Prognostic Value of ^{11}C-Choline PET/CT and CT for Predicting Survival of Bladder Cancer Patients Treated with Radical Cystectomy

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Introduction

In Europe, approximately 110,000 cases of bladder cancer (BCa) are newly diagnosed each year and the overall BCa mortality rate per year ranges from 1.2 (for women) to 5.5 (for men) per 100,000 inhabitants [1, 2]. At initial diagnosis, about 70% of patients with BCa present with non-muscle-invasive disease whereas 30% show muscle-invasive cancer [1]. Especially muscle-invasive BCa (MIBCa) and high-risk non-muscle-invasive BCa (NMIBCa) represent an aggressive and potentially life-threatening disease requiring optimal treatment strategies.

The standard treatment for MIBCa is radical cystectomy (RCX) with pelvic lymph node dissection (PLND) whose extent is currently still under discussion [1]. However, in locally advanced disease with high risk for development of metastases, platinum-based neoadjuvant chemotherapy regimes improve cure rates while palliative treatment is advocated for metastatic disease [3, 4].

Therefore, accurate pre-treatment staging of patients with high-risk BCa or MIBCa has direct implications on further management and patient outcome. Unfortunately, current clinical staging procedures (computed tomography [CT] or magnetic resonance imaging [MRI]) for BCa are insufficient since upstaging from organ-confined (OC) lymph node-negative BCa to non-organ-confined (NOC) BCa or BCa with lymph node metastases on final pathology occurs in approximately 40% of patients [1, 5, 6]. Several risk factors either leading to pathological upstaging in BCa patients after RCX and PLND or compromising recurrence-free and overall survival (OS) rates have been established. These include presence of preoperative hydronephrosis, evidence of lymphovascular invasion, deep muscularis propria infiltration and non-papillary or solid tumor growth pattern in the histological specimen after transurethral resection as well as multiplicity of tumors and age of patients [7–11]. Clinical nomograms incorporating these factors have been proposed to pre-therapeutically identify patients in whom upstaging is likely and who might benefit from neoadjuvant regimens [10, 11]. However, some authors support the use of neoadjuvant chemotherapy even in patients with clinically OC disease – also because upstaged patients on final pathology after RCX often do not receive adjuvant chemotherapy [12].

Recently, positron emission tomography (PET) as functional imaging with tracers like ^{18}F-FDG, ^{11}C-choline or ^{11}C-acetate in combination with CT has been introduced [13–26]. However, these studies present conflicting data as to whether these new imaging modalities are able to improve clinical staging in comparison to results of the 'gold standard' histopathology. The accuracy of this 'gold standard' on the other hand heavily depends on meticulous lymph node preparation (omitting sampling error by incomplete dissection of lymphatic tissue) as well as subtle pathological evaluation to identify even small metastatic lesions especially in normal-sized lymph nodes (omitting analytical error) and might therefore be subject to bias, especially when reporting lymph node-negative disease [27, 28].

Relevant endpoints for the individual patient, however, represent recurrence-free survival, disease-specific survival or OS after potentially curative treatment – endpoints that may be difficult to assess preoperatively. To our knowledge, so far there are only two studies correlating the results of pre-therapeutic PET/CT imaging (both with ^{18}F-FDG) with survival [13, 17]. Thus, the aim of our study was the definition of prognostic accuracy of preoperative staging with ^{11}C-choline PET/CT and sole CT regarding OS and cumulative incidence of cancer-specific death (CSD) in comparison to histopathological evaluation. Therefore we followed the patients of our previously published prospective study, examining the diagnostic accuracy of lymph node staging with ^{11}C-choline PET/CT in comparison to sole CT and histopathological evaluation in patients with BCa treated with RCX and PLND [23].

Patients and Methods

Patients

After approval by the local ethics committee and obtaining informed consent, 44 patients with histologically proven high-grade or muscle-invasive localized urothelial carcinoma of the bladder underwent standardized RCX and PLND within a mean of 13.5 days (median 6.0 days, range 1–89 days) after ^{11}C-choline PET/CT from June 2004 to May 2007 [23]. Patients with metastatic disease were not included since they did not undergo surgery but palliative treatment. All patients received a standard template PLND up to the aortic bifurcation. In 20 patients with suspicion of locally advanced disease (≥T3) or lymph node involvement (LN+) by imaging, an extended PLND up to the origin of the inferior mesenteric artery was performed in addition.

Histopathological diagnosis of local BCa and the presence or absence of lymph node metastases was based on histological examination of surgical specimens and the TNM classification system [29]. To minimize pathological understaging and to maximize histological lymph node yield, tissue from each anatomical

Table 1. Three- and 5-year OS and cumulative incidence of CSD for patients with ≤T2 N0, ≥T3 N0 or T1–4 N+ BCa according to ^{11}C-choline PET/CT, sole CT examination or postoperative histological evaluation (estimated means and 95% CIs are presented)

	Category	n	OS		CSD	
			3 years	5 years	3 years	5 years
^{11}C-choline PET/CT	≤T2 N0	18	67% (48–92)	61% (42–88)	22% (7–44)	22% (7–44)
	≥T3 N0	8	38% (15–92)	38% (15–92)	38% (7–70)	38% (7–70)
	T1–4 N+	18	61% (42–88)	50% (32–79)	28% (10–50)	33% (13–55)
CT	≤T2 N0	13	69% (48–99)	62% (40–95)	15% (2–40)	15% (2–40)
	≥T3 N0	9	78% (55–100)	67% (42–100)	22% (3–53)	22% (3–53)
	T1–4 N+	22	46% (29–72)	41% (25–68)	36% (17–56)	41% (20–61)
Histology	≤T2 N0	20	75% (58–97)	65% (47–90)	20% (6–40)	20% (6–40)
	≥T3 N0	12	50% (28–88)	42% (21–81)	17% (2–43)	25% (5–52)
	T1–4 N+	12	42% (21–81)	42% (21–81)	50% (19–75)	50% (19–75)

field was dissected separately by experienced uropathologists [27]. In total, 19 patients showed OC lymph node-negative disease (≤pT2 pN0), 13 patients presented with NOC lymph node-negative disease (≥pT3 pN0) and 12 patients with metastatic lymph node involvement (pT1–4 pN+) on final histological evaluation. Follow-up information from each patient was obtained regularly through contact of patients and primary physicians as well as through the local tumor register (Tumorzentrum München). The median follow-up was 78.2 months (range 1–98 months).

Image Analysis

Imaging was performed as previously described [23]. Briefly, two independent board-certified nuclear medicine physicians who were also board-certified radiologists analyzed CT images solely or ^{11}C-choline PET/CT images for evidence of NOC disease and lymph node involvement. For determination of NOC, thickening of the bladder wall, suspicion of infiltration of the paravesical fat and standard uptake values of ^{11}C-choline were evaluated. Bladder lesions were classified as OC versus NOC according to findings on CT images solely or ^{11}C-choline PET/CT images in consensus. For determination of lymph node involvement, size, shape and contrast enhancement as well as focally increased, not physiological ^{11}C-choline uptake was evaluated and lesions were graded for CT alone or ^{11}C-choline PET/CT according to a grading system in consensus (1: metastatic infiltration; 2: probably metastatic; 3: equivocal; 4: probably benign; 5: benign). For correlation with histopathology, lesions scored 1 and 2 were considered as positive for tumor, and lesions scored 3, 4 and 5 as negative for tumor, as this had proved to exhibit best discriminatory power in our initial report [23].

Statistical Analysis

The median follow-up time was determined by the Kaplan-Meier estimate for potential follow-up [30]. OS for relevant groups was determined by the Kaplan-Meier method. Cumulative incidence of CSD, denoting the estimated probability of CSD up to a given time point, was assessed using the library *cmprsk* [31] of the statistical software R version 2.15.1 accounting for death from other causes as competing risks. The log-rank test was performed to compare survival curves and cause-specific hazard rates for CSD between groups. 95% confidence intervals (CIs) are presented for 3- and 5-year OS and CSD. Additionally, Cox regression was applied to estimate hazard ratios (HRs) and cause-specific HRs with 95% CIs. All statistical tests were performed on a two-sided level of significance of $\alpha = 5\%$.

Results

Estimated 5-year OS probabilities for patients with stage ≤T2 N0 as classified by ^{11}C-choline PET/CT, sole CT examination or histology was 61, 62 and 65%, for patients with ≥T3 N0 38, 67 and 42%, and for patients with T1–4 N+ disease 50, 41 and 42%, respectively. In total, the estimated 5- and 3-year OS by ^{11}C-choline PET/CT, sole CT or histology did not show relevant differences for patients diagnosed within these groups (table 1).

Also, no significant differences could be observed when patients were stratified for OC and NOC disease irrespective of lymph node status (fig. 1a–c) or for lymph node involvement irrespective of T classification (fig. 1d–f). While ^{11}C-choline PET/CT showed a slightly superior p value and HR concerning OS compared to CT ($p = 0.262$ vs. $p = 0.518$; HR = 1.60 vs. HR = 1.34) when stratifying for extent of local bladder tumor (OC vs. NOC), sole CT examination demonstrated a moderate improvement compared to ^{11}C-choline PET/CT when stratifying for lymph node involvement ($p = 0.228$ vs. $p = 0.527$; HR = 1.67 vs. HR = 0.76). However, in our patient cohort ^{11}C-choline PET/CT as well as CT did not prove to be a significant predictor for OS.

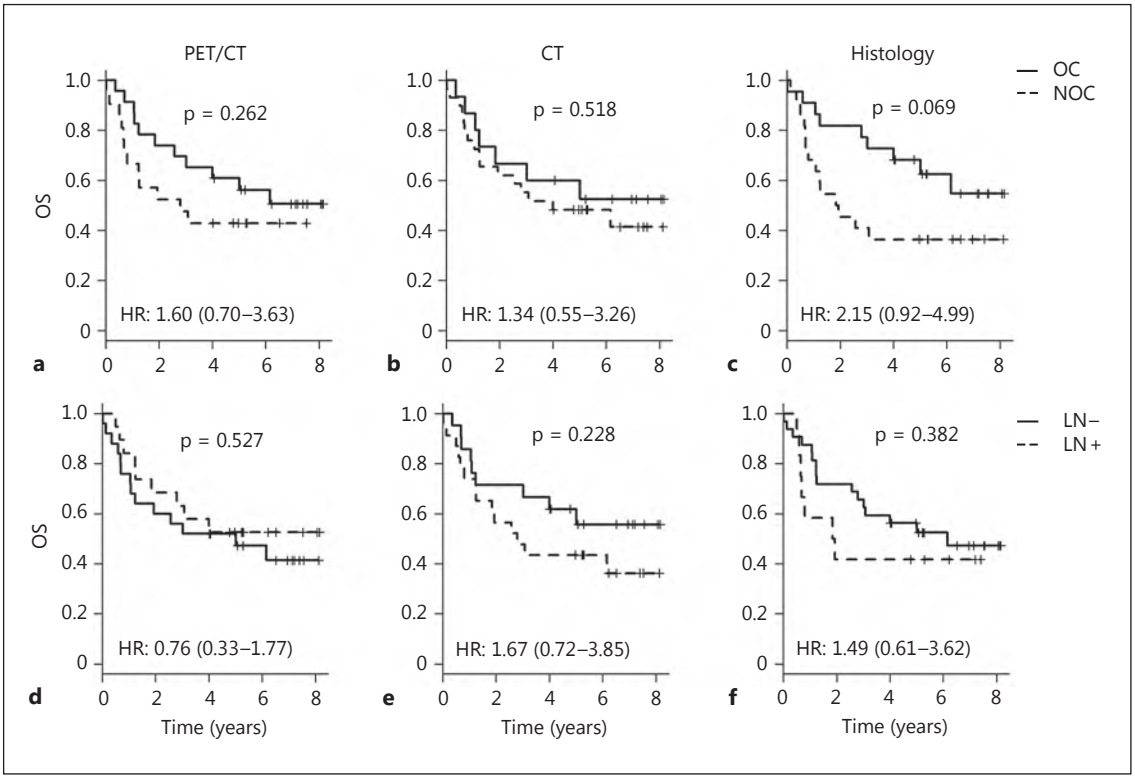

Fig. 1. OS of BCa patients with OC (≤T2) versus NOC (≥T3) disease and of BCa patients with or without metastatic lymph node involvement (LN+ vs. LN–) as determined by ^{11}C-choline PET/CT, sole CT examination or histopathological analysis. p values of log-rank tests as well as HRs of Cox regression analysis with 95% CIs are shown.

Concerning cumulative incidence of CSD, estimated probabilities for ^{11}C-choline PET/CT, sole CT examination or histology after 5 years were 22, 15 and 20% for patients with ≤T2 N0, 38, 22 and 25% for patients with ≥T3 N0, and 33, 41 and 50% for patients with T1–4 N+ disease, respectively (table 1).

For CSD, no significant differences could be observed when patients were stratified for OC and NOC disease irrespective of lymph node status (fig. 2a–c) or for lymph node involvement irrespective of T classification (fig. 2d–f). Here, ^{11}C-choline PET/CT showed almost equal p values concerning CSD compared to CT (p = 0.144 vs. p = 0.323; HR = 2.25 vs. HR = 1.90) when stratifying for extent of local bladder tumor (OC vs. NOC), while sole CT examination demonstrated an observable, yet insignificant improvement compared to ^{11}C-choline PET/CT when stratifying for lymph node involvement (p = 0.136 vs. p = 0.976; HR = 2.38 vs. HR = 0.98). Taken together, in our patient cohort both imaging modalities could not reliably identify patients with increased risk of CSD in contrast to postoperative histological analysis. Not surprisingly, postoperative histological analysis proved to be a significant predictor of CSD when patients were stratified according to local tumor (p = 0.042; HR = 3.19) or lymph node involvement (p = 0.036; HR = 3.05).

Negative results of ^{11}C-choline PET/CT and CT were found in 12 (27%) and 14 (32%) patients with histopathologically confirmed lymph node metastasis, and suspicious findings on ^{11}C-choline PET/CT and CT were described in 5 (11%) and 3 (7%) patients without lymph node involvement on histopathological analysis. Postoperative assessment of prognosis combining results of imaging (^{11}C-choline PET/CT or CT) and histopathological evaluation concerning lymph node status for patients with positive findings on imaging and histologically confirmed lymph node metastases showed a weak trend for worse OS (p = 0.700 vs. p = 0.166; HR = 1.25 vs. HR = 2.12), but a pronounced tendency for higher CSD (p = 0.207 vs. p = 0.029; HR = 2.63 vs. HR = 4.94) compared to patients with negative findings on imaging and histological analysis. However, the patient groups were too small to adequately analyze subgroups of patients – especially subgroups with diverging results for imaging and histopathological analysis.

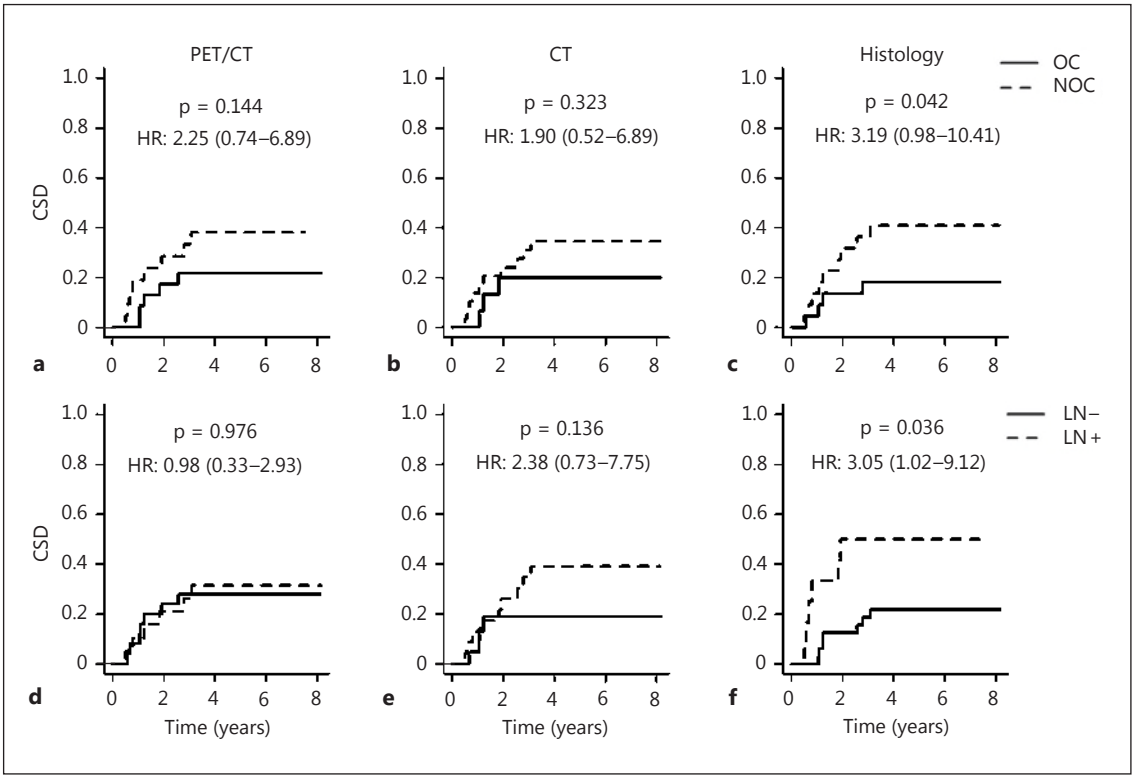

Fig. 2. Cumulative incidence of CSD of BCa patients with OC (≤T2) versus NOC (≥T3) disease and of BCa patients with or without metastatic lymph node involvement (LN+ vs. LN–) as determined by ^{11}C-choline PET/CT, sole CT examination or histopathological analysis. p values of log-rank tests as well as HRs of Cox regression analysis with 95% CIs are shown.

Discussion

Cross-sectional imaging remains a mainstay in the staging and the pre-therapeutic decision-making process in patients with extensive high-grade NMIBCa or MIBCa. The most widely used imaging modalities, however, rely solely on morphology and show accuracy rates for determination of locally advanced (≥T3) disease between 55 and 92% (for CT) and between 73 and 96% (for MRI), with sensitivity rates for detection of metastatic lymph nodes from 48 to 87% limited by low specificity rates for both imaging techniques [1]. Thus, upstaging on final pathology after RCX and PLND is a common finding for both CT and MRI [6, 32]. Especially metastatic disease to the lymph nodes has a great impact on prognosis, with lymph node density and extracapsular extension rather than size of the metastatic lesion representing the strongest prognostic factors [33–36].

Over the last few years PET/CT with the tracers ^{18}F-FDG, ^{11}C-choline or ^{11}C-acetate has evolved as a new staging modality combining cross-sectional anatomical and functional imaging [13–26]. Several studies described increased accuracy and high specificity rates especially in the detection of lymph nodes or distant metastases to bone and visceral organs with ^{18}F-FDG-based [13, 16, 17, 19, 20], ^{11}C-choline-based [14, 24, 37] or ^{11}C-acetate-based [24] PET/CT, which had an impact on further clinical management in a significant number of patients. Therefore, those authors concluded that PET/CT might have the ability to replace standard cross-sectional imaging or bone scintigraphy in the staging of BCa. This view is challenged by others who could not observe a significant improvement, mainly because of unspecific tracer uptake caused by inflammatory changes after instillation of immuno- or chemotherapeutical agents or transurethral resection [18, 22, 23, 25, 26]. In our patient cohort, for example, we could not observe an improved diagnostic efficacy of preoperative lymph node staging by ^{11}C-choline PET/CT compared to conventional CT alone either [23]. However, up to now, no final conclusion on the value of PET/CT for staging of local tumor, lymph node involvement and distal organs in BCa patients can be drawn, mainly since these data are based on relatively small and in part heterogeneous study cohorts.

Furthermore, in most studies the performance of imaging is determined by comparison to the 'gold standard' of postoperative histopathological evaluation and not directly to recurrence-free survival, disease-specific survival or OS, which represent relevant endpoints for the individual patient. So far, only two studies correlated the results of ^{18}F-FDG PET/CT imaging with time to recurrence, overall or disease-specific survival [13, 17]. In the study by Drieskens et al. [13], 55 patients with non-metastatic invasive BCa were subjected to ^{18}F-FDG PET followed by CT within 14 days. 32 patients received curative treatment consisting of RCX and PLND alone or in combination with either neoadjuvant or adjuvant chemo- or radiotherapy, while 23 patients were only treated with chemo- or radiotherapy or did not receive any treatment. The median OS of patients with positive findings on ^{18}F-FDG PET and CT was 13.5 months versus 32 months for patients without suspicious results. However, only 42% (5/12) of patients with positive ^{18}F-FDG PET and CT received curative treatment compared to 63% (27/43) of patients with negative findings, and therefore the results have to be considered with caution. Kibel et al. [17] reported on 42 BCa patients without locally advanced or metastatic disease on conventional imaging who underwent preoperative ^{18}F-FDG PET/CT before RCX and PLND. One patient with suspicion of metastatic disease on ^{18}F-FDG PET/CT did not undergo surgery, while another patient received neoadjuvant chemotherapy after lymph node biopsy before RCX. In this homogenous patient cohort the recurrence-free, overall and disease-specific survival at 24 months was 0, 23 and 23% for patients with positive findings on preoperative ^{18}F-FDG PET/CT (n = 9), compared to 55, 62 and 58% for patients without evidence of lymph node metastases (n = 33). Therefore it was concluded that ^{18}F-FDG PET/CT yields high diagnostic and prognostic accuracy that might be useful in the decision-making process and selection of the appropriate treatment strategy prior to RCX.

Our study with 44 patients all treated with RCX and PLND without prior neoadjuvant chemotherapy was only able to demonstrate non-significant trends for ^{11}C-choline PET/CT or CT alone in predicting OS or CSD in patients with OC vs. NOC BCa or LN+ versus LN– disease with moderately increased HRs for patients with evidence of NOC in ^{11}C-choline PET/CT or of NOC and LN+ disease in CT. These at first glance contradictory findings can at least partly be explained by the low number of included patients in our prospective study as well as by the fact that our study included patients with less advanced disease, since our survival rates are greater than in the study by Kibel et al. [17]. Also, the fact that 20 patients with suspicion of locally advanced disease (≥T3) or lymph node involvement by imaging received a more extended PLND up to the origin of the mesenteric artery might have influenced our findings. Additionally, six patients with newly diagnosed metastatic disease (M+) by ^{11}C-choline PET/CT (visible also on sole CT examination) were not operated and excluded from the initial study and from further analysis [23].

Although in our prospective trial neither CT nor ^{11}C-choline PET/CT were able to significantly predict patients' OS and CSD, the potential value of these preoperative imaging modalities with respect to prognosis should be evaluated in larger patient cohorts in the future since their results very well might have an impact on patient counseling. The development of BCa-specific radiopharmaceutical tracers is desirable to further improve diagnostic staging and the predictive value of PET-based imaging. New imaging modalities like a combination of PET and MRI, however, could potentially improve the diagnostic and prognostic value of preoperative imaging [38].

Disclosure Statement

The authors have no conflict of interest.

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