and hierarchical ROC curve for CT

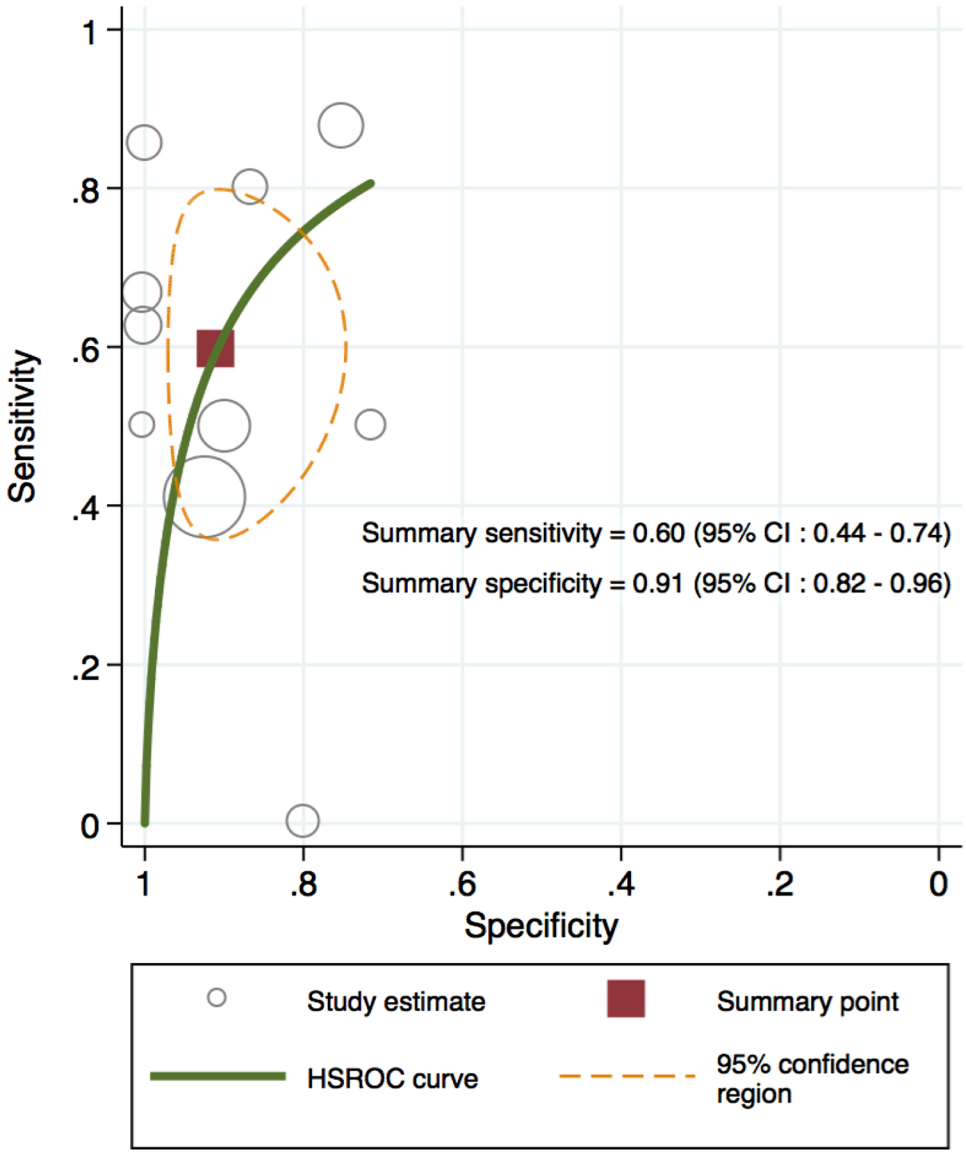

Fig. 4 Summary pooled sensitivity, specificity and hierarchical ROC curve for MRI

Other factors hold great influence over the staging accuracy of these imaging modalities. Factors we've identified that vary between studies include experience of reporting radiologist, enhancement technique, tracer selection, criteria defining positive or suspicious lymph nodes, imaging equipment and extent of lymphadenectomy. It is important to consider how these factors impact on our ability to detect positive nodes. For example, we would expect fewer false positives and more false negatives to be observed as the cut-off diameter on imaging that defines a positive lymph node increases. This was demonstrated by Amendola et al. [22] whose study had the highest cut-off diameter (15 mm) of all computed tomography papers in our analysis. This large diameter resulted in the lowest reported sensitivity and highest specificity of all CT studies [22]. This highlights how careful management of these factors ensures greater consistency in image interpretation. Further analysis is required to determine which factors exert the most influence on imaging accuracy. Tritschler et al. [23] suggested interobserver variability was responsible for the limited accuracy of CT in reporting lymph node involvement of bladder cancer. It is foreseeable that some factors hold greater sway over accuracy than others.

Our study is limited by a number of factors. Standardised location-based lymph node packets were not consistently reported to allow correlation with lymph node location on imaging. Only patient-based analysis was possible for a review on this scale. In addition, lymph node dissection templates were not standardized. We have not excluded patients who received neoadjuvant chemotherapy. And it is important to consider that imaging devices have evolved over time and

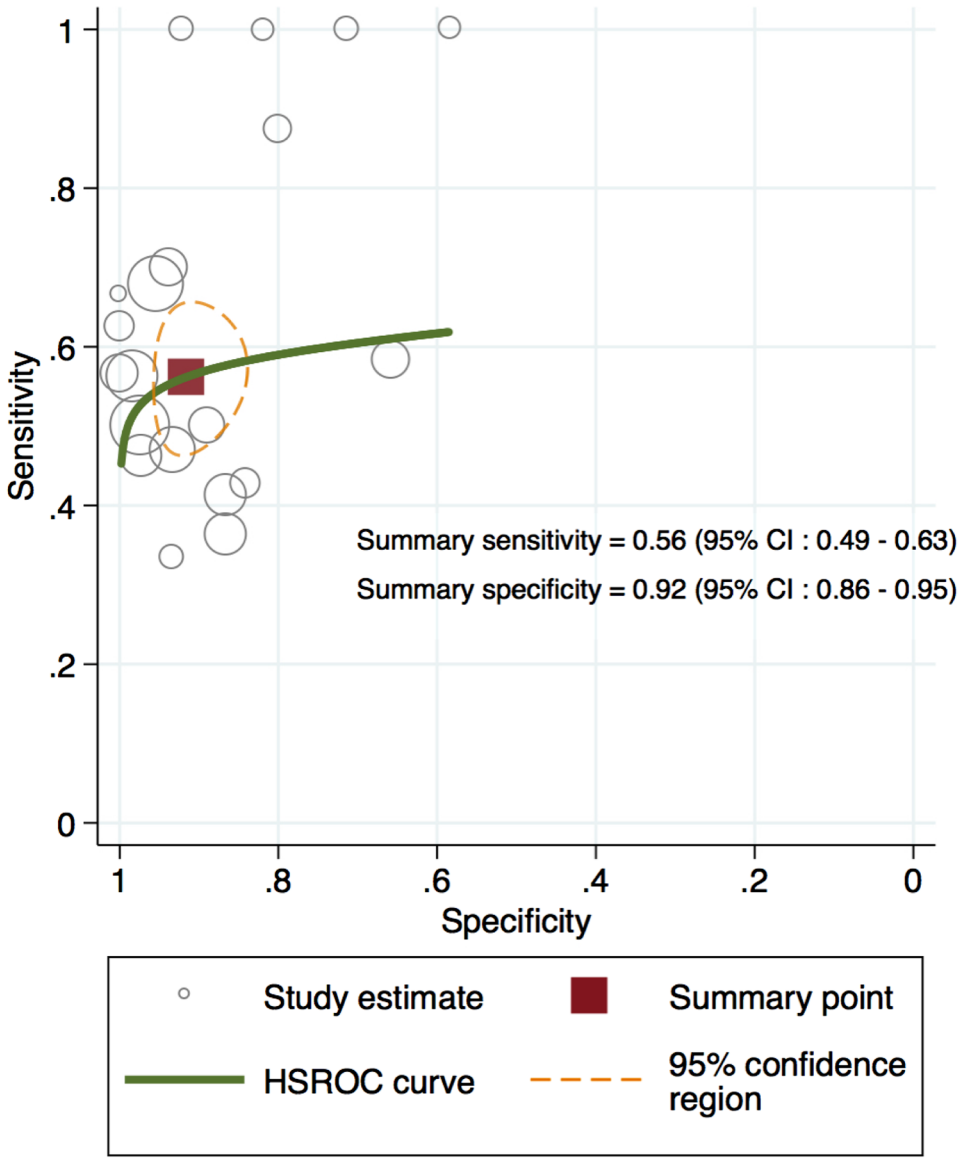

Fig. 5 Summary pooled sensitivity, specificity and hierarchical ROC curve for PET

reported specificities and sensitivities are a summary of current and past technology.

Conclusion

Our analysis shows that MRI and PET/CT have a higher sensitivity than CT while the specificity is similar for all imaging modalities. There is variability in the accuracy that the imaging modalities achieve across different studies. A number of other factors impact on detection accuracy and these must be considered.

Author contributions JC: project development, data collection, data analysis, manuscript writing/editing; NP: project development, data collection, data analysis, manuscript writing/editing; MP: data collection, data analysis, manuscript writing/editing; BN: data collection, data analysis; DB: manuscript editing; SS: manuscript editing; NL: project development, manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. This project did not require formal ethics committee approval.

Ethical approval For this type of study formal ethics approval is not required.

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