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

Slawomir Poletajew¹, Bogdan Braticevici², Antonín Brisuda³, Victor Cauni⁴, Viacheslav Grygorenko⁵, Martyn–Zenovii Lesnyak⁶, Janusz Lisiński⁷, Cristian Persu⁸, Kacper Renk⁹, Piotr Radziszewski¹

¹Medical University of Warsaw, Department of Urology, Warsaw, Poland
²Burghele Clinical Hospital, Department of Urology, Bucharest, Romania
³Charles University, 2nd Faculty of Medicine, Teaching Hospital in Motol, Department of Urology, Prague, Czech Republic
⁴Colentina Clinical Hospital, Department of Urology, Bucharest, Romania
⁵National Academy of Medical Sciences of Ukraine, Institute of Urology, Department of Restorative Urology and Newest Technology, Kyiv, Ukraine
⁶Lviv Regional Clinical Hospital, Department of Urology, Lviv, Ukraine
⁷Pomeranian Medical University, Department of Urology and Urological Oncology, Szczecin, Poland
⁸Carol Davila Medical University, Department of Urology, Bucharest, Romania
⁹Ceynowa Hospital, Department of Urology, Wejherowo, Poland

Citation: Poletajew S, Braticevici B, Brisuda A, Cauni V, Grygorenko V, Lesnyak M-Z, et al. Timing of radical cystectomy in Central Europe – multicenter study on factors influencing the time from diagnosis to radical treatment of bladder cancer patients. Cent European J Urol. 2015; 68: 9-14.

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-
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 T0 | 34 (3.6%) |
| Stage T1 | 101 (10.7%) |
| Stage T2 | 726 (82.0%) |
| Stage not available | 7 (0.7%) |
| Number and percentage of patients according to stage of bladder cancer diagnosed after RC | |
| Stage T0 | 34 (3.6%) |
| Stage T1 | 10 (1.1%) |
| Stage T2 | 81 (8.6%) |
| Stage T3 | 244 (25.9%) |
| Stage T4 | 318 (33.8%) |
| Stage not available | 23 (2.4%) |
| Number of patients | 941 |
| Number and percentage of patients qualified for RC due to NMIBC | 17 |
| TURBT–RC time in days | |
| Mean value | 73.8 |
| Standard deviation | 92.8 |
| Range | 0–1587 |
| Percentage of patients in whom TURBT–RC time exceeded 84 days | 25.3 |

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

References

1. Witjes JA, Compérat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al. EAU guidelines on muscle–invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol. 2014; 65: 778–792.
2. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, et al. EAU guidelines on non–muscle–invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013; 64: 639–653.
3. Booth CM, Siemens DR, Li G, Peng Y, Tannock IF, Kong W, et al. Perioperative chemotherapy for muscle–invasive bladder cancer: A population–based outcomes study. Cancer. 2014; 120: 1630–1638.
4. Linder BJ, Frank I, Cheville JC, Tolleson MK, Thompson RH, et al. The impact of perioperative blood transfusion on cancer recurrence and survival following radical cystectomy. Eur Urol. 2013; 63: 839–845.
5. Sonpadve G, Khan MM, Lerner SP, Svatke RS, Novara G, Karakiewicz PI, et al. Disease–free survival at 2 or 3 years correlates with 5–year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. J Urol. 2011; 185: 456–461
6. Ossoliński K, Gilarowska A, Peller M, Dybowsi B, Radziszewski P, Borkowski A. Total survival after radical cystectomy in patient with urothelial bladder cancer. Cent European J Urol. 2012; suppl 1: 56.
7. Lemirski A, Pusużyński M, Kupś M, Słojewski M, Sikorski A: Treatment of invasive bladder tumors in Polish conditions – single center observations of 402 patients after radical cystectomy. Cent European J Urol. 2012; suppl 1: 55.
8. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS; Urologic Diseases in America Project. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results–Medicare analysis. Cancer. 2009; 115: 988–996.
9. Lee CT, Madri R, Daignault S, Dunn RL, Zhang Y, Montie JE, Wood DP Jr. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006; 175: 1262–1267.
10. May M, Nitzke T, Helce C, Vogler H, Hoschke B. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. Scand J Urol Nephrol. 2004; 38: 231–235.
11. Chang SS, Hassan JM, Cookson MS, Wells N, Smith JA Jr. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. J Urol. 2003; 170: 1085–1087.
12. Sánchez–Ortiz RF, Huang WC, Mick R, Van Arsdenl WK, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol. 2003; 169: 110–115.
13. Hara I, Miyake H, Hara S, Gotoh A, Okada H, Arakawa S, Kamidono S. Optimal timing of radical cystectomy for patients with invasive transitional cell carcinoma of the bladder. Jpn J Clin Oncol. 2002; 32: 14–18.
14. Poletajew S, Lisiński J, Moskal K, Ornat J, Renk K, Szlaga M, et al: The time from diagnosis of bladder cancer to radical cystectomy in Polish urological centres – results of Cystiming Poland study. Cent European J Urol. 2014; 67: 329–332.
15. Liedberg F, Anderson H, Mansson W. Treatment delay and prognosis in invasive
14

bladder cancer. J Urol. 2005; 174: 1777–1781.

16. Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA. Prognosis of muscle–invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol. 2004; 45: 292–296.

17. Jäger W, Thomas C, Haag S, Hampel C, Salzer A, Thüroff JW, Wiesner C. Early vs delayed radical cystectomy for ‘high–risk’ carcinoma not invading bladder muscle: delay of cystectomy reduces cancer–specific survival. BJU Int. 2011; 108: E284–288.

18. Hautmann RE, Volkmer BG, Gust K. Quantification of the survival benefit of early versus deferred cystectomy in high–risk non–muscle invasive bladder cancer (T1 G3). World J Urol. 2009; 27: 347–351.

19. Denzinger S, Fritsche HM, Otto W, Blana A, Wieland WF, Burger M. Early versus deferred cystectomy for initial high–risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder–sparing approach? Eur Urol. 2008; 53: 146–152.

20. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol. 2001; 166: 1296–1299.

21. Konety BR, Dhawan V, Allareddy V, Joslyn SA. Impact of hospital and surgeon volume on in–hospital mortality from radical cystectomy: data from the health care utilization project. J Urol. 2005; 173: 1695–1700.

22. Konety BR, Dhawan V, Allareddy V, O’Donnell MA. Association between volume and charges for most frequently performed ambulatory and nonambulatory surgery for bladder cancer. Is more cheaper? J Urol. 2004; 172: 1056–1061.

23. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003; 349: 2117–2127.

24. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002; 346: 1128–1137.

25. Miller DC, Taub DA, Dunn RL, Montie JE, Wei JT, et al. The impact of co–morbid disease on cancer control and survival following radical cystectomy. J Urol. 2003; 169: 105–109.

26. Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy? J Urol. 1998; 159: 1845–1850.

27. Adamowicz J, Kowalczyk T, Drewa T. Tissue engineering of urinary bladder – current state of art and future perspectives. Cent European J Urol. 2013; 66: 202–206.