Outcomes of palliative cystectomy in patients with locally advanced pT4 bladder cancer

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1. Introduction

Bladder cancer (BCa) is the second most common genitourinary malignancy and the ninth most common cancer overall. The incidence rate is 5.3 per 100,000 persons/years leading to an estimated 165,000 deaths per year [1,2]. At first diagnosis, about 2% of patients present with locally advanced pT4 BCa [3].

In this challenging therapeutic setting of advanced or metastatic BCa, patients' quality of life and general health can be severely restricted by local complications such as gross hematuria, pain, dysuria, urinary retention in the kidneys and

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urinary obstruction. If the control of these symptoms is not possible by less invasive methods, patients may be offered a palliative cystectomy (Cx) to locally control the tumor.

Even in advanced BCa, Cx leads to an effective local tumor control and thereby an effective control of symptoms. The local recurrence rate of nonorgan confined tumors is reported to be between 11% and 16% [4,5]. Due to a shorter duration of surgery and less postoperative complications patients should be offered an incontinent urinary diversion [6].

The careful patient selection for Cx is critical due to the known peri- and postoperative complication rates. Moreover, many patients with locally advanced or metastatic BCa are in bad general condition with several comorbidities. Although a high rate of complications is known in locally advanced tumor stage, available data for the outcome of Cx in patients with pT4 BCa is limited to a few retrospective cohort studies with a maximum of 20 patients included [7−9].

Due to this lack of information on the outcome, the aim of this retrospective analysis was to analyze the surgical outcome of Cx in patients with locally advanced pT4 BCa with focus on complication rates, overall survival (OS), and cancer-specific survival (CSS) as well as related subgroup analyses to identify patients that might benefit most from surgery.

2. Patients and methods

2.1. Study design

Between January 2008 and September 2017, a total of 905 patients underwent radical Cx in the Department of Urology, Technical University of Munich, Germany. Of these, 76 patients were diagnosed having histologically confirmed locally advanced stage pT4 BCa and were included in this retrospective analysis. Performing radical cystectomy as a standard procedure, hysterectomy and bilateral oophorectomy in female patients was included and prostatectomy was included in male patients. All patients uniformly received an ileal conduit as urinary diversion in an open procedure.

This retrospective analysis was approved by the independent ethics committee of the Technical University of Munich, Germany.

2.2. Data collection and classification of complications

Patients' data were collected from the hospitals electronic database. Included data were patients' comorbidities, preoperative laboratory values, preoperative radiologic findings, preoperative patients' symptoms, surgical treatment, duration of surgery, histopathology, rate of complications, intra- and postoperative blood transfusion rate, OS, and CSS.

We used the Charlson Comorbidity Index (CCI) for summarizing patients' comorbidities [10]. The American Society of Anaesthesiologists' (ASA) classification of physical health was applied to describe the patients' preoperative general health status (ASA 1: normal healthy patient (pt.), ASA 2: pt. with mild systemic disease, ASA 3: pt. with severe systemic disease, ASA 4: pt. with severe systemic disease that is a constant threat to life, ASA 5: moribund pt. who is not expected to survive without the operation) [11]. For our analysis, we grouped the patient population with ASA-score 1-2 and ASA-score ≥3, as an ASA-score ≥3 is associated with higher risk of surgical complications and an increased risk of mortality [12,13]. Clavien-Dindo grading was used for postoperative classification of complication rates 30 and 90 days after to surgery [14].

2.3. Outcomes

OS and CSS were defined as time from surgery to death from any cause or death from BCa, respectively. Subgroup analyses for OS and CSS were performed for the parameters: pT4a/b, presence of visceral and lymph node metastases, surgical margin status, histological subtype, gender, age, ASA-score, CCI, hemoglobin, and intraoperative blood transfusion.

2.4. Statistical analysis

Time-to-event variables and associated 95% confidence intervals (CIs) with log-rank statistics were calculated with the use of the Kaplan-Meier method. We used the median value to dichotomize ASA-score, CCI, and hemoglobin. We performed a multivariate Cox-regression analysis for OS with oncological relevant variables (N-/M-/R-status) and with those variables being significant in univariate analysis (hemoglobin, ASA-score). Data analysis was performed using SPSS version 25.0.

3. Results

3.1. Patient population and perioperative characteristics

Overall, 76 patients were treated with Cx for pT4 BCa. The median age of patients was 74 (range 42−90) years and the median value of the CCI 9 (range 2−13). Overall, 46 (61%) patients presented with symptomatic disease including urinary retention, chronic pain, recurrent macrohematuria, considering that no information is available for 15 (20%) patients (Table 1).

Preoperative imaging indicated 44 (58%) patients not having metastasis or locally advanced tumor infiltrating neighboring organs or bone (cT4b). A total of 21 (28%) patients were suspected of having lymph node or visceral metastasis. In 7 (9%) patients, imaging showed a locally advanced tumor infiltrating neighboring organs. However, no preoperative imaging results were available for 4 (5%) patients.

Preoperatively, the physical status was estimated as poor (ASA-score ≥3) in 40 (52%) patients. Neoadjuvant chemotherapy with gemcitabine/cisplatin was conducted in 9

Table 1
Baseline patient characteristics and final histopathology

Gender, number of patients (%)	
Male	56 (74)
Female	20 (26)
Age, years	
Median	74
Interquartile range	67-81
Absolute range	42-90
ASA-score, number of patients (%)	
1	6 (8)
2	30 (40)
3	39 (51)
4	1 (1)
Preoperative laboratory values, median (range)	
Hemoglobin (g/dl)	11.7 (8.9−16.2)
Preoperative radiologic findings, number of patients (%)	
No lesion	44 (58)
N1 pelvis	3 (4)
N2 pelvis	11 (14)
N+ distant	2 (3)
M+	5 (7)
cT4b	7 (9)
No information available	4 (5)
Preoperative symptoms, number of patients (%)	
No symptoms	15 (20)
Urinary retention kidney	12 (16)
Urinary retention bladder	1 (1)
Chronic pain	8 (11)
Recurrent macrohematuria	23 (30)
Urge symptoms	2 (3)
No information available	15 (20)
pT4-status, number of patients (%)	
pT4a	57 (75)
pT4b	19 (25)
pN-status, number of patients (%)	
c/pN0	35 (46)
c/pN+	41 (54)
cM-status, number of patients (%)	
c/pM0	62 (82)
c/pM1	14 (18)
Peritoneal carcinomatosis	7 (9)
Bone	4 (5)
Lung	4 (5)
R-status, number of patients (%)	
R0	43 (57)
R1/2	33 (43)
Histopathologic subtype, number of patients (%)	
Urothelial carcinoma (predominant)	62 (82)
Squamous cell carcinoma	13 (17)
Adenocarcinoma	1 (1)
Chemotherapy, number of patients (%)	
Neoadjuvant	9 (12)
Adjuvant	8 (10)

(12%) patients, but was only completed with 3 to 4 cycles by 2 patients. The reasons for discontinuation of the chemotherapy were progressive disease ($n = 2$), adverse effects ($n = 2$), patients' incompliance ($n = 1$) and for 2 patients, the reason is unknown. The median duration of surgery was 4 hours 48 minutes (range 2:39−8:32 minutes). An intraoperative blood transfusion was necessary in 36 (47%) patients. Within 30 days postoperatively, 32 (42%) patients were given blood transfusion, whereas for 11 (15%) patients, no postoperative data on blood transfusion rate was available.

3.2. Clinical outcome

At a median postoperative follow-up of 8 months (range 0−85) 53 (70%) patients were dead. Median follow-up of patients being alive without disease recurrence was 86 months (range 28−144). During the follow-up period, 35 (46%) patients died due to progressive disease, 12 (16%) patients died of a noncancer-specific cause and for 6 (8%) patients the reason of death remains unknown.

Fifty-seven (75%) patients had pT4a and 19 (25%) patients had pT4b BCa. Preoperative imaging and postoperative histopathologic examination led to clinical or pathologic evidence of lymph node metastases in 41 (54%) patients (c/pN+) and distant metastases (c/pM+) were present in 14 (18%) patients. Any positive surgical margin (R+) was found in 33 (43%) patients.

Within the group of patients diagnosed with pT4a BCa, 14 (25%) patients presented with a combination of c/pN0 and c/pM0 and R0. Furthermore, 33 (58%), 12 (21%), and 18 (32%) patients showed a c/pN+, c/pM+, and R+ status, respectively. Only 3 (16%) patients with pT4b BCa had a favorable combination of c/pN0 and c/pM0 and R0. The number of patients with c/pN+, c/pM+, and R+ in this group was 8 (42%), 2 (11%), and 15 (79%), respectively.

The median OS for all patients was 13.0 months (95% CI 9.7−16.3). Analyzing the association between gender, age, tumor stage, metastases, surgical margin status, histological subtype, hemoglobin, intraoperative blood transfusion, CCI, and ASA-score with OS, the ASA-score of 1 to 2 and a hemoglobin value ≥11.7 g/dl correlated significantly with prolonged OS (Table 2). OS for patients with ASA-score 1 to 2 was 17.0 vs. 7.0 months for patients with ASA-score ≥3 (P = 0.03). OS for patients with a hemoglobin value ≥11.7 g/dl was also 17.0 vs. 7.0 months for patients with hemoglobin <11.7 g/dl (P = 0.03). The corresponding Kaplan-Meier curves are shown in Fig. 1. The 12-and 24-month OS rate was 38% and 10%, respectively.

For all patients, the median CSS was 16.0 months (95% CI 11.2−20.8). None of the analyzed parameters showed any statistically significant association with CSS (Table 2).

In a multivariate analysis, we included oncologic relevant variables (N-, M-, R-status) together with those variables being significant on univariable analysis (ASA-score, hemoglobin). However, none of the variables in the multivariate analysis presented significantly as an independent prognostic marker (Table 3). Nonetheless, an ASA-score ≥3 showed a trend but did not reach conventional level of significance (P= 0.06).

Table 2
Univariate analysis for overall survival and cancer-specific survival

	No. patients (%)	Median 0S, months (95% CI)	*P*	Median CSS, months (95% CI)	*P*
All patients		13.0 (9.7−16.3)		16.0 (11.2−20.8)	
Female	56 (74)	8.0 (1.8−14.2)		16.0 (11.8−20.2)	
Male	20 (26)	13.0 (9.3−16.7)	0.9	N.A.	0.3
>75 years	37 (49)	13.0 (8.8−17.2)		14.0 (9.5−18.5)	
<75 years	39 (51)	13.0 (6.8−19.2)	0.9	16.0 (6.0−26.0)	0.8
pT4a	57 (75)	12.0 (7.1−16.9)		17.0 (11.8−22.2)	
pT4b	19 (25)	13.0 (10.4−15.6)	0.9	16.0 (10.1−21.9)	0.9
c/pM0	62 (82)	13.0 (9.0−17.0)		17.0 (10.1−23.9)	
c/pM1	14 (18)	9.0 (0.0−20.1)	0.4	13.0 (4.8−21.2)	0.4
c/pN0	35 (46)	13.0 (6.5−19.5)		25.0 (9.9−40.1)	
c/pN+	41 (54)	12.0 (7.8−16.2)	0.6	14.0 (10.4−17.6)	0.2
R0	43 (57)	14.0 (7.2−20.8)		17.0 (3.2−30.8)	
R1/2	33 (43)	11.0 (6.0−16.0)	0.4	13.0 (10.0−16.0)	0.3
Urothelial subtype	57 (75)	13.0 (1.1−15.2)		20.0 (11.0−41.0)	
Other subtype	19 (25)	6.0 (2.4−10.7)	0.9	16.0 (2.2−20.3)	0.8
ASA 1−2	36 (47)	17.0 (13.9−20.1)		20.0 (14.6−25.4)	
ASA ≥3	40 (53)	7.0 (4.2−9.8)	**0.03**	13.0 (11.2−17.3)	0.3
CCI <9	36 (47)	15.0 (5.1−25.0)		17.0 (10.1−24.0)	
CCI ≥9	40 (53)	12.0 (9.1−15.0)	0.6	13.0 (11.0−15.2)	0.4
Intraop. transfusion	40 (53)	16.0 (11.0−21.0)		17.0 (8.9−25.1)	
No intraop. transfusion	36 (47)	8.0 (1.7−14.3)	0.1	14.0 (9.8−18.2)	0.3
Hb <11.7 (g/dl)	39 (51)	7.0 (3.3−11.0)		13.0 (8.0−18.1)	
Hb ≥11.7 (g/dl)	37 (49)	17.0 (7.8−26.2)	**0.03**	20.0 (12.0−28.5)	0.1

Significance for bold values is < 0.05.

3.3. Complication rates

Most common complications were respiratory insufficiency, pneumonia, ileus/subileus, and urinary tract infection. Detailed information on complications classified by organ system within 30 and 90 days is reported in the Supplementary Table 1. Within 30 and 90 days after surgery 21% ($n = 16$) and 30% ($n = 24$) of the patients, respectively, developed severe complications (Clavien grade ≥3; Table 4).

Overall, 30- and 90-day mortality rates (Clavien grade 5) were 9% ($n = 7$) and 11% ($n = 8$), respectively (Table 4). Reasons of death were acute coronary syndrome ($n = 1$), respiratory insufficiency ($n = 3$), asystolic event ($n = 3$) and pneumonia ($n = 1$). Of patients who died within 30 and 90 days postoperatively, 86% (6 of 7 pts.) and 75% (6 of 8 pts.) had an ASA-score ≥3, respectively.

4. Discussion

Radical cystectomy is still the standard of care procedure for patients with muscle-invasive BCa [15]. At the time of diagnosis up to 2% of these patients present with locally advanced pT4 BCa [3]. In order to treat or prevent local complications including gross hematuria, pelvic pain, urinary retention, dysuria, or rectovesical fistula palliative Cx may be necessary.

However, available data for the outcome of Cx in patients with pT4 BCa are limited to a few retrospective cohort studies with a limited number of patients included. Nagele et al. reported a series of 20 patients with Cx due to local complications. Two out of 20 patients showed major complications of acute renal failure and enterocutaneous fistula due to surgery [7]. Seven patients had minor complications (minor wound infection, lower extremity paresthesia/-edema, clinically insignificant pulmonary embolism). After a follow-up of 20 months, 11 patients were alive. In a study of Zebic et al., 7 patients aged ≥75 years underwent Cx in palliative intent, but only in 3 of these patients surgery was performed due to BCa stage pT4a [8]. Three patients died due to complications within 3 months after surgery.

In our retrospective cohort study, 76 patients were treated with Cx for pT4 BCa, whereof 61% had local symptomatic disease and 78% had diagnosis of metastatic disease or positive surgical margin. The 30- and 90-day mortality rates for patients with locally advanced BCa were 9% and 11%, respectively. The mortality rate is relatively high compared to curative Cx series for patients with bladder cancer ≥ pT2, which has been reported in the range of 1.2% to 3.2% at 30 days and 2.3% to 8.0% at 90 days [15−21]. An explanation for this observation is given by the results of the subgroup analysis. At association analyses with OS, only a poor general patient condition defined by ASA-score ≥3 and a hemoglobin value <11.7 g/dl was significantly associated with shorter OS. Moreover, 86% of the patients who died within 30 days postoperatively had an ASA-score ≥3. Our finding correlates with previously published cystectomy series [17,18]. Thus, our study revealed that the ASA-score strongly indicates to be a relevant and

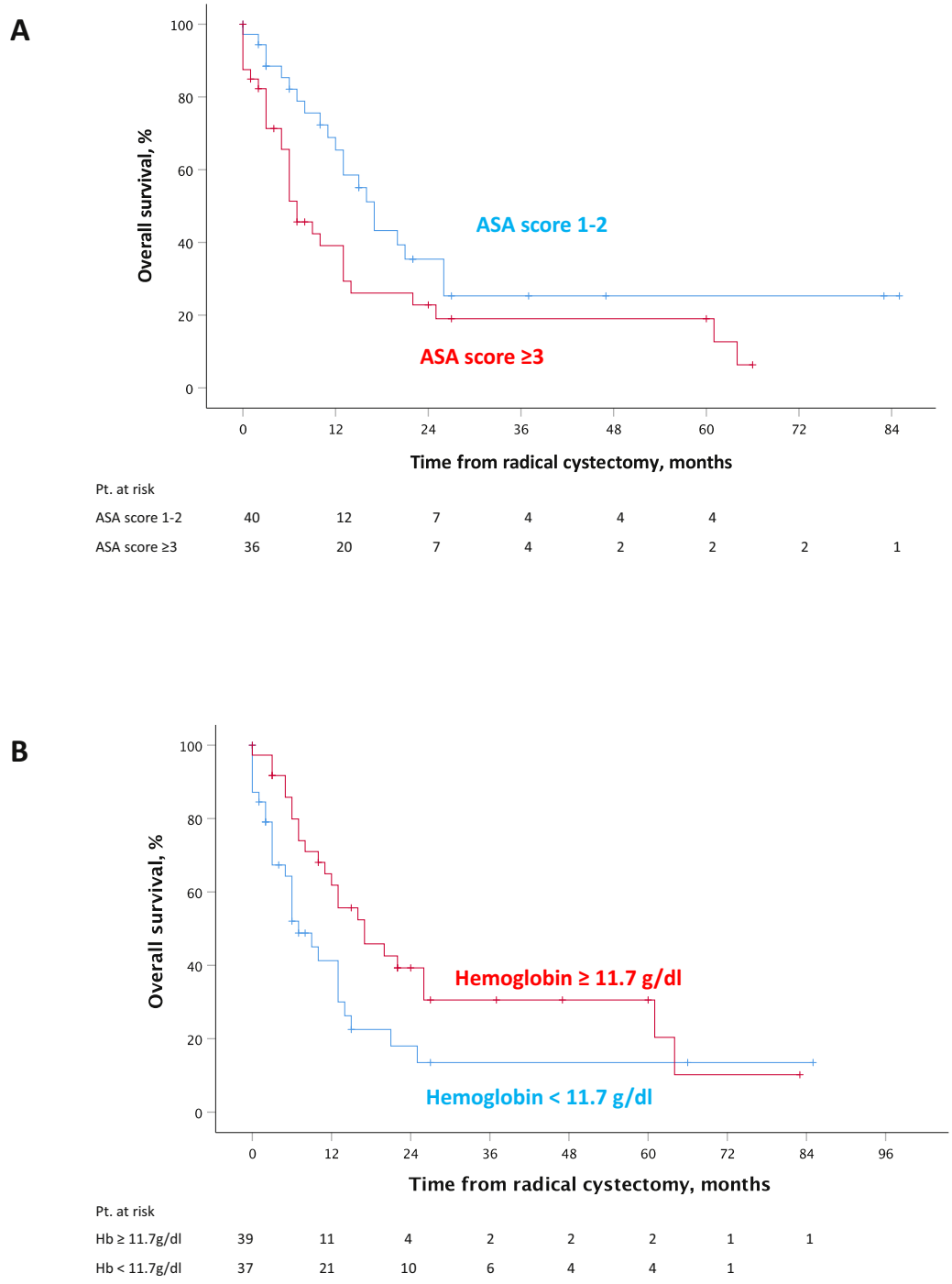

Fig. 1. Overall survival of patients with ASA-score 1-2 vs. ASA-score ≥3 (A) and hemoglobin ≥11.7 g/dl vs. <11.7 g/dl (B).

easily accessible tool, to rate the patient's condition and estimate postoperative outcome for palliative Cx in addition to cancer-specific variables. Our results regarding the preoperative hemoglobin value are comparable to those of other studies. For patients with BCa, Schubert et al. reported a decreased hemoglobin value (<12 g/dl) to be associated with significant lower 3-year OS rates [22].

However, neither tumor stage, metastasis status, margin status, gender, or age were significantly associated with OS or CSS. This differs to the abovementioned studies, as age (<70 vs. >70 years), tumor stage (organ confined vs. not organ confined, lymph node negative vs. lymph node positive) had prognostic relevance for OS. However, a lack of statistical significance may be due to the limited number of patients in our analysis.

Patients' characteristics ($n = 8$) surviving 36 months or more are heterogeneous. Only 3 of these 8 patients had a favorable pathology of pT4a, pN0, cM0, R0. One patient

Table 3
Multivariate analysis

	Category	HR	95% CI	*P*
ASA-score	≥3 vs. 1−2	1.8	1.0−3.3	0.06
Lymph node metastasis (pN)	+ vs. 0	1.3	0.7−2.3	0.4
Distant metastasis (c/pM)	+ vs. 0	1.3	0.5−3.2	0.6
Margin status (R)	+ vs. 0	1.3	0.8−2.0	0.3
Hemoglobin	≥11.7 vs. <11.7	0.6	0.4−1.1	0.12

Table 4
Complications classified by Clavien grade and reason of death[a]

Clavien grade	Within 30 days, number of patients (%)	Within 90 days, number of patients (%)
No complication	23 (30)	17 (22)
1	4 (5)	2 (3)
2	25 (33)	25 (33)
3	11 (14)	19 (23)
3a	5 (7)	9 (10)
3b	6 (8)	10 (13)
4	5 (7)	5 (7)
5	7 (9)	8 (11)
Reason of death		
Acute coronary syndrome	1	
Respiratory insufficiency	3	
Asystolic event	3	
Pneumonia		1

[a] For complications classified by organ system, see Supplementary Table 1.

had a pT4b, pN0, cM0, R0 histology. Five patients presented with pT4a, pN+ or R+ (ureter both sides) BCa. Patients' perioperative or palliative chemotherapy treatment due to progression was heterogeneous as well (1 patient: neoadjuvant chemotherapy, 1 patient: adjuvant chemotherapy, 3 patients: palliative chemotherapy). Due to this heterogeneity of patient characteristics and the small number of patients, no statement can be made about possible influencing variables on long-term survival.

As a validated instrument the ASA-score can be applied to assess the risk of postoperative complications. For bladder cancer patients with an ASA-score ≥3, a higher risk for complications has been reported [23−25]. Subsequently, patients should be informed preoperatively about possible postoperative complications related to their general condition.

The rate of patients with severe complications (Clavien grade ≥3) 90 days after surgery was 30%, which is comparable to curative Cx studies. In a large single-center study including 1,000 patients as well as in a large prospective mutlicenter study including more than 400 patients with BCa, the rate of severe complications was reported with 22% and 29%, respectively, within 90 days after Cx [17,21].

Median OS in our study population is 13.0 months. Hautmann et al. reported data for OS in patients with pT4a/b, pN0, cM0 BCa with a median OS of about 66 months [18]. However, in the same study population, OS for patients with any T category (pT1-4) and a pN+ status was significantly reduced to an OS of 14% after 20 years. Finally, the comparability with our data is limited due to different patient characteristics.

Limitations of this study are its retrospective design and the limited number of patients. Even in a high-volume university hospital, the number of patients with very advanced BCa selected for surgery is limited in a time period of almost 10 years. These data should be validated in prospective multicenter studies along with collection of quality of life data as it is an essential endpoint for patients.

5. Conclusion

To our knowledge, this is the largest series for patients with locally advanced pT4 BCa undergoing Cx. Cx performed in patients with locally advanced pT4 BCa is associated with an increased mortality rate within 90 days postoperatively. Our study revealed that the ASA-score is a relevant and easily accessible tool to rate the patient's condition and estimate the postoperative outcome rather than detailed cancer-specific variables. Subsequently, patients should be informed preoperatively about possible postoperative complications and their risk of fatal complications related to their general condition.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.11.042.

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