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Timing of radical cystectomy in Central Europe – multicenter study on factors influencing the time from diagnosis to radical treatment of bladder cancer patients

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Introduction Time that passes between an unfavourable diagnosis to a radical cystectomy (RC) affects oncological outcomes in patients with bladder cancer. Unsatisfactory survival of patients after RC in Central Europe can potentially result from this factor.

Material and methods The aim of this study was to assess the time interval between transurethral resection of the bladder tumor (TURBT) and RC in Central Europe and to identify clinical factors of possible delays. 941 consecutive patients who underwent RC in nine Central European urological centers were enrolled into the study. After the TURBT–RC time was calculated, selected clinical and pathological parameters were tested as potential factors influencing the timing of RC.

Results On average, RCs were performed 73.8 days after TURBTs (median – 53, range 0–1587). In 238 patients (25.3%) the time exceeded 12 weeks. Patients with muscle–invasive cancer were operated earlier on than patients with nonmuscle–invasive cancer (67.6 *vs.*105.2 days, RR = 1.41, p = 0.00). In high volume centers (>30 RC per year) longer TURBT–RC intervals were observed (97.6 *vs.* 66.3 days, RR = 2.49, p = 0.00). Simultaneously, factors such as female sex (RR = 1.21), more advanced age of patient (>65 years, RR = 1.23), presence of concomitant CIS (RR = 2.43), grade of cancer cells (RR = 1.67) and final post–RC stage (RR = 1.51) had no statistically significant effect on the results (p >0.05).

Conclusions The mean time interval between the diagnosis and radical treatment of patients with bladder cancer in Central Europe is adequate. However, there are still a relatively high number of patients waiting for radical cystectomy longer than 8 weeks. A lower stage of disease as well as a higher case load within of a hospital may delay the surgery.

Key Words: bladder cancer ‹› cystectomy ‹› time to treatment ‹› preoperative care ‹› clinical practice pattern

INTRODUCTION

Radical cystectomy (RC) remains the treatment of choice in patients with muscle–invasive bladder cancer (MIBC), as well as with nonmuscle–invasive bladder cancer (NMIBC), which has the highest risk of progression [1, 2]. Despite improvements in diagnosis and surgical techniques, the oncologi-

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cal results of the surgery are far from being satisfactory. Currently reported 5–year overall survival in large series of patients is as low as 29–63% [3, 4, 5]. In Central Europe these numbers may be even be lower [6, 7]. There are many factors potentially influencing outcomes of RC, including patient–, cancer– and urologist–related factors. The time from undertaking the decision about RC to surgery is one of the most prominent. While the general rule is "the shorter the time, the better the results", it is proven that exceeding the 12–week or 3–month time period is associated with more advanced cancer stages and reduced survival [8–13]. Until now the data on the timing of RC has been limited, while in Central Europe only Polish data has been recently published [14].

The aim of this study was to assess the time that patients with bladder cancer wait from TURBT to RC in Central European countries and to determine the underlying factors for possible delays.

MATERIAL AND METHODS

Retrospective analysis, covering 941 consecutive patients who underwent RC between 2007 and 2013 in nine Central European hospitals from 4 countries was performed. The single inclusion criterion was RC performed due to bladder cancer within the analysed study period. Exclusion criteria were not established. Table 1 presents the detailed characteristics of this study population.

Primary study endpoint was the time from TURBT to RC. In patients with a history of multiple TURBT, the date of the last resection was analysed. Additionally, an attempt to identify clinical factors influencing primary endpoint was taken. These factors included patient age and sex, cancer grade and stage diagnosed histologically in the TURBT specimen,

Table 1. *Detailed characteristics of study population resection of bladder tumor*

Number of patients	941
Number and percentage of men	729 (77.5%)
Number and percentage of women	212 (22.5%)
Mean age of patients and standard deviation	65.2 ±8.6 years
Range	29–89 years
Number and percentage of patients according to stage of bladder cancer diagnosed after TURBT	
Stage Ta	10 (1.1%)
Stage T1	139 (14.8%)
Stage T2–T4	762 (81.0%)
Carcinoma in situ	7 (0.7%)
Stage not available	23 (2.4%)
Number and percentage of patients according to stage of bladder cancer diagnosed after RC	
Stage T0	34 (3.6%)
Stage Ta	10 (1.1%)
Stage T1	81 (8.6%)
Stage T2	244 (25.9%)
Stage T3	318 (33.8%)
Stage T4	233 (24.8%)
Carcinoma in situ	14 (1.5%)
Stage not available	7 (0.7%)

RC – radical cystectomy; TURBT – transurethral resection of bladder tumor

Table 2. *Time from TURBT to RC observed within the study group in total and separately for each study center. Study centers are randomly named with successive letters of the alphabet*

Study center	Character of study center	Number of RC performed within analysed period	Percentage of patients qualified for RC due to NMIBC	TURBT–RC time in days			Percentage of patients in whom TURBT–RC time exceeded 84 days
				Mean value	Standard deviation	Range	
TOTAL	Academic and regional hospitals	941	17	73.8	92.8	0–1587	25.3
A	Academic hospital	101	26.0	62.2	65.8	7–570	17.2
B	Regional hospital	28	10.7	71.2	103.8	12–562	17.9
C	Academic hospital	227	13.7	97.2	74.3	8–617	46.1
D	Academic hospital	175	17.6	76.4	95.6	0–1217	33.9
E	Regional hospital	58	10.3	52.5	22.3	4–90	10.3
F	Regional hospital	107	18.4	70.1	66.9	4–575	23.2
G	Academic hospital	29	41.4	93.3	284.6	3–1587	10.3
H	Academic hospital	137	0.0	44.5	6.1	33–68	0.0
I	Regional hospital	101	34.7	78.0	120.8	3–720	22.8

NMIBC – non muscle–invasive bladder cancer; RC – radical cystectomy; TURBT – transurethral resection of bladder tumor

final cancer stage diagnosed histologically in the RC specimen, as well as the case load of the hospital.
All statistical calculations were performed using Statistica 10.0 Software. Shapiro–Wilk test confirmed the normal distribution of all variables. Levene test was applied for the assessment of the equality of variances. If the result was <0.05, F–Welch test was used for comparison of the differences between subgroups. Otherwise, results were compared with an unpaired t–test.

RESULTS

The mean time from TURBT to RC was 73.8 days and the 12–week (84 days) interval was exceeded in 238 patients (25.3%). Table 2 summarizes the results and presents data obtained in each study center. Table 3 presents the influence of basic clinical and pathological features on the primary study endpoint. Time to RC occurred to be dependent with statistical significance on muscle invasiveness of the cancer diagnosed in the TURBT specimen and the case load of the hospital. Patients with NMIBC were operated on average 38 days later than patients with MIBC. This led to a 10% increase in the absolute risk and 1.4 fold higher relative risk of exceeding the 84–day time frame in the group of NMIBC patients. Interestingly, in high volume centers defined as hospitals, there were over 30 cystectomies performed annually, with the mean time from TURBT to RC being longer by 31 days. The absolute risk increase and the relative risk of performing RC beyond the 84–day time frame in patients operated in high volume centres was 28% and 2.5, respectively. Finally, the impact of patient age, patient sex, presence of concomitant CIS foci, cancer grade, as well as final cancer stage was found to be statistically insignificant in relation to the time from TURBT to RC.

The age of patients operated within 8 weeks from TURBT was lower by 1.12 years in comparison to patients operated after 8 weeks (64.7 *vs.* 65.8 years, p = 0.05). No residual tumor at RC was found in 34 cases (3.6%). Among patients who qualified for RC due to NMIBC, MIBC were finally diagnosed in 96 cases (61.5%).

DISCUSSION

Time from establishing indications for RC to surgery correlates with the chance of diagnosis of an organ confined disease and affects recurrence–free, as well as overall survival [8–13]. Many studies addressed this issue in the past, as presented in table 4. Only one study did not reveal the relationship between the timing of RC and its outcomes [15]. With relatively consistent conclusions from these papers, experts of the European Association of Urology advise to not delay RC by more than 3 months [1].

We performed a retrospective analysis of the time from clinical qualification to RC in selected and representative urological centers of Central Europe. The study was conducted in both academic and non–academic hospitals to bring reliable data, that could be extrapolated to the region of Central Europe. The main finding was that mean and median time intervals remained within a frame of 3 months. However, one fourth of the patients waited for RC more than 12 weeks (84 days). Even if we would start counting days not from TURBT, but from pathological diagnosis, there would still be a 20% – portion of patients in whom RC was delayed. While we adopted the time from TURBT to RC as the most unequivocal, authors of papers cited in table 4 adopted time from initial diagnosis to RC. This can be defined as time from a pathological report, from additional imaging or from some additional clinical tests.

Table 3. *The influence of basic clinical and pathological features on the timing of radical cystectomy*

Variable	Definition	Number of cases	ARI >84 days	RR >84 days	Time (mean value)	P value
Patient age	>64 yrs *vs.* <65 yrs	501 *vs.* 439	5.2%	1.23	79.1 *vs.* 67.9 days	0.06
Patient sex	Female *vs.* male	212 *vs.* 729	5.1%	1.21	75.0 *vs.* 73.5 days	0.83
Initial cancer stage (TURBT)	NMIBC *vs.* MIBC	156 *vs.* 762	9.7%	1.41	105.2 *vs.* 67.6 days	0.00
Concomitant Cis	Present *vs.* absent	7 *vs.* 911	33.5%	2.43	90.4 *vs.* 73.9 days	0.64
Grade of cancer cells	HG tumors *vs.* LG tumors	582 *vs.* 343	11.9%	1.67	75.7 *vs.* 71.7 days	0.53
Final MIBC stage (RC)	T3&T4 tumors *vs.* T2 tumors	551 *vs.* 244	8.6%	1.51	73.2 *vs.* 63.6 days	0.15
Case load	>15 op/yr *vs.* <15 op/yr	690 *vs.* 251	9.4%	1.51	75.2 *vs.* 70.0 days	0.45
	>30 op/yr *vs.* <30 op/yr	226 *vs.* 715	27.6%	2.49	97.6 *vs.* 66.3 days	0.00

ARI > 84 days – absolute risk increase of RC performed >84 days from diagnosis; Cis – carcinoma in situ, HG – high–grade; LG – low–grade; MIBC – muscle–invasive bladder cancer; NMIBC – non muscle–invasive bladder cancer, op/yr – mean number of RC performed in a centre per year; RC – radical cystectomy, RR > 84 days – relative risk of RC performed >84 days from diagnosis; TURBT – transurethral resection of bladder tumor; yrs – years.

The strongest predictor for delayed RC in a recent study was qualification to surgery due to NMIBC. The subgroup of NMIBC patients that qualified for RC required special attention. Schrier et al. first showed that patients initially diagnosed as MIBC have more favourable prognosis compared to patients with progressive NMIBC [16]. The subgroup of patients with NMIBC who require RC is not always easy to identify. In addition, these patients are more likely to refuse RC compared to MIBC patients. However, in these cases RC should not be delayed, since with increasing time to RC, the survival decreases significantly [17–20]. What is more, the risk of being upstaged to MIBC increases with time to RC [18]. Interestingly, as much as 61.5% of NMIBC patients from a recent analysis were finally staged as MIBC. Hautmann et al. found also that the rate of non–organ confined disease and nodal metastasis is higher in patients qualified for RC after initial diagnosis than after recurrence [18]. However, nodal status was not analysed in our study.

Another statistically significant factor for the delay of RC in our study was the high case load of the hospital. This was probably the effect of the transfer time from other hospitals. Liedberg et al. observed significantly longer time to RC among patients who were referred to surgery from other hospitals. In the group of 141 patients they noticed the difference of 22 days (63 *vs.* 41 days) [15]. However, having an increased risk of delayed RC, patients operated on in high volume centers have lower surgical morbidity and mortality [21–24]. We should be very careful then when formulating final conclusions.

Within this analysis the impact of patient age on the time from TURBT to RC was also analysed. In older patients RC was associated with increased morbidity, which could potentially hamper the decision about surgery in both the urologist and patient [25]. In the recent study, clinically significant difference in time to RC was observed between representative groups of patients aged below and above 65 years. However, this difference remains statistically insignificant with a borderline p–value of 0.06. Also patient sex, presence of concomitant CIS foci, cancer grade and final cancer stage had no statistically significant effect on time from TURBT to RC.

Within this study, not all reasons for the possible delay of RC were analysed. Therefore, their identification is of utmost importance. From literature review the most common were patient–related, including the search for second medical opinion and the preference of surgery date. They covered 50–84% of cases [9, 10, 12]. Others included comorbidities and temporary medical contraindications, need for a transfer to the reference center, fear of surgery and related morbidity, as well as unsuccessful attempts of bladder–sparing treatment. In a historical cohort presented by Hautmann et al., the option of an ileal neobladder shortened the time to RC

Table 4. *The influence of RC timing on clinical outcomes*

Author, year	Number of patients*	Mean time from initial diagnosis to RC	Established maximal time interval	Percentage of patients operated within maximal time interval	Mean follow–up	Consequences of exceeding maximal time interval
Gore et al. 2009 [8]	441	n.a.	12 weeks	n.a.	n.a.	Increased risk of disease–specific mortality in 2–year follow–up – HR 7.7
Lee et al. 2006 [9]	214	61 days	93 days	87.9%	40 months	Higher overall mortality – 54% *vs.* 39% Higher disease–specific mortality – 35% *vs.* 25% No effect on the risk of non–organ confined disease
May et al. 2004 [10]	189	1.8 months	3 months	77.8%	40 months	Higher rate of T4 disease – 31 *vs.* 14% Decreased 5–year overall survival – 26% *vs.* 54% Decreased 5–year progression–free survival – 34% *vs.* 55%
Chang et al. 2003 [11]	153	63 days	90 days	87.6%	–	Higher rate of stage T3 or higher – 81% *vs.* 52%
Sanchez–Ortis et al. 2003 [12]	189	7.9 weeks	12 weeks	89.9%	36 months	Higher rate of extravesical (T3 or T4 and/or N+) disease – 84% *vs.* 42.8% Decreased 3–year overall survival – 34.9% *vs.* 62.1%
Hara et al. 2002 [13]	50	2.65 months	3 months	56%	50.8 months	Reduced 5–year recurrence–free survival – 52.5% *vs.* 86.9% Reduced 5–year overall survival – 47.3% *vs.* 80.3% Increased risk of vascular involvement – 73% *vs.* 46% No effect on the risk of non–organ confined disease

*Papers cited in table covers only MIBC cases

by almost one year. As a consequence, the survival rates were much higher in the neobladder group compared to the ileal conduit group [26]. We can suspect that the implementation of tissue engineering to reconstruction of the lower urinary tract will further improve this data; however, this technology is still challenging [27]. Recent analysis also did not include data on additional imaging, necessary before RC. While this issue was not addressed in previously published papers, authors cannot exclude that selection and extent of the imaging, as well as its availability also influence the time to RC. Finally Gore et al. noticed a longer time to RC among nonwhites and unmarried individuals. However, the differences were not statistically significant [8].

The Polish data on timing of RC was recently published [14]. The comparison of Central European data with Polish data seemed to be interesting. Both studies outlined the impact of the profile of the hospital on the time from TURBT to RC. In the Polish study, regional, but not university hospitals noticed the shortest time to RC. In our study, the longest time to RC was observed in high volume centers. However, the comparison of Polish and Central European results were significantly limited by at least two factors. First, Central European analysis covered data from 3 centers included into Polish analysis. Second, Polish analysis covered significantly less patients, which influenced statistical calculations.

The most important limitation of this study was the retrospective nature and hence the inclusion criterion of performed RC instead of qualification for RC. This probably reduced the number of patients requiring RC by ignoring patients who died before RC was performed, as well as patients who refused to be operated on.

CONCLUSIONS

The mean time interval between the diagnosis and radical treatment of bladder cancer patients in Central Europe is adequate. However, a significant percentage of patients wait for radical cystectomy longer than 12 weeks. Special attention must be paid to patients with high risk NMIBC, as well as those who need transfer to a reference hospital, since lower stage of the disease and higher case load of a hospital may delay the surgery.

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