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The time from diagnosis of bladder cancer to radical cystectomy in Polish urological centres – results of CysTiming Poland study

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Introduction The aim of the study was to assess the waiting time, from establishing the indications for radical cystectomy to surgery, in patients with urothelial carcinoma of the bladder at different Polish urological centres and to determine its influencing factors.

Material and methods Retrospective analysis of data was performed on all consecutive radical cystectomies, performed in 2008–2012, at 10 Polish urological centres. The waiting time of patients from establishing the indications for radical cystectomy to surgery, as well as factors potentially influencing this time, were assessed. University (3), provincial (3) and regional (4) hospitals were defined as the 3rd, 2nd and 1st level referral hospitals, respectively.

Results A total of 575 patients qualified for radical cystectomy due to muscle invasive urothelial carcinoma of the bladder (MIBC, 68% of cases) or failure of previous treatment of non–muscle invasive urothelial carcinoma of the bladder (NMIBC, 32%) were included in the analysis. The average time after the establishment of indications to surgery was 73.4 days, with a median of 56 days. In the case of 121 patients (22.1%), the waiting time exceeded 90 days. Significant differences in waiting time were found when the hospital referral levels were taken into consideration. In the 3rd level referral hospitals the median time for cystectomy was 61.5 days (p = 0.035), in the 2nd level referral hospitals – 45 days (p = 0.000) and, in the 1st level referral hospitals – 58 days (p = 0.051).

Conclusions The waiting time from establishing the indications for radical cystectomy to surgery for most cases in Poland does not exceed 90 days.

Key Words: bladder cancer ‹› cystectomy ‹› timing of cystectomy

INTRODUCTION

Radical cystectomy is a standard method of treatment of muscle invasive bladder cancer (MIBC) which has been clinically and/or pathologically assessed as T2–T4a, N0–Nx, M0 stage [1, 2]. However, the frequency of patients diagnosed with non–muscle invasive bladder cancer (NMIBC) with poor prognostic

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factors (high–risk and recurrent superficial tumors, BCG–resistant CIS, T1G3) that undergo surgery is increasing and nowadays accounts for 15% of cases [3]. Many authors emphasize that the appropriate timing of surgery is crucial in terms of improving oncological results. A cystectomy delay of over 90 days since primary diagnosis of muscle invasive disease has been associated with local tumor progression [4], worsened progression–free survival [5], decreased cancer–specific survival, and decreased overall survival (OS) [6]. Reducing the time from establishing the indications for radical cystectomy to surgery increases the chance of diagnosis of organ confined disease, as well as decreases recurrence rates and improves overall survival of patients. According to current standards, as mentioned above, efforts should be made to reduce the time from diagnosis to surgery to less than 3 months. The aim of the study was to assess the waiting time of patients, with urothelial carcinoma of the bladder, from establishing the indications for radical cystectomy to surgery in Polish urological centres and to determine its influencing factors.

MATERIAL AND METHODS

Retrospective data analysis on all consecutive radical cystectomies that were performed in 2008–2012 in 10 Polish representative urological centres was performed. The time delay (in days) was calculated as follows. In cases of muscle invasive tumor it was the time from receiving the result of post transurethral tumor resection specimen to the radical surgery. In cases of NMIBC, it was again time to the radical surgery, but calculated from the moment when the histopathological result of post transurethral tumor resection specimen, pinpointing the failure of previous treatment (BCG failure, pT1G3 + Carcinoma in situ), was received.

The primary diagnosis of bladder tumors was established based on post transurethral tumor resection specimens. No neoadjuvant chemotherapy was administered. All of the patients underwent open radical cystectomy with extended lymphadenectomy. The waiting time of patients from establishing the indications for radical cystectomy to surgery, as well as factors potentially influencing this time, were assessed. The diversity of the centres together with an experience in radical cystectomies was of greatest importance when forming CysTiming Poland study group members. University (n = 3), provincial (n = 3) and regional (n = 4) hospitals were defined as the 3rd, 2nd and 1st level referral hospitals, respectively. Four centres, in which during the study period more than 60 cystectomies had been performed, were defined as high–volume centres (HV), while the remaining low–volume centres (LV). The statistical significance was calculated with Mann–Whitney U test with Statistica® software.

RESULTS

A homogenous contemporary series of 575 patients with MIBC (78% of cases) or with failure of previous treatment of NMIBC (32%) were included in the analysis. There were 105 women, with a mean age of 66 years (range 46–85 years), and 470 men with a mean age of 65 years (range 43–90 years). The average time from the establishment of indications to surgery was 73.4 days, with a median of 56 days, and within a range from 0 to 1217 days. For 127 patients (22%), the waiting time exceeded 90 days. The effects of the analyzed factors on timing of radical cystectomy are shown in Table 1.

In the majority of cases, the pathological T stage after cystectomy was discordant with post transurethral bladder resection of bladder tumor (TURBT) specimen, but the median time to surgery was similar (discordant *vs.* concordant 52 *vs.* 56 days, p = 0.12). In case of NMIBC the median time to surgery was the same as in MIBC, at 56 days (p = 0.77). Additionally, the cancer grade was not observed to impact timing of radical cystectomy. Median time

Table 1. *Potential effects on timing of radical cystectomy that were assessed in the study*

	Tumor stage		pT stage: TURBT *vs.* radical cystectomy		Cancer WHO grade		Patients' gender		Patients' age				Referral level of the hospital			Case load in the centre	
	MIBC, n=417	NMBIC n=133	Concordant, n=98	Discordant, n=445	1–2, n=190	3, n=362	Male, n=459	Female, n= 102	<60 yrs, n=136	>60 yrs, n=425	<70 yrs, n=361	>70 yrs, n=200	IIIrd, n=208	IInd, n=151	Ist, n=202	HV, n=315	LV, n=246
Mean	68	90	71	73	79	70	74	70	72	73.5	73	73	76	63	77	70	77
Median	56	56	52.5	56	53.5	56	56	55.5	54	56	56	56	61.5	45	58	55	58
Range	0–480	2–1217	6–735	0–1217	2–1217	0–575	0–1217	3–480	6–427	0–1217	2–735	0–1217	0–1217	2–480	6–575	0–1217	2–735
p value	0.77		0.12		0.94		0.67		0.78		0.86		0.035	0.000	0.051	0.11	

MIBC – muscle invasive bladder cancer, NMIBC – non-muscle invasive bladder cancer; TURBT – transurethral resection of bladder tumor; HV – high volume center, LV – low volume center. The statistical significance was calculated with Mann–Whitney U test.

noticed among patients with tumors graded as 1 or 2 and graded as 3 according to WHO classification was 53.3 and 56 days (p = 0.94).
For the patients aged below 60 years, the median time to cystectomy was 54 days and for patients aged over 60–56 days (p = 0.78). Furthermore, when one changed the age limit for the analysis to 70 years, for both people over 70 years old and younger, the median time was 56 days (p = 0.86). In case of gender, the median time was the same for female and male patients and amounted to 56 days (p = 0.67).
In centres in which there were >60 cystectomies performed during the study period, the median time to cystectomy was 55 days. In low–volume centers (LV, number of patients n= 246) median time to cystectomy was 58 days (p = 0.11).
Significant differences were noted when referral levels of hospitals were analyzed. In the 3rd level referral hospitals the median time for cystectomy was 61.5 days (p = 0.35, III *vs.* I+II), in the 2nd level referral hospitals it was 45 days (p = 0.00001, II *vs.* I+III), and finally, in the 1st level hospitals it was 58 days (p = 0.051, I *vs.* II+III).

DISCUSSION

The Polish urological community lacks detailed knowledge on the outcomes of the radical cystectomies performed in Poland, especially as far as oncological data are concerned (overall survival, cancer specific survival) [7]. Some authors emphasize that the common scenario in Poland, as for the primary diagnosis of bladder cancer after episode of hematuria, is a few month delay in the appropriate treatment, which in turn hampers the already poor oncological results post surgery [7]. However, this delay may not be the only factor increasing the time span until cystectomy as analyzed in the study. The data on 5–year overall survival (OS) and median survival (12–14 months) from a few Polish centres (OS = 21–24.6%) [7, 8] does not correlate with worldwide data (e.g. from USA), which although is far from satisfactory is still far more optimistic (OS = 66%) [9]. In Western Europe, 5–year overall survival after radical cystectomy performed due to non–muscle invasive disease reaches 68%. However, in patients with advanced T3 and T4 tumors, it does not reach 30% [10]. The oncological outcome is connected with the lymph node status, as well. Hautmann reported only 20% 5–year progression free survival when lymphadenectomy revealed metastases [11]. It is assumed, however, that aggressiveness of the disease and clinical stage at the time of diagnosis determine the outcome, but the data from the literature is not unambiguous. For example, there are no analyses available concerning the influence of transurethral resection of the bladder tumor (TURBT) performed prior to cystectomy on the resulting oncological outcome [7]. Moreover, several other therapeutic options for MIBC have been developed, which may affect the cystectomy timing e.g. radical transurethral resection and chemotherapy [12, 13].
In this study we analyzed some of the factors that may influence the timing of cystectomy after primary diagnosis, as established by TURBT. A relevant and unfavorable effect of time delay of initiating therapy before radical cystectomy on oncological results has been proven in many studies. Herr et al. reported that only when the duration of conservative treatment does not exceed 2 years, can one obtain better results of cystectomy in patients treated due to non–muscle invasive bladder cancer unresponsive to BCG therapy [14, 15]. Furthermore, Chang et al. revealed that a 90–day span until cystectomy leads to an increased frequency of more advanced tumors (>T2) from 50 and up to 80% [4]. Finally, the inappropriate timing may affect not only the oncological results but also the method of urinary diversion. In the paper by Hautmann et al, in case of organ–confined disease, the average time from diagnosis to cystectomy was 12.2 months in the group of orthotopic neobladder recipients, and 19.1 months in the group of ileal conduit recipients [16]. However, in case of disease >T2, the difference reached 12 months, i.e. in patients with orthotopic neobladder formation, the time to surgery was 3.1 months, while in patients with ileal conduit – 15.1 months. Similar results were reported by Sanchez–Ortiz, who emphasized that the 90–day span defines the border, which if crossed, leads to significantly worse oncological results in the future [17].
In Polish centres the median span from primary diagnosis to cystectomy was 56 days. That number differed scarcely when various factors were analyzed (e.g gender, muscle invasiveness, cancer grade, age, hospital case load). However, some authors claim that patient's age, gender (male), and type of hospital facility were associated with longer waiting times [18]. It should be emphasized that in the substantial number of cases (22%) radical cystectomy was postponed significantly, i.e. over 90 days. In case of NMIBC the time span reached 56 days. In a paper by Cookson et al. [19], a group of 86 patients with high–risk T1, Ta, and Tis bladder tumors who received repeated TURs and BCG therapy were followed for 15 years and the median time to cystectomy among patients having had early cystectomy was 9 months, *versus* 54 months for patients having had delayed cystectomy. Significant differences were found when the hospital referral level was estimated as a factor influencing the timing. It was proved that in provincial centres,

the median time to cystectomy was shorter than in university and regional hospitals. Inversely, median time to cystectomy in university hospitals was significantly longer than in provincial and regional centres. In a paper by Alva et al., the most common factor contributing to time span to cystectomy was "scheduling issues" [20].

Some studies reported that earlier cystectomy is proposed and accepted by patients when orthotopic bladder is chosen for urinary diversion [16, 21]. In our paper, the majority of patients received ileal conduit and this data was not analyzed further in terms of acceptance of such a method of diversion.

CONCLUSIONS

In conclusion, the waiting time from establishing the indications for radical cystectomy to surgery in most cases in Poland does not exceed the limit of 90 days. It was shown that in provincial centres, the median time to cystectomy is shorter than in both university and regional centres.

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