Review Article

How to optimally manage elderly bladder cancer patients?

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Abstract: Bladder cancer (BCa) is a disease of the elderly and as the population is aging, BCa will become an even bigger public health challenge in the future. Nowadays the correct management of BCa in the elderly remains controversial. The purpose of this article was to review the previous literature to summarize the current knowledge. Using Medline, a non-systematic review was performed including articles between January 2000 and February 2016 in order to describe the management of BCa in the elderly in all its aspects. English language original articles, reviews and editorials were selected based on their clinical relevance. In the literature, the definition of elderly is variable and based on chronological, not biological, age. BCa seems to be more aggressive in the elderly. The management of non-muscle invasive bladder cancer (NMIBC) does not strongly differ from younger patients, except for the role of adjuvant immunotherapy. In patients with muscle invasive bladder cancer (MIBC) the role of a multidisciplinary geriatric evaluation is potentially beneficial. The curative treatment in MIBC remains radical cystectomy (RC) and elderly patients should not be withheld a potentially life-saving intervention only based on chronological age. Patients unsuitable to a major surgical approach may be eligible for bladder-sparing techniques. Geriatric assessment could help identify the frail elderly and customize their perioperative care (i.e., pre and re habilitation). In conclusion the treatment of BCa in the elderly has to be patient-centered and focused on biological age and functional reserves.

Keywords: Bladder cancer (BCa); old; elderly; geriatric patients; radical cystectomy (RC); chemotherapy (CHT)

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Introduction

Bladder cancer (BCa) is mainly a disease of the elderly with a median age at diagnosis of 73 years; and the majority of new diagnoses occurring in the decade between 75 and 84 years (1). With the aging of population, BCa in the elderly will become even more frequent and develop in an even bigger public health challenge in future (2). Management of BCa in the elderly differs from that in younger ones both because of the patient reserves and his cancer behaving differently. For these reasons, knowledge of these peculiarities is essential for all physicians approaching this growing frail category of patients. Unfortunately, nowadays, the optimal treatment of BCa in this setting remains unclear and debated. The purpose of this review is to report the evidences on BCa treatment in the elderly, from non-muscle invasive bladder cancer (NMIBC) to advance disease, in order to help urologists in their everyday practice.

Evidence acquisition

A non-systematic Medline/PubMed literature search was performed with different combinations of terms as "bladder cancer", "elderly", "old", "aged", "BCG", "cystectomy", "chemotherapy", "radiation therapy" and "multi-modal therapy". Only articles in English language were retained for the analyses. Time period included articles between January 2000 and February 2016, with special regards to those published in the last 5 years. Original articles, reviews and editorials were selected based on their clinical relevance. In the literature, the definition of elderly is variable and based on chronological, not biological, age.

Evidence synthesis

Non-muscle invasive bladder cancer (NMIBC)

General considerations

Surgical procedures for NMIBC are usually performed endoscopically and are at low risk of diathesis. Also the anesthetic support, being generally performed with spinal anesthesia or sedation analgesia, has not a great impact on organ systems and don't provide significant life-threatening risk. For these reasons surgical treatment of NMIBC is generally well tolerated in the elderly, even when it has to be repeated several times. Adjuvant intravesical therapies with chemotherapeutic agents, such as mitomycin C (MMC) or epirubicin, are usually well tolerated and have a low risk of side effects, mainly due to the absence of systemic absorption of these drugs (3). Despite these findings, it is clear that the length of follow up and the subsequent need of repeated endoscopic procedures may affect the quality of life of patients, especially the older ones. In order to reduce this therapeutic burden several alternatives to transurethral resection (TUR) have been proposed, based on the evidence that relapses after low-stage low-grade tumors are low grade themselves in >90% of cases, with a negligible risk of progression (4). Office fulguration of small papillary recurrences or even temporary surveillance have been proposed in selected cases (5,6). Also ablative intensive schedules of intravesical chemotherapy (CHT) with MMC have been tested with promising results even if further trials are needed in order to confirm these first findings (7). The treatment of low risk NMIBC in old patients does not usually differ from that performed in younger ones, on the other hand the presence of comorbidities or a poor general status in these patients may drive to a more conservative and tailored management.

Intravesical immunotherapy

Data suggest that efficacy of BCG is reduced in the elderly and carries a non-negligible rate of adverse events (8,9). Adjuvant intravesical immunotherapy is recommended for NMIBC patients with intermediate and high risk of disease recurrence and progression (10). BCG is superior to chemotherapeutic agents such as MMC and epirubicin in preventing disease recurrence and lowers the likelihood of disease progression (11,12). Treatment with BCG consists in an induction cycle of 6 weekly instillations followed by a maintenance course in general (10). Many different maintenance schedules have been proposed. At this time the optimal frequency and duration of maintenance instillations is already unknown even if at least of one year on maintenance BCG is required (13). The complex mechanism of action of BCG is not completely clear yet. BCG is known to attach to the urothelium, thereby inducing inflammation and releasing proinflammatory cytokines which attract innate immune cells such as macrophages and neutrophil granulocytes. The following production of cytokines and chemokines attract T cells and NK cells which, through cytolysis, are responsible for the final anticancer effect (14). This immunologic cascade points out the need of an efficient activity of the immune system. As previously demonstrated aging progressively weakens immune system, due to a decline of the adaptative immune response (15). The influence of age on the response to intravesical immunotherapy in patients with NMIBC has been evaluated. Joudi *et al.* examined recurrence-free survival rates 2 years after the initiation of immunotherapy by incremental age decade. Patients who were 61 to 70 years old had higher recurrence-free survival rates compared to patients older than 80 years (61% versus 39%, respectively). At the multivariable analysis age was an independent predictor of response (8). Age was found to have a measurable impact in high-risk NMIBC as independent inverse predictor of CSS (9). Oddens *et al.* tested the efficacy of BCG in patients included in the EORTC Genito-Urinary (GU) Group. Two age groups were defined: <70 and ≥70 years. At a median follow up of 9.2 years, patients ≥70 years had a shorter time to disease progression, lower overall survival and NMIBC-specific survival rates compared to their younger counterparts. BCG, however, was more effective than epirubicin for all the end points considered and there was no evidence that BCG was any less effective compared with epirubicin in patients ≥70 years (16). These studies well demonstrate a reduced response to current immunotherapeutics in the

elderly even if treatment with BCG remains superior to intravesical CHT.

These results have to be interpreted also in the light of the potential side effects related to immunotherapy. BCG may be not so well tolerated in frail patients with reduced vascular, cardiac, immunologic and pulmonary reserves. These patients could be exposed to a higher risk of intravascular dissemination of tubercle bacillus and subsequent potential pulmonary compromise, sepsis and cardiovascular collapse (3). In literature there are numerous reports about serious adverse events in old patients (17-19). The age is also a major risk factor for adverse events such as fever, hematuria, urinary symptoms and clot retention. Heiner *et al.* reviewed a clinical course of 58 consecutive patients receiving BCG between 1999 and 2004. The complication rates were 17.6% and 48.6% for patients <70 and ≥70 years old, respectively. Patients who had complications (mean age 76.0 years) were significantly older than those who had no complications (70.3 years) (20). The non-negligible incidence of side effects has a strong impact on treatment compliance, leading to high discontinuation rates. In the report by Lamm *et al.* on maintenance BCG, only 16% of patients were able to complete the 3 years schedule (21). In order to solve this problem a regimen with a reduced dose of BCG has been proposed. The EORTC GU group tested the efficacy of one-third dose (1/3D) of BCG versus full dose (FD) regimen with 1 or 3 years of maintenance. The 1/3D with 1 year of maintenance resulted suboptimal compared to standard FD during 3 years. No differences in toxicity between 1/3D and FD have been shown (22). Moreover, the administration of a reduced regimen in patients in which the BCG efficacy is limited remains questionable. In summary, even if intravesical BCG seems less effective in the elderly, it is still superior to intravesical CHT. The caveat to consider is its higher risk of adverse events and therefore the need to manage the elderly closely for them.

New experimental conservative therapies

High risk patients intolerant to BCG or failing it have to be counseled for radical cystectomy (RC). However, major surgery in the elderly could be too risky or unfeasible, mainly due to the high rates of age-related comorbidities. In selected cases, the physician has to consider other conservative therapies. Nowadays, device assisted therapies as electromotive drug administration (EMDA) and chemohyperthermia are considered by guidelines as still oncologically marginal and to be only tested in clinical trials. However, efficacy results of device assisted therapies in NMIBC are promising. The early results of these approaches are very promising with an acceptable eater of side effects making them a probable alternative in well selected patients, specifically in the frail elderly (23-25). Therefore studies assessing the role of device assisted therapies in the elderly should be encouraged, as it could become an effective therapy in this setting.

Muscle invasive bladder cancer (MIBC)

MIBC is an aggressive tumor with a poor prognosis; the 5- and 10-year overall survival rates are around 65% and 45% respectively, closely related to the disease stage (10,26). MIBC may arise *de novo* or as the result of a progression of NMIBC. If untreated it will lead to local invasion of adjacent structures, hydronephrosis, incoercible hematuria, lymph node and distant metastases (27). Nowadays the only treatment with a curative intent is RC, eventually preceded by neoadjuvant CHT when possible. Despite these evidences, many older patients do not receive curative treatments. Analyzing the report of the SEER, Gore *et al.* found that only 21% of MIBC patients older than 65 years received a RC (28). The predictors for this were urologist choice, longer travel distances and residence in rural areas. These observations have been confirmed analyzing data from the USA National Cancer Database. Cystectomy rate was 55% in patients younger than 70 years, 45% in those 70 to 79 years, and it decreased to 21% in those older than 79 years. Half of patients older than 85 years received no treatment (29). Reasons for denying old patients major surgery are multi-factorial, but they are mainly based on the perception that many patients will not tolerate RC and urinary diversion because of age and comorbidities. For this reason, an integrate and multidisciplinary approach to this category of patients is mandatory. The evaluation has to be run by the urologist, oncologist, radiotherapist and geriatricians.

Geriatric evaluation

This evaluation is essential and has to be performed in order to identify the best treatment for every single patient with MIBC. It could provide information not only about treatment decision but also about preoperative and postoperative care, as well as the risk of complications after surgery or any other therapies. The geriatric evaluation has to be individualized and has to take into consideration every aspects of patient's life. Ideally it has to answer to

the following questions: how is the nutritional status of the patient? What is his level of mobility? How is his social support system? How many medications does he take every day? How are his cognitive functions (1)? To help the physician in this evaluation several assessment tools have been developed, such as the G8 and the Flemish version of the Triage Risk Screening Tool (fTRST) (1,30). These prediction tools could help the physician in the treatment planning and in calculating the risk of treatment-associated adverse events as well as 90-day morbidity and mortality (31). Moreover, they are useful to mitigate subjective confounders that could influence the clinicians' decision process. As clearly emerged, when approaching a geriatric patient with MIBC, physicians have to consider the physiological and not only the chronological age of the subject.

Open radical cystectomy (RC)

RC represents the standard in the treatment of MIBC and has to be proposed even to elderly patients as there is no accepted oncological equivalent alternative to date. Analyzing the association of treatment strategy on survival in octogenarians, RC shows to have the greatest risk reduction in death from BCa and death from any cause among the primary treatment modalities (32). However it is true that elderly go worse oncologically after RC. Nielsen *et al.* found that higher age at RC was associated with extravesical disease and pathological upstaging and, subsequently, to higher risk of disease recurrence and cancer-specific and overall mortality (33). Similarly, Resorlu *et al.* reported a decreasing in 5-year cancer-specific survival rates with age advancing (P<0.001) (26,34). This could be due to several reasons. With age, tumor cells could change their grown pattern increasing their biological potential and the host's immune system progressively loses its efficacy. Moreover, other conditions may influence these results, such as a delay in performing RC (33), a decrease administration of neoadjuvant or adjuvant therapies and/or decrease performance of lymphadenectomy (3). In conclusion, when diagnosing a MIBC or a high risk NMIBC in a patient fit for major surgery at the multidisciplinary evaluation, he still has to be recommended for RC as the primary option, irrespective of his chronological age.

Minimal invasive radical cystectomy (RC)

Laparoscopic and robot-assisted radical cystectomy (LRC and RARC) are becoming more widely used. They seem not oncological inferior but their benefits in safety and convalescence have not been fully proven yet (35,36). Oncological quality of care indicators such as the number of removed lymph nodes and soft tissue surgical margins seem not to be affected by the approach even if adjusted comparative analyses are lacking. Taken together, LRC and RARC provide decrease blood loss and transfusion rates, similar intraoperative complications and decrease hospital stays at the cost of longer operative times. For these reasons, LRC and RARC have been suggested to potentially benefit the elderly. Winters *et al.* retrospectively evaluate a monocentric series of 87 patients >75 years who underwent to RC (58 open, 29 robotic). RARC had significant longer operative times while blood loss and mean hospital stays were significantly improved after adjustment for the effects of standard features in multivariable analysis (37). Guillotreau *et al.* compared the perioperative outcomes of LRC and RARC in patients younger and older than 70 years. Intraoperative and postoperative complication rates were similar and conversion to an open procedure was only 4% for both. Surprisingly mean hospital stay was significantly lower in older patients. Authors concluded that LRC and RARC does not have worse perioperative outcomes and could be offered to elderly patients (38).

Node dissection

Pelvic lymph-node extended dissection (PLND) has to be performed in all patients undergoing RC because its role in staging, management, and survival (35). Nevertheless, still around 25% of patients undergoing RC do not receive PLND (39). This is even more true in the elderly population (40). This is probably because of the thought to reduce operative morbidity and length. Such assumptions would undermine the reason and efficacy of RC. Not to say that the elderly are undertreated by giving them a worse procedure based on misjudged risk benefit calculations. We strongly believed that elderly patients should not be withheld a potentially beneficial PLND only because of their chronological age.

Urinary diversion

Ileal conduit (IC) is the most performed urinary diversion in the elderly. Wuethrich *et al.* reviewed a single center series of 244 patients over 75 years who underwent RC between 2000 and 2013. Overall, 17% of patients received an ileal orthotopic bladder substitution (OBS), 78% an IC and 5% an ureterocutaneostomy (UCST). The 90-day complication rate was 54.3%, 56.7% and 63.6% in OBS, IC and UCST respectively (41). These differences may be

attributed to different patients' selection; in fact, patients receiving OBS had significantly lower pT stages compared with those receiving IC or UST. Not only the presence of advanced cancer but also the longer operative time of OBS, and the consequent stress on each organ system, could influence the selection of patients. For these reasons elderly patients are more frequent offered an IC rather than an OBS. The choice for IC in older patients varies from 72% to 87%, depending on the series (3). Again, the preoperative evaluation is mandatory to identify which patients could benefit from an OBS: this diversion could be offered to selected patients with low comorbidities and low disease stage. Conversely, IC could be offered to the majority of patients, being technically easier, more reproducible, quicker, and with low impact on perioperative and outcomes renal function.

Cutaneous ureterostomy (UCST) represents a great opportunity in the frail poor performing elderly patients. UCST does not require bowel isolation and manipulation and allows to perform an extraperitoneal RC (42,43). Moreover, it is simpler and less time-consuming compared to the other diversions. It is reported that UCST has a shorter hospital stay, less blood loss and lower intraoperative complication rate, compared to IC (44). UCST, therefore, could be a simplified alternative choice for unfit and frail patients.

Complications of radical cystectomy (RC)

In the last two decades perioperative mortality of RC has dropped from 10% to 3% in high volume centers. Still, surgical complications are more than 60% in contemporary series regardless of age. Major complications and reoperations rates are around 10% and 3%, respectively. Age and ASA score are independent predictors of high grade complications (45). Nevertheless, comorbidities and functional status seem to be better predictors than age alone for complications of major surgery. Froehner *et al.* reviewed complications and mortality rates after RC in the elderly. Total complications rate was 72% versus 64% in older and younger group; major complications rate was on the other hand not different (17% *vs.* 13%). However there is a lack of standardized reporting criteria that lead to under-reporting, wide variations between series (i.e., incidence of postoperative ileus rates range from 2% to 32%) and/or missing complications (mainly delirium and disorientation) (46). Perioperative mortality rates are, however, clearly higher in the elderly. Schiffmann *et al.* reviewed the mortality rates after RC analyzing more than 5,000 patients from the SEER database. Ninety-day mortality rates resulted 6.4%, 10.1% and 14.8% in age groups 65–69, 70–79 and ≥80 years, respectively (P<0.001). Predictors of perioperative mortality were age (OR 2.4 in patients ≥80 years) and Charlson comorbidity index (CCI) (47). These perioperative mortality rates are higher than those reported at centers of excellence; there is, indeed, a well-known relationship between hospital volume and outcomes of RC. In conclusion, to reduce morbidity and mortality of RC, elderly patients should be referred to high volume centers with expertise in RC.

Chemotherapy (CHT)

Neoadjuvant chemotherapy (CHT)

Current international guidelines recommend neoadjuvant CHT for all T2–T4a, cN0M0 BCa (35). Moreover, neoadjuvant CHT should always be a cisplatin-based combination therapy and, therefore, it is not recommended in patients ineligible for cisplatin. It is difficult to investigate the usage of neoadjuvant CHT in the elderly because of the lack of data in this group of patients. Trials about CHT, indeed, have been usually performed in healthier and younger patients. Moreover, it is well-known that one of the major limitations is the impaired renal function, making cisplatin too toxic. This is a common reality in the older population, who suffers from a decrease in renal function. Dash *et al.* found an impaired renal function in 16%, 36% and 68% of patients with MIBC in age groups 60–69, 70–79, and ≥80 years, respectively (48). For these reasons the majority of older patients could be unfit for neoadjuvant CHT or may be less likely to receive optimal regimen of CHT. Galsky *et al.* defined the criteria for cisplatin eligibility and proposed the ineligibility for patients with one of the following: ECOG PS of 2 (KPS of 60–70), creatinine clearance <60 mL/min, New York Heart Association class III, grade 2 or greater hearing loss, grade 2 or greater neuropathy (1). Age is not included in the definition but it is clear that a great percentage of patients >75 years may be not eligible for this therapy. Even in suitable patients, a single complication occurrence may be disastrous, leading to long hospitalization and compromising the functional reserves and the possibility to undergoing the main therapy that is the surgery. Concluding, nowadays, neoadjuvant CHT in the elderly has to be proposed to well selected patients with optimal performance status and low comorbidities rate (i.e., Galsky criteria) (1). New trials on the use of neoadjuvant CHT in the old population are needed in order to better define

which patient could benefit from this therapy.

Adjuvant chemotherapy (CHT) and CHT alone

Adjuvant CHT is recommended in some patients with pT3–4 and/or N positive disease (35). As for neoadjuvant CHT, also in the adjuvant setting, CHT has to be based on cisplatin and, subsequently, has the same limitations of use in the elderly. This is even truer after a debilitating operation that RC still is. At this time, there are no studies focused on adjuvant CHT in the elderly and no definitive conclusions can be made.

CHT is the treatment of choice in metastatic BCa setting. Cisplatin-based CHT is the preferred first-line treatment in metastatic BCa and patients should not be excluded only for their chronological age (1). Several other schedules have been proposed for patients ineligible to cisplatin. The EORTC group tested two carboplatin-based regimens of CHT (gemcitabine/carboplatin *vs.* methotrexate/carboplatin/vinblastine) in a randomized phase II/III trial. The authors showed no significant differences in efficacy between the two regimens but higher incidence of severe toxicity in patients treated with methotrexate/carboplatin/vinblastine, making gemcitabine/carboplatin the reference treatment in patients ineligible for cisplatin (49).

Radiotherapy alone

External beam radiotherapy alone is not recommended as primary therapy for MIBC and should be considered as a therapeutic option only when the patient is unfit for RC or in cases of multimodality bladder-sparing approach. The feasibility of pelvic radiation alone with a curative intent in an elderly population with MIBC and in poor general conditions (CCI >2) was firstly established in 2002. In this study, 45 unfit patients were treated with radiation fields encompassing bladder and grossly involved lymph-nodes. Treatment was considered safe and achieved a 3- and 5-year OS of 36% and 19.5%, respectively; with a median survival of 21.5 months (50). A recent study reported similar results but included patients with T1 to T4 BCa, making difficult to compare this population to MIBC patients. Concluding, nowadays the role of radiation therapy with a curative intent in the elderly is limited and has to be reserved to patients unsuitable for surgery and trimodal therapy (TMT).

Bladder saving trimodal therapy (TMT)

TMT combines radical TURB, CHT and external beam radiation therapy. This treatment should be proposed to patients unfit for surgery or asking a bladder sparing technique but eligible for CHT with a curative intent. CHT is usually performed with radiosensitising drugs such as cisplatin or MMC plus 5-fluorouracil, even if other schedules have also been investigated. TMT leads to favorable oncological results if given in an optimal setting: a recent meta-analysis reported a complete response after TMT in 78% of treated patients. After 5 years 79% of patients retained their bladder and 56% were alive (51). However, to date, no prospective trials comparing TMT to RC have been performed. TMT has also been tested in a cohort of 24 patients >70 years (median age 79 years). All patients completed the radiation treatment cycle and 19 patients tolerated all the 4 cycles of CHT. The CSS and OS at 3 years were 71% and 61%, respectively. Moreover, 75% of surviving patients were disease-free and had a functioning bladder (52). These results are promising and further studies have to be performed in elderly patients with MIBC and unfit for RC, for whom TMT could become an alternative with curative intent.

Conclusions

(I) In the literature, the definition of elderly is variable and based on chronological, not biological, age;

(II) In the treatment decision the evaluation of chronological age is not determinant compared to performance status that is biological age;

(III) Management of NMIBC in the elderly is relatively simple and doesn't substantially differ from that adopted in younger patients;

(IV) In MIBC, often a suboptimal therapy is given to elderly patients;

(V) RC, when feasible, is still the standard treatment for MIBC;

(VI) The administration of CHT in the elderly is difficult due to their low functional reserves;

(VII) More focus is needed in this steadily growing segment of our population in order to allow high quality, evidence based, personalized care.

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Footnote

Conflicts of Interest: Shahrokh F. Shariat owns or co-owns the following patents—Methods to determine prognosis after

therapy for prostate cancer. Granted 2002-09-06. Methods to determine prognosis after therapy for bladder cancer. Granted 2003-06-19. Prognostic methods for patients with prostatic disease. Granted 2004-08-05. Soluble Fas: urinary marker for the detection of bladder transitional cell carcinoma. Granted 2010-07-20. He is advisory board member of Astellas, Cepheid, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, Wolff. He is speaker for Astellas, Ipsen, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, Wolff. R Mathieu—Consultant: Astellas, Ipsen, Janssen; Speaker: Janssen, Sanofi, Novartis, Takeda. The other authors have no conflicts of interest to declare.

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