Early radical cystectomy or bladder sparing therapy in high-risk patients with non-muscle invasive bladder cancer

I. Sinescu[1], A. Iordache[1], C. Surcel[1], C. Mirvald[1], C. Gîngu[1], A. Omer[1], C. Pavelescu[1], Carmen Savu[2], V. Olaru[1]

[1] *Center of Uronephrology and Renal Transplantation, Fundeni Clinical Institute, Bucharest*

[2] *ICU, Fundeni Clinical Institute, Bucharest*

Abstract

Some patients with non-muscle invasive bladder cancer (NMIBC) have an increased risk of recurrence and progression. According to the EAU guidelines, high-risk are considered one of the following features: pT1 tumors, G3 (poorly differentiated), CIS (carcinoma in situ), pT1-G3 with concomitant CIS, pT1-G3 with CIS in the prostatic urethra, multiple and recurrent tumors pTa-G1-G2 larger than 3cm (well and moderately differentiated), micropapilary TCC.

In today's literature, there is an ongoing debate regarding the management of these patients. There are two feasible options: transurethral resection of bladder tumor (TUR-BT) followed by reTUR after 2-6 weeks and afterwards adjuvant BCG (Bacillus Calmette-Guerin) with maintenance for 1-3 years (option recommended by the EAU guidelines as the first treatment option) or early radical cystectomy with orthotopic neobladder in selected patients.

In the light of increased morbidity and mortality, quality of life impairment and perioperative complications, radical cystectomy may seem an over-treatment at first glance. However, we must bear in mind that high-risk patients have an impaired prognosis with a poor overall survival, with metastatic disease at the time of the first diagnosis in some cases.

Patients who refuse radical cystectomy and those unfit for this procedure due to associated comorbidities may receive adjuvant device-assisted chemotherapy, immunotherapy (especially interferon) or combination therapy, although these are considered inferior in terms of oncologic results.

Given the current global BCG shortage due to production pending of BCG Connaught strain by the Sanofi Pasteur company in June 2012, the urologist is placed in the delicate situation of being unable to provide proper treatment according to the European guidelines and is forced sometimes to resort to early cystectomy in order not to compromise the survival rate of these high-risk patients.

Key words: high-risk non-muscle invasive bladder cancer, early cystectomy, TUR-BT, BCG, reTuR-BT

Correspondence: Vlad Olaru

Center of Uronephrology and Renal Transplantation, Fundeni Clinical Institute

Şoseaua Fundeni Nr. 258, Sector 2, 022328, Bucharest

E-mail: drvladolaru@gmail.com

Introduction

Approximately 75% of patients with bladder cancer have a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). They represent the group with non-muscle-invasive bladder cancer NMIBC [1].

A number of these patients have a high rate of recurrence and progression. According to the European Guidelines they present one of the following features: pT1 tumor, G3 (high grade) tumor, CIS, multiple, recurrent or large (> 3 cm) Ta G1-G2 tumors (all conditions must be presented in this point) [1].

High-risk patients represent ~20-30% of NMIBC and are a challenge for the urologist [2]. There is an ongoing debate regarding the management of these patients. The primary goal is to increase survival, decrease recurrence and progression rates to muscle invasive disease.

There are two feasible options:

- Transurethral resection of bladder tumor (TUR-BT) followed preferably by reTUR-BT after 2-6 weeks and afterwards, adjuvant full dose Bacillus Calmette Guerin (BCG) with maintenance 1-3 years [1].
- Early radical cystectomy with orthotopic neobladder in selected patients [1].

Early radical cystectomy

In light of increased morbidity and mortality, quality of life impairment and perioperative complications, radical cystectomy may seem an over-treatment at first glance. However, we must bear in mind that high-risk patients have an impaired prognosis with a poor survival, with metastatic disease at the time of the first diagnosis in some cases [3].

Recent studies have shown that many authors are in favor of early radical cystectomy as first-line treatment in high-risk patients [3-6].

In a large non-randomized comparative study, Hautman et al. states that, despite a good quality pathological report, radical treatment may be delayed due to a clinical under-staging estimated in 20% of cases. The 5-year recurrence-free survival was 83.9% in the early cystectomy group versus 74.8% in the deferred group. He concludes that early radical cystectomy has good oncological results and the usage of modern techniques of nerve sparing and orthotopic neobladder, which provide a better quality of life, may also improve survival, saving up to 15-20% of the high-risk patients [3].

Another study states that early radical cystectomy in high-risk patients who have concomitant CIS significantly increases survival [6]. Stein JP considers that in carefully selected high-risk patients, early radical cystectomy is a viable option [5].

In a review of the literature comparing survival rates after conservative treatment or radical cystectomy, Malavaud B. concludes that young patients with "deep" T1 tumors (>T1a or >1.5mm in depth) with at least one additional factor of poor prognosis, such as multifocality, association of carcinoma-in-situ, prostatic involvement or a site difficult to resect, should be considered for radical cystectomy [6].

Against the above, several studies that evaluated the disease specific survival of high-risk patients found no significant differences between patients with early radical cystectomy and bladder sparing procedures [7, 8]. E. De Berardinis et al. reports a cancer specific survival at 10 years of 22.5% for radical cystectomy versus 22.2% for patients with bladder sparing approach [7].

As a general rule, Kulkami et al. states that radical cystectomy can be a viable option for young, fit patients, while bladder sparing treatment is recommended for old patients with multiple comorbidities [9].

Bladder sparing treatment

Regarding bladder sparing treatment for high-risk patients, the most viable option is a good quality TUR-BT followed by re-TUR and adjuvant BCG therapy.

The quality of TUR-BT can vary from surgeon to surgeon, influencing the rate of recurrence [10]. In a recent study, Mariappan P. et al. reports that a complete first resection with muscle present on the specimen performed by an experienced surgeon is associated with a lower risk of recurrence [11].

Re-TUR is strongly recommended by most authors after the first resection, the degree of residual neoplastic tissue varying between 30-70% [12-13]. A good quality TUR, as previously mentioned, plays an important role. A recent study revealed a rate of residual tumor of only 17% in experienced hands (high-risk patients were included) [13].

In re-TURBT an important role can be played by the photodynamic diagnosis (PDD). This is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL) [1]. After analyzing 27 studies on the effectiveness of PDD, Mowatt G. et al. states that using 5-aminolevulinic acid increased the diagnostics' sensibility to 96% of recurrences as compared to 77% using

normal cystoscopy [15].

However, multiple studies have shown that despite the increased sensibility, the usage PPD has a modest impact on recurrence or progression rates. The urologist should consider the benefits of PDD usage in regards to the oncological outcomes and weight them against the disadvantages of an increased false positive rate.

To overcome the limitations of white light cystoscopy (WLC), Narrow Band Imaging (NBI) alone or in combination with optical coherence tomography (OCT) have been extensively studied in an attempt to reduce the recurrence and progression rates of these patients. In a recent study, the authors report a difference of 94.7% versus 79.2% in favor of NBI in the diagnostic primary or recurring NMIBC [16].

Ren H. et al., comparing detection rates of WLC, NBI, OCT and PDD have reported a detection rate of up to 93% for OCT, underlining the importance of imaging methods for the diagnosis of NMIBC [17]. Even though NBI and OCT have shown promising results, further studies with larger numbers of patients are needed in order to validate these techniques in current practice.

Regarding BCG therapy, a large number of studies have been conducted in an effort to lower the recurrence and progression rates. Malmström reported that in intermediate and high-risk patients undergoing BCG maintenance 1-3 years or Mitomicin C there is a 32% difference in recurrence in favor of BCG [18]. Also, another review of the literature found a 27% reduction in the odds of progression in patients using BCG maintenance [19].

The optimal BCG maintenance continues to be debated even though for high-risk patients, the EORTC study 30962 found that BCG maintenance in full Dose for 3 years reduces recurrences as compared with full Dose for 1 year, but has no impact on progression or mortality. No differences in toxicity between 1/3 Dose and Full Dose BCG were noted [20].

Given the reported data, the optimal bladder sparing strategy for patients with high-risk should be: TUR-BT, followed in 2-6 weeks by re-TURBT, then BCG maintenance in full dose for three years.

Another BCG dose can be administered in case of early BCG recurrence. Herr HW. concluded that 57% of patients respond to this therapeutic strategy, being recurrence free at 3 months and up to 80% at 6 months [21]. However, in case of recurrence in high-risk patients, radical cystectomy is recommended [1]. As mentioned above, in case of BCG recurrence, recent studies consider radical cystectomy with orthotopic neo-bladder as the treatment of choice [22]. Raj G.V. et al. concludes that radical cystectomy performed for recurrent T1 disease following intravesical BCG therapy is associated with better disease specific survival [23].

Giving the decline of global BCG Connaught strain reserves due to activity pending of Sanofi-Pasteur factory, the urologist is placed in a critical situation of being unable to provide the proper treatment according to the European guidelines and is forced sometimes to resort to early cystectomy in order not to compromise the survival rate of these high-risk patients [24].

For patients who refuse radical cystectomy or are unfit due to associated co-morbidities, there are other options like immunotherapy (especially with interferon); device assisted chemotherapy and combination therapy, although these are considered inferior in terms of oncologic results. Some agents are especially effective in BCG-failure patients – gemcitabine, thermochemotherapy, taxane chemotherapy [25].

Conclusions

Managing high-risk patients with non-muscle-invasive bladder cancer is particularly challenging. Since no consensus has been reached regarding the optimal management of these patients, the need for large randomized studies is imperative. High-risk patients should be well informed regarding treatment options and their decision should be fully respected. If a bladder sparing approach is chosen, the most viable option is represented by a TUR-BT, followed in 2-6 weeks by a reTUR and afterwards BCG maintenance full dose for 3 years. In young patients with “deep” T1 tumors (>T1a or >1.5mm in depth) with at least one additional factor of poor prognosis: multifocality, association of carcinoma-in-situ or prostatic involvement, early radical cystectomy should be considered.

References

1. M. Babjuk, M. Burger, R. Zigeuner et. al. *Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS).* European Association of Urology 2013
2. Babjuk M (2010) *What is the optimal treatment strategy for T1 bladder tumors?* Eur Urol 57:32–34
3. Richard E. Hautmann, Bjoern G. Volkmer et al. *QuantiWcation of the survival benefit of early versus deferred cystectomy in high-risk non-muscle invasive bladder cancer (T1 G3).*
4. Malavaud B: *T1G3 bladder tumours: the case for radical cystectomy.* Eur Urol. 2004 Apr; 45(4): 406-10.

5. Stein JP, Penson DF. *Invasive T1 bladder cancer: indications and rationale for radical cystectomy.* BJU Int. 2008 Aug; 102(3):270-5
6. Bianco FJ Jr, Justa D, Grignon DJ, et al. *Management of clinical T1 bladder transitional cell carcinoma by radical cystectomy.* Urol Oncol. 2004 Jul-Aug; 22(4): 290-4.
7. De Berardinis, G. M. Busetto, G. Antonini et al. *T1G3 high-risk NMIBC (non-muscle invasive bladdercancer): conservative treatment versus immediate cystectomy.* Int Urol Nephrol. 2011 Dec;43(4):1047-57.
8. Badalato GM, Gaya JM, Hruby G, et al. *Immediate radical cystectomy vs conservative management for high grade cT1 bladder cancer: is there a survival difference?* BJU Int. 2012 Nov; 110(10):1471-7.
9. Kulkarni GS, Finelli A, Fleshner NE, et al. *Optimal management of high-risk T1G3 bladder cancer: a decision analysis.* PLoS Med 4:e284
10. Brausi M, Collette L, Kurth K et al (2002) *Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies.* Eur Urol 41:523–531 16.
11. Mariappan P, Finney SM, Head E et al (2012) *Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking.* BJU Int 109(11):1666–1673
12. Herr HW (2005) *Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy.* J Urol 174:2134–2137
13. Jahnson S, Wiklund F, Duchek M et al (2005) *Results of secondlook resection after primary resection of T1 tumour of the urinary bladder.* Scand J Urol Nephrol 39:206–210
14. Gaya JM, Palou J, Cosentino M et al. (2012) *A second transurethral resection could be not necessary in all high grade nonmuscle-invasive bladder tumors.* Actas Urol Esp (Epub ahead of print; English, Spanish) (2012 Jun 16)
15. Mowatt G, N'Dow J, Vale L, et al; Aberdeen Technology Assessment Review (TAR) Group. *Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis.* Int J Technol Assess Health Care 2011 Jan;27(1):3-10.
16. Cauberg EC, Kloen S, Visser M, et al. *Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer.* Urology 2010 Sep; 76(3):658-63
17. Ren H, Park KC, Pan R. et al. *Early detection of carcinoma in situ of the bladder: a comparative study of white light cystoscopy, narrow band imaging, 5-ALA fluorescence cystoscopy and 3-dimensional optical coherence tomography.* J Urol. 2012 Mar;187(3):1063-70. doi: 10.1016/j.juro.2011.10.131. Epub 2012 Jan 15.
18. Malmström PU, Sylvester RJ, Crawford DE et al: *An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer.* Eur Urol 2009: 56: 247
19. Sylvester RJ, van der MA, Lamm DL (2002) *Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials.* J Urol 168: 1964–1970
20. J. Oddens M. Brausi, R. Sylvester, et al. Bacillus Calmette-Guerin: *One Third Dose Versus Full Dose And One Year Versus Three Years Maintenance. Final Result Of An EORTC Cancer Group Randomized Trial in Non Muscle Invasive Bladder Cancer (TRIAL 30962),* Eur Urol 2012 Suppl 3: 15
21. Herr HW, Dalbagni G. *Defining bacillus Calmette-Guerin refractory superficial bladder tumors.* J Urol. 2003 May; 169(5): 1706-8.
22. Yates DR, Brausi MA, Catto JW, et al. *Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer.* Eur Urol. 2012 Dec;62(6):1088-96
23. Raj GV, Herr H, Serio AM, et al. *Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer.* J Urol 2007 Apr;177(4):1283-6.
24. Babjuk M, Bohle A., Burge M. et al. *Statement concerning the shortage of BCG immunotherapy by the EAU Guidelines Panel on Non-muscle invasive bladder cancer.* Eur Urol. 2012.
25. Yates DR, Brausi MA, Catto JW et al. *Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer.* Eur Urol. 2012 Dec;62(6):1088-96. doi: 10.1016/j.eururo.2012.08.055. Epub 2012 Sep 3.