Evaluation of Computed Tomography for Lymph Node Staging in Bladder Cancer Prior to Radical Cystectomy

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Introduction

Muscle-invasive bladder cancer (BCa) is an aggressive malignancy, for which, in the absence of distant metastases, radical cystectomy (RC) with bilateral pelvic lymphadenectomy currently represents the standard treatment [1–3]. Survival rates strongly depend on the lymph node (LN) status. The likelihood of metastatic LN involvement depends on the pathological T stage and ranges from 10

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to 50% in different studies [3–5]. While in LN, negative disease 5-year recurrence-free survival rates dependent on pT stage are reported to be between 50 and 89%, these drop to 35% with LN metastases [2, 3]. Thus, in the treatment of BCa, accurate pretherapeutic LN staging is of utmost prognostic importance. Additionally, it may determine the extent of lymphadenectomy during RC if suspicious nodes are detected outside the standard lymphadenectomy template. Also, it may guide the treatment strategy within a multimodal concept. For example, suspicious LN may provide a rationale to employ an inductive or neoadjuvant chemotherapeutic strategy as this may prolong survival [6, 7]. There are only a few studies determining the accuracy of staging with conventional CT in the last 10 years [8–12]. These studies demonstrate a limited value of CT imaging with a significant fraction of both over- and understaging in comparison with the final histology after RC [8, 9]. Diagnostic accuracy for CT in pelvic LN staging is reported to be between 50 and 60% [5, 13, 14]. Current guidelines for the treatment of muscle-invasive BCa by the European Association of Urology list many publications before the year 2000. Furthermore, several studies listed there did not focus on BCa but focused on gynecological cancer patients instead [15–17].

In the above-mentioned series, usually a low sensitivity is described due to the inability of CT imaging to detect LN metastases smaller than 8–10 mm in diameter. Additionally, inflammatory changes after staging transurethral resection (TURB-T) are often hypothesized to lead to reactive LN enlargement and hence to limit specificity of LN staging. Staging TURB-T may induce inflammatory changes not only in LN but also in the bladder itself, so that there may be significant overstaging. This study aimed at determining the accuracy of the currently used gold standard of conventional CT for BCa staging in a large cohort of contemporary patients with state-of-the-art CT scans. Therefore, not only a patient-based analysis was applied but also an approach based on standardized anatomical fields. Furthermore, we evaluated our patient cohort with regard to local pT staging of BCa extension.

Patients and Methods

Patients

We retrospectively evaluated all patients who underwent RC for BCa at our tertiary care center between 2006 and 2012. Preoperatively, a conventional CT imaging of the chest, abdomen and pelvis was performed for local and LN staging and to rule out distant metastases. Only patients with a digital dataset of a state-of-the-art contrast-enhanced CT imaging were included into this analysis. Patients with native imaging only or low-dose CT, patients with lacking pelvic lymphadenectomy concomitant with cystectomy and patients after neoadjuvant chemotherapy were excluded from the analysis (see online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000440889). The maximum slice thickness was 5 mm with a minimum number of 4 detector rows. All CT scans were analyzed at a digital workstation. Imaging was not necessarily performed at our institution, as many patients were referred to our department for RC after external imaging. Patients with a time interval of more than 120 days between CT imaging and RC were excluded from further analyses.

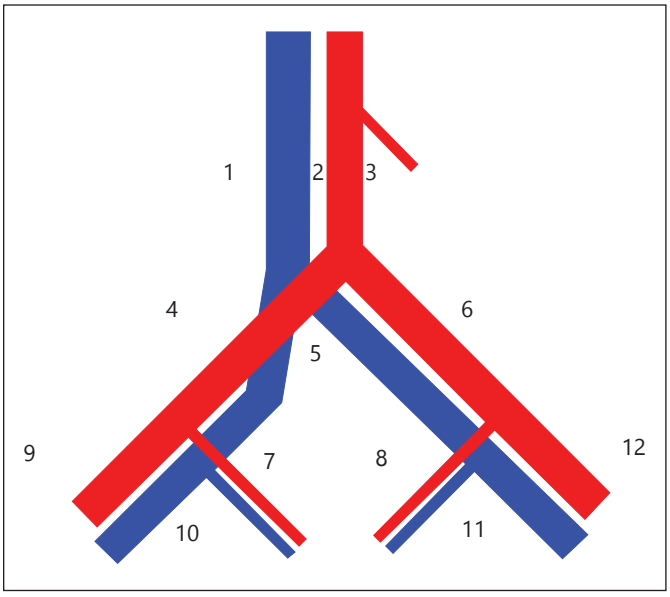

Fig. 1. Standardized anatomical fields, according to which the LNs were sent to pathology during surgery and radiologically evaluated. 1 = Paracaval (positive in 3 patients/dissected in 55); 2 = interaortocaval (1/44); 3 = paraaortal (3/55); 4/6 = common iliac right/left (4/121) (7/106); 5 = presacral (3/60); 7/8 = internal iliac right/left (11/187) (8/181); 9/12 = external iliac right/left (21/213) (18/214); 10/11 = obturator fossa right/left (23/211) (13/213).

A standard lymphadenectomy was performed in all patients including the obturator fossa and tissue surrounding the external and internal iliac arteries. A more extended lymphadenectomy up to the origin of the lower mesenteric artery was performed in patients with suspicious LN in these regions on preoperative staging.

Methods

All CT scans were retrospectively reevaluated by 2 independent radiologists (3 and 7 years of experience in urogenital imaging) who needed to come to an agreement regarding radiographic evaluation and who were blinded for histopathological results. Both radiologists evaluated CT scans independently in a standardized manner. Measurements for LNs were rounded to the closest millimeter. In a second step, results of both radiologists were compared. Differences were minor. Only in a few cases with measurement differences >1 mm, the mean of both results was calculated.

We used a 12-field template for radiological analysis according to the lymphadenectomy regions during RC (fig. 1). The lymphat-

ic tissue of the 12 anatomical regions was sent separately for histological analysis. Besides a patient-based analysis, we also chose this field-based approach because it allows better tracking of LN in terms of their anatomic origin. The lymphatic tissue of all dissected regions was examined separately by experienced uropathologists.

The radiological likelihood of anatomical fields to be metastatically involved was graded according to a 5-step model as previously described (1: benign; 2: probably benign; 3: equivocal; 4: probably tumor manifestation; 5: tumor manifestation) [8]. This score was based on size, shape, presence of fat in the nodal hilum, extracapsular extension as well as regional clustering of LN. Concerning size, all LN with a short axis diameter of more than 10 mm were graded as '4' or '5'. The only exception to this was the presence of a fatty hilum in such a node (grade '3'). If LNs were smaller than 10 mm, but lacked a fatty hilum, were round in shape, and/or there was suspicious clustering of LNs, they were at least categorized as '3', a few times as '4' (if all criteria were present and suspicious).

Calculations of test quality parameters and further statistical analyses were performed both at patient- and field-based levels using binary ratings of the CT results (positive or negative for presence of metastatic LN). Therefore, the cutoff for the radiological assessment yielding optimum discriminatory ability was determined by receiver operating characteristics (ROC) and application of the Youden index (sensitivity + specificity – 1) in the patient-based approach. To account for multiple assessments of each patient in the field-based approach, logistic GEE models were fit to the data as described in [18]. Separate models were fit for estimation of sensitivity, specificity and predictive values. The binary result of the CT scan was considered the dependent variable in an intercept-only model including only patients with a positive (for estimation of sensitivity) or a negative (specificity) histological finding, respectively. For estimation of predictive values, the histological finding was defined as a dependent variable and only patients with positive (estimation of positive predictive value; PPV) or negative (negative predictive value; NPV) CT scan were included. For estimation of accuracy, an intercept-only model with a dependent variable indicating agreement between CT Scan and histological finding was used. An exchangeable correlation structure was assumed for all models. For all relevant quantities, 95% CIs are presented. For the patient-based measures, exact binomial CIs (Clopper-Pearson) were estimated and for the field-based analyses, CIs were derived from the GEE models. Statistical analysis was conducted using SAS version 9.3.

For the evaluation of local staging, the patient group was split as those with 'organ-confined (OC)' (≤T2) and 'locally advanced (LA)' (>T3) tumors based on both CT imaging and histopathology. For uniformity reasons, patients were included into this analysis only if their CT scan was performed after staging TURB-T, as this represents the standard of routine care, although it may induce reactive changes in the adjacent tissue and regional changes.

Results

A total of 231 patients with a mean age of 68 years (range 39–91 years) were included. A median of 25 LNs were removed (first quartile: 18; fourth quartile: 35). Pathological T and N stages of the patients are shown in table 1.

Table 1. T stages of study patients and absolute and relative frequencies of LN positive patients

	Patients with pT stage	LN + patients, n (%)
pTa	6	–
pTis	12	–
pT1	35	1 (2.9)
pT2	76	12 (15.8)
pT3	76	31 (40.8)
pT4	26	15 (57.7)
Total	231	59 (25.5)

The term T stage refers to the maximum pT stage in combination of TURB-T and radical cystectomy.

We observed an expected increased frequency of LN metastases with higher pathological T stages. Fifty-eight patients (25.1%) had metastatic LN involvement. Among them were 2 patients with LN metastases in the perivesical soft tissue, which is an uncommon region for LN metastases in BCa and was consequently not represented in the 12 anatomical regions depicted in figure 1. These 2 patients were included into the field-based analysis, but excluded from the patient-based approach.

Aiming at the detection of the best cutoff for radiological assessment of an anatomic region between suspicious and not suspicious, an ROC curve showed optimum separational abilities for considering categories '1', '2' and '3' not suspicious in contrast to suspicious categories '4' and '5'. For this allocation, a Youden index (sensitivity + specificity – 1) of 0.46 was calculated (sensitivity 0.526; specificity 0.936). Switching category '3' from not suspicious to suspicious, the Youden index decreased marginally to 0.42 (sensitivity 0.754; specificity 0.669), whereas all other cutoffs performed clearly in a worse manner. According to the highest Youden index, we considered all fields with a radiological grade '4' or '5' as suspicious for the following analyses.

Thus, for further evaluations, categories '1', '2' and '3' were grouped (not suspicious) in contrast to categories '4' and '5' (suspicious). In the patient-based analysis, CT imaging showed an accuracy of 191/229 (83.4%, 95% CI 77.9–88.0). Of the 57 patients with positive LN, on final histology, CT imaging was able to detect 30 corresponding to a sensitivity of 52.6% (95% CI 39.0–66.0). On the other hand, there were 41 patients with CT imaging suspicious for LN involvement, of which 30 were proven to be LN metastases, yielding a PPV of 73.2% (95% CI 57.1–85.8). Furthermore, specificity and NPV were calculated

Table 2. Test quality parameters for the performance of CT staging in bladder cancer prior to radical cystectomy for both the patient- and the field-based analysis regarding LN metastases (95% CI in brackets)

	Patient-based analysis, n (%)	Field-based analysis, n (%)
Sensitivity	52.6 (39.0–66.0)	30.2 (21.8–40.2)
Specificity	93.6 (88.8–96.8)	98.0 (97–98.7)
PPV	73.2 (57.1–85.8)	51.5 (39.6–63.2)
NPV	85.6 (79.8–90.3)	94.5 (92.1–96.2)
Accuracy	83.4 (77.9–88.0)	93.3 (91.1–94.9)

Table 3. Results for local staging both for histopathology and CT imaging

	Histology		Total
	OC	LA	
CT			
OC	70	21	91
LA	8	30	38
Total	78	51	129
Sensitivity, n (%)	58.8 (44.2–72.4)		
Specificity, n (%)	89.7 (80.8–95.5)		
PPV, n (%)	78.9 (62.7–90.4)		
NPV, n (%)	76.9 (66.9–85.1)		
Accuracy, n (%)	77.5 (69.3–84.4)		

as 93.6% (95% CI 88.8–96.8) and 85.6% (95% CI 79.8–90.3), respectively (table 2).

Switching radiological category '3' to suspicious, sensitivity would increase to 75.4% (95% CI 62.2–85.9) and specificity decrease to 66.9% (95% CI 59.3–73.8) in the patient-based analysis. However, accuracy would also drop to 69.0% (95% CI 62.6–74.9). PPV and NPV were calculated as 43.0% (95% CI 33.1–53.3) and 89.1% (95% CI 82.5–93.9), respectively.

Performing the field-based analysis, a total of 1,649 fields with 114 fields yielding LN metastases (6.9%) were detected. Applying the above-mentioned GEE models for sensitivity, specificity, PPV, NPV and accuracy, we obtained 30.2% (95% CI 21.8–40.2), 98.0% (95% CI 97.0–98.7), 51.5% (95% CI 39.6–63.2), 94.5% (95% CI 92.1–96.2) and 93.3% (95% CI 91.1–94.9; table 2) for each of these fields respectively.

The median duration between CT and RC was 20 days (range 1–119 days). As mentioned earlier, we had excluded patients in whom this time interval exceeded 120 days. To investigate the necessity of even more restrictive requirements, we included only those patients with a time interval of 60 days or less in a subgroup analysis. However, we could not detect relevant differences in the results.

Concerning local staging, the results of 129 patients with evaluable CT scans performed after TURB-T could be analyzed (table 3). The lower number of evaluable scans is due to either low quality of the scan (status post hip replacement, empty bladder) or a CT before TURB-T. CT imaging was able to detect 30 out of 51 LA tumors (sensitivity 58.8%, 95% CI 44.2–72.4); on the other hand, 70 of 78 OC tumors were staged correctly (specificity 89.7%, 95% CI 80.8–95.5). The results translate into a PPV of 78.9% (95% CI 62.7–90.4) and an NPV of 76.9% (95% CI 66.9–85.1); overall accuracy was 77.5% (100/129, 95% CI 69.3–84.4). Overstaging occurred in 8 patients (6.2%) and understaging occurred in 21 patients (16.3%).

Discussion

Modern imaging modalities aim at organ-specific targets like 99mTc for thyroid imaging or, as only recently evolved, PSMA for prostate cancer imaging [19]. Unfortunately, in BCa, no specific targets have been identified for imaging so far. Moreover, our group has recently shown the lack of benefit in adding 11C-Choline-PET to conventional CT for LN staging of BCa [8]. Other groups have shown similar data for 18F-FDG-PET/CT with no or only a modest benefit in LN staging [20, 21]. Thus, staging with conventional CT imaging will remain the most widely used imaging modality in the near future. Considering the fact that many studies analyzing the value of conventional CT imaging for BCa staging are by far outdated as they were published in the 1980s or 1990s, we wanted to address this issue on the basis of a large series of contemporary patients using state-of-the-art CT scans analyzed at digital workstations.

On a patient-basis, we observed a sensitivity of 52.6% and a specificity of 93.6% for LN staging, yielding PPV and NPV of 73.2 and 85.6%. The low sensitivity most likely is due to the low ability of CT imaging to detect metastases in normal-sized LN. Patients with suspected LN metastases are frequently considered apt for inductive or neoadjuvant chemotherapy prior to RC according to a risk-adapted approach. Being aware that CT imaging was only able to detect about 50% of LN metastases, every second patient with a possible indication for presurgical treatment would be missed. Also the PPV of a suspicious

Table 4. Summary of studies published after the year 2000 evaluating the quality of CT imaging in bladder cancer LN staging

	n	Sensitivity, %	Specificity, %	Accuracy, %
Baltaci et al. [10]	100	30.7	94.3	86
Ficarra et al. [12]	156	42.2	100	76.9
Maurer et al. [8]	44	75	56	61
Tritschler et al. [11]	219	30.4	90	71.2

CT scan was only 73.8%, meaning that 1 out of 4 patients with suspicious LN in CT imaging showed only benign changes in the histopathology report. These are patients who may be mistakenly referred to inductive chemotherapy, although we acknowledge a possible benefit by neoadjuvant treatment for these patients.

On the other hand, out of 183 patients without LN metastases, 172 were correctly identified by CT imaging. A negative CT imaging meant a likelihood of 85.1% for LN histology to show no malignant changes. Overall, 83.2% of all patients were staged correctly.

In table 4, the summary of studies published after the year 2000 analyzing the value of CT imaging for BCa LN staging is shown. With the exception of the study from our group by Maurer et al., which compared CT with PET/CT imaging and therefore was limited by a rather small patient number, all studies had similar results to ours. In all studies, CT imaging showed a rather high specificity and a rather low sensitivity with the accuracy of CT around 75–80%.

For the first time in the evaluation of CT imaging for BCa staging, we used an anatomical field-based approach allowing a more exact tracking of LN. This approach further underlined the results of the patient-based evaluation, as approximately only every fourth metastatically involved field could be correctly detected due to the low sensitivity of CT scanning. Nevertheless, only 2% of fields without LN metastases were falsely classified as suspicious (specificity 98%). In summary, it can be stated that CT imaging, which is currently considered the gold standard in BCa staging, is able to detect only 50% of patients with metastatic LN. These are patients who, if identified correctly, should be strongly considered for primary systemic treatment prior to RC. Imaging modalities, which improve the sensitivity for LN metastasis detection in BCa while maintaining a high specificity, are urgently needed.

Concerning local staging, a common concern is overstaging because of TURB-T-artefacts. However, there is only one study in the literature reporting a higher rate of overstaging (22%) compared to understaging (6%) [10]. In contrast, Tritschler et al. [11] reported similar over- and understaging rates (23.4 and 24.7%); other studies reported even a higher chance of understaging with rates of 39% [5] and 50% [12]. We also observed a higher understaging rate with 16% compared to only 6% overstaging in our cohort with CT scans performed after TURB-T. Tritschler et al. [11] also reported a similar accuracy of local staging with CT before and after TURB-T. We conclude that available data point to the conclusion that TURB-T does not frequently induce changes suggestive for overstaging. Hence, patients with a CT scan showing LA BCa (cT3/4) should also be considered for neoadjuvant chemotherapy.

Ethical Statement

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosure Statement

The authors declare no conflict of interest.

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