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Management of bladder cancer in older patients: position paper of a SIOG Task Force

Running title: Bladder cancer in older patients: SIOG position paper

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Conflict of interest

Tullika Garg, Maria J. Ribal, Philippe Caillet and Patrick Wüthrich declare that they have no COIs.

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Abstract

Median age at bladder cancer (BC) diagnosis is older than for other major tumours. Age should not determine treatment, and patients should be fully involved in decisions. Patients should be screened with Mini-Cog™ for cognitive impairment and the G8 to ascertain need for comprehensive geriatric assessment. In non-muscle invasive disease, older adult patients should have standard therapy. Age does not contraindicate intravesical therapy. Independent of age and fitness, patients with muscle-invasive BC should have at least cross-sectional imaging. Data suggest extensive undertreatment in older adult patients, leading to poor outcomes. Standard treatment for a fit patient differs between countries. Radical cystectomy and trimodality therapy are first-line options. Radical cystectomy patients should be referred to an experienced centre and prehabilitation is mandatory. Older adult patients should be considered for neoadjuvant and adjuvant therapy, according to guidelines. In urinary diversion, avoiding bowel surgery for reconstruction of the lower urinary tract significantly reduces complications. If a patient is unfit for or refuses standard treatment, RT alone, or TURBT in selected cases should be considered. In metastatic BC, older adult patients should receive standard systemic therapy, depending on fitness for cisplatin and prognosis. Efficacy and tolerability of immunotherapy (IO) appears similar to younger patients. Second line IO is standard in platinum pre-treated patients, with benefit and tolerability in the older adult similar to younger patients. The toxicity profile seems to favour IO in the older adult but more data are needed. Patients progressing on IO may respond to further systemic treatment. In metastatic disease, palliative care should begin early.

Highlights

- Of the major tumours, patients with bladder cancer (BC) are the oldest at diagnosis
- Treatment should be determined by fitness, prognosis and patient preference
- Undertreating non-invasive BC risks poor outcome; intravesical therapy is an option
- In invasive BC, consider radical cystectomy with prehab and trimodality therapy
- In advanced disease consider cisplatin in the fit. Immunotherapy could have a role

Table 1 Summary conclusions and recommendations (with strength of consensus)

General approach to geriatric assessment

- Patients and caregivers should be fully involved in all decisions. (Strong)
- No treatment should be denied based on age alone. This includes involvement in trials. (Strong)
- In assessing frailty, use a short screening test to detect cognitive disorders (the Mini-Cog™) and establish competence in making decisions, followed by the G8 tool to determine whether there should be a simplified geriatric assessment (GA) including ADL and IADL, followed if necessary by comprehensive GA. This may identify remediable geriatric conditions. (Weak)

Assessing malnutrition with the ESPEN questionnaire, sarcopenia using the SMI, and frailty with the Fried Frailty index may help in making appropriate treatment decisions. (Weak)

Non-muscle invasive bladder cancer

- Most older adult patients should receive standard therapy according to accepted national or international guidelines. (Strong)
- In very high risk NMIBC as well as in BCG refractory disease, the significant morbidity of radical cystectomy must be cautiously balanced against prolonged intravesical treatments. (Weak)
- In older patients, anticholinergics to manage the side effects of intravesical therapy should where possible be avoided. If needed, they should be used with caution. (Strong)

Muscle invasive bladder cancer (MIBC)

- There is extensive undertreatment in older adult patients. If MIBC is untreated, outcomes are poor both for survival and symptomatic progression.
- Independent of age and fitness, patients with MIBC should have cross-sectional imaging not only for staging but as a means of identifying bone disease and to optimise best supportive care (BSC). (Strong)
- The choice of standard treatment for a fit patient differs between countries and practitioners. Radical cystectomy and trimodality therapy are first-line options. (Weak)
- If radical cystectomy is decided on, the patient should be referred to an experienced centre. (Strong)
- Without unduly delaying surgery, patients should be made as fit as possible for their operation. Prehabilitation includes enhancing nutrition and fitness, and treatment of anaemia. (Strong)
- To maximize the potential for cure, older adult patients fit enough to receive cisplatin-based chemotherapy should be considered for neoadjuvant /adjuvant systemic therapy if needed, in addition to local treatment, according to guidelines. (Weak)
- In terms of urinary diversion, avoiding bowel surgery for reconstruction of the lower urinary tract significantly reduces the rate of perioperative complications in frail patients but is more

likely to require stenting and potentially increases the risk of bacterial colonisation of the upper urinary tract. While the ileal conduit is the most used urinary diversion, in fit patients, a continent pouch or a neobladder are feasible and have similar postoperative complication rates compared to those in younger patients. (Weak)

- There is insufficient evidence to consider omitting nodal dissection in senior adults without compromising oncological outcome. (Weak)
- If a patient is unfit for or refuses standard treatment, consider radiotherapy or TURBT alone if needed in selected cases (Strong).

Metastatic bladder cancer

- In older adult patients, prognosis and goals of care should be discussed with patients and caregivers. Consideration of appropriate palliation should begin at the time of diagnosis. (Strong)
- First-line, older adult patients should receive standard systemic therapy, but this will depend primarily on fitness for cisplatin and, secondly, on prognostic factors. Carboplatin is an alternative in cisplatin-unfit patients, as are immunotherapy (IO) agents in patients with positive PD-L1 staining. (Strong)
- The efficacy and tolerability of IO agents in older adult patients appear to be much the same as in younger patients. (Weak)
- Second line IO is currently standard treatment in platinum pretreated patients and the benefit and tolerability in older adult and younger patients seem similar. (Strong)
- Patients progressing on IO may respond to further systemic treatment. (Weak)
- Palliative RT may be considered for intractable gross haematuria and control of pain. (Strong)

Need for research

There is a lack of clinical trial data on the treatment of older adult bladder cancer patients. To help guide choice of treatment, efforts should be made to enroll such patients in controlled trials and in studies of routine practice. Studies should include at least a minimum of geriatric data (the G-CODE, Geriatric Core Dataset) to provide a representative description of the older adult patients treated.

Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide, and, in Europe and North America, the fifth most common.¹ In the US, patients diagnosed with BC have a median age of 73 -- the highest age at diagnosis of all cancer sites.¹ BC is projected to have one of the greatest increases in incidence by 2030.² According to the WHO, the world population aged 65 or older will grow from 500 million in 2010 to nearly 1.5 billion in 2050.³ Given such a rapidly aging population, the majority of BC patients will soon be over the age of 75, and their management will inevitably pose a serious challenge to healthcare systems.⁴

There is a presumption in favour of giving the most effective treatment possible, since untreated BCs have a very poor prognosis. In Prout and Marshall's early series of 59 essentially untreated patients, the one year survival rate was 37%, with only 14% of patients living for two years or longer.⁵ Even in treated non-muscle invasive BC (NMIBC), the risk of cancer-specific death at 15-years' follow-up of patients with high-risk disease treated with transurethral resection alone (TUR) or combined with intravesical bacillus Calmette-Guerin (BCG) was 34%.⁶

On the other hand, in relation to the older adult, there is growing recognition of the impact of chronic conditions and multimorbidity on eligibility for treatment. By the Charlson Comorbidity Index, over 50% of BC survivors have a moderate to severe comorbidity burden, and BC patients a median of eight chronic conditions.⁷

Given such considerations, it is not surprising that older BC patients are less likely to receive standard treatment. However, untreated disease may progress and severely impair quality of life and cancer-specific survival. Taking into account an individual's life expectancy and goals and preferences, clinical decision-making must balance the benefits and risks of treatment against the morbidity and mortality arising from untreated or under-treated cancer.

Methods

In this context, a multidisciplinary Task Force of the International Society of Geriatric Oncology (SIOG) was convened to consider the management of BC in the older adult. Each author reviewed their area of particular expertise in the light of the published literature, but all contributed to the paper in general and our recommendations reflect consensus.

Given the relative lack of trial and other data relating to the older adult bladder cancer population, this review relied to an unusual extent on expert opinion. For this reason, care was exercised in recruiting to the task force clinicians experienced in bladder cancer in older patients, and in the moderation of their opinions by panel discussion during two face-to-face meetings.

Careful attention was paid to views on the management of bladder cancer (irrespective of age) contained in existing guidelines based on formal systematic review.

Since few randomised trial data relate specifically to older adult patients with BC, our recommendations – although graded – are based in large part on clinical experience and lower levels of evidence. The grading of “weak” was given when more than 50% of the authors agreed on a recommendation, and “strong” when all but two or fewer disagreed with a recommendation. Though made by an expert group, they should be regarded as a basis for further research and discussion.

Geriatric assessment: general approach

Since age per se is a poor guide to the physiological and functional status of older individuals with cancer, the concept of geriatric assessment (GA) prior to initiating treatment is gaining support in oncology in general, and among those dealing with specific tumours such as prostate cancer and metastatic renal cell carcinoma.⁸⁻¹⁰ A recent review of potentially curative treatments in older adult patients with MIBC also concluded that GA should be used to select patients who are likely to benefit.¹¹

Although the value of such an approach -- compared with standard management -- has not been subjected to randomised controlled trial, comprehensive GA has face validity since it provides information on a patient’s physical function, cognition, nutrition, comorbidities, psychological status, and sources of social support.⁸ However, a full assessment is time consuming, not routinely available, and not always required. As a first step, older adult BC patients should be assessed for competence to make decisions using the Mini-Cog™, followed by the G8 screening tool. This identifies a level of problems which justifies a simplified GA, including assessment of Activities of Daily Living (ADL) and Independent Activities of Daily Living (IADL) in a subgroup of patients. In turn,

the simplified GA identifies a further subgroup in need of a comprehensive GA. This structured, sequential approach has recently been recommended in prostate cancer and in metastatic renal cell cancer.^{9,10}

In relation to chemotherapy in the older adult, the opinions of the SIOG Bladder Cancer Task Force accord broadly with those of the ASCO Expert Panel¹² which in 2018 emphasised the need for i) GA to identify vulnerabilities not routinely captured in oncology assessment; ii) estimation of the toxicities related to specific forms of chemotherapy by using either the CARG (Cancer and Aging Research Group) or CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients); iii) estimation of life expectancy in the absence of cancer; and iv) the communication of all of these data to patients and caregivers in an effort to optimise treatment decisions. The section on metastatic BC includes further discussion in relation to the CARG and CRASH scales.

Detailed recommendations on pre-operative assessment and perioperative management of the older adult BC patient undergoing radical cystectomy are given in the MIBC section below. They represent important means of optimising patient outcome.

Non muscle-invasive bladder cancer (NMIBC)

In general, treatment of NMIBC does not differ in the older adult and should follow national and international guidelines.¹³ NMIBC is managed by transurethral resection (TURBT) with or without intravesical instillations (BCG or chemotherapy). Surgery and anaesthetics are generally well tolerated.¹⁴ However, in older adult patients with extensive comorbidities, TURBT under general anaesthesia can be a high risk procedure. TURBT can be performed under regional or spinal anaesthesia. Fulguration under local anaesthesia may be an alternative in small volume and low-risk disease.¹⁵

NMIBC is a burdensome chronic condition in its own right with frequent outpatient visits needed for surveillance cystoscopies, intravesical treatments, and, in selected cases, imaging. Many older patients and caregivers may find it difficult to complete all visits, especially within the context of other chronic diseases and geriatric conditions. Follow-up could be less frequent and active surveillance employed instead of immediate therapy for recurrence, especially in low-risk disease.¹⁶ In NMIBC, it may be more effective in older adults to use tailored surveillance schedules.¹⁷

older adultolder adult Tumour size, stage, grade and number of sites within the bladder increase with age,^{18,19} while surgical retreatments²⁰, frequency of instillations²⁰ and response to intravesical treatments²¹⁻²² decrease. These factors result in a shortened time to recurrence^{18,19}, shorter progression free survival^{18,23} and increased BC-specific mortality^{20,23} in the older adult.¹⁵

Adjuvant intravesical therapy should be used independent of patients' age.¹³ Although there is some evidence that BCG is less effective in patients over the age of 80,²⁴ this would not be sufficient in practice to lead to earlier use of radical cystectomy or an alternative regimen. In the EORTC 30911 trial investigating maintenance BCG in NMIBC, there was no association between age and toxicity leading to treatment discontinuation.²⁵

In intermediate- and high-risk NMIBC treated with BCG, patients over 70 years have a worse long-term prognosis²⁶ which might be due to changes in immune response.²⁷ But the effect of age on response to BCG treatment is minor. No difference was observed between age groups at two years, while the 27% five-year cancer-free rate in patients over 70 was less than the 37% rate in younger patients.²⁸ The applicability of intravesical therapies is influenced by bladder storage and voiding problems, which should be evaluated before planning instillations. Novel strategies (e.g. device-assisted intravesical mitomycin C) might be an option in patients unfit for or unwilling to undergo radical cystectomy for refractory or recurrent high risk NMIBC.²⁹ Radical cystectomy for very high risk NMIBC is associated with significant sequelae, to the extent that in older adult frail patients consecutive intravesical salvage strategies may be a preferred option in shared decision making, balancing the oncological benefits of a radical cystectomy with the increased risks associated with this major surgical procedure. In cases of BCG-refractory disease, participation in a clinical trial is also a possibility.

In summary, it is important to weigh the risks associated with TURBT and intravesical treatments against the benefits that these and follow-up procedures can provide in the context of an individual's life expectancy and quality of life.³⁰ Generally, TURBT and intravesical therapies are well tolerated in most older adult patients. However in frail older adults, intravesical therapies and TURBTs may lead to higher rates of urinary side effects and urinary tract infection³¹; and repeated administration of general anaesthesia in older adults is associated with cognitive impairment.³²

Muscle-invasive bladder cancer

In developed countries, muscle-invasive BC (MIBC) accounts for approximately 25% of cases at primary diagnosis. Overall, the natural history of untreated MIBC is not well documented. However, it is likely that outcomes are poor in terms of survival, local progression and transfusion-dependent haematuria.^{5,6}

Older adults with MIBC tend to have poorer cancer-specific survival than younger patients, probably due at least in part to lower rates of standard-of-care radical treatment and perioperative chemotherapy.²⁰ Noon et al investigated outcome in more than 3000 cancer registry patients (all ages). Five years after diagnosis, 19% had died from BC and 19% from other causes. For MIBC, the five-year cancer-specific mortality rate in this series was 49.7%. Within this cohort, older adult patients were significantly less likely than their younger counterparts to have undergone radical therapy for invasive cancer (12% among patients aged 80 years and older compared to 52% in patients under the age of sixty) and exhibited higher cancer-specific mortality. The authors concluded that clinicians should consider offering more aggressive and potentially curative treatment to older but still sufficiently fit patients.

This view is supported by an analysis of the US National Cancer Data Base of almost thirty thousand patients in whom stage II-IV MIBC had been diagnosed.³³ Aggressive therapy was defined as radical or partial cystectomy or definitive radiotherapy/chemoradiotherapy with a total dose of at least 50 Gy. Use of such therapy became significantly less likely as patient's age increased.

These studies – along with clinical experience -- suggest that there is extensive under-treatment of older adult patients with potentially curative MIBC.

Though functional age is increasingly recognised as more important than chronological age, there is understandable concern about treatment-related complications due to co-morbidities, polypharmacy and poor physiological reserve. Hence decision making remains challenging,³⁴⁻³⁶ and further research is needed to determine fitness for curative therapy.

However, patients in whom non-aggressive treatment is considered must weigh the potential quality of life trade-offs between treatment on the one hand and increased risk of disease progression on the other. MIBC may cause a variety of bladder-related symptoms such as painful haematuria, urgency, frequency, and nocturia. Pain and dysuria often accompany the irritative symptoms, and all urinary symptoms have significant impact on quality of life. Gross haematuria from uncontrolled tumour growth results in frequent emergency department visits, catheterizations, surgical

intervention, hospitalization for continuous bladder irrigation, and transfusions. Extravesical tumour progression causes local symptoms due to infiltration of pelvic nerves and organs.

The choice of standard treatment for a fit MIBC patient differs between countries and practitioners. Radical cystectomy (RC) and chemoradiotherapy are first-line options.

Radical cystectomy

Pre-operative assessment

Anaesthesiologic assessment

With increased age, functional reserve diminishes, resulting in a decreased resistance to stressors like surgery. In a review of more than 6000 RC patients, in-hospital mortality increased with age over 70 and three or more comorbidities. Compared with patients aged less than 50 years, those older than 80 had an OR for in-hospital death of 4.6 and an OR of 11.6 for discharge to an institution.³⁷

Pre-operative assessment should involve relatives, caregivers and the general practitioner to fully understand medical history and living conditions. Clinical examination must look for general cardiorespiratory symptoms and for specific conditions (oral pathology, dental appliances, spinal osteoarthritis). Assessment also needs to consider age-related changes that increase drug side-effects.³⁸ For example, decreased lean mass and increased fat mass may lead to a larger distribution volume for liposoluble drugs and a delay in elimination. Decreasing GFR delays elimination of many anaesthetic agents. Hypoalbuminaemia increases free drug fraction, leading to more side effects or more pharmacological effect. It is preferable to use medications with a short half-life at the lowest dose and for the shortest duration.

The American Society of Anesthesiologists (ASA) physical status score is widely used for assessment of surgical risk. Although not designed to assess comorbidities, it is highly predictive of 30 day surgical mortality and complications (with ASA 2, the OR is 2.05; ASA 3, OR 4.99; ASA 4, OR 16.8).³⁹ Three retrospective series have found a predictive value of ASA score for RC patients with an OR of 2.2-3.2.⁴⁰⁻⁴² Surgical risk is better estimated through comorbidities and geriatric parameters like the frailty index since they are associated with postoperative morbidity and mortality. As frailty significantly increases postoperative complications, prolonged hospital stay and institutionalization in patients aged over 65, and also improves the predictive power of the ASA score, preoperative frailty assessment should be recommended.⁴³ In frail patients having RC, 30 day mortality and

incidence of Clavien Dindo grade IV complications increased by 30% compared to non-frail patients.⁴⁴

Nutritional status

Around 20-40% of RC patients are malnourished. Malnutrition, indicated by decreased preoperative serum albumin level and sarcopenia, predicts perioperative complications and 90-day mortality.^{45,46} There is limited time to fully improve nutritional status.⁴⁷ Preoperative administration of enteral formulas with high quality protein foods (for around two weeks) and immunonutrients (for five days before surgery) reduces the rate of postoperative complications by up to one third and the risk of infectious complications by up to 40%.⁴⁸

Hydration needs special attention in old patients since they have a diminished sensation of thirst and preoperative dehydration has been associated with increased postoperative morbidity. This is part of the Enhanced Recovery After Surgery (ERAS) protocol, as is carbohydrate loading with 800 ml in the evening and 400 ml 2-3 hours before surgery.^{49,50}

Fitness

Even limited exercise has a strong cardioprotective effect.^{51,52} Preoperative fitness can be assessed by the cardiopulmonary exercise test (CPET). Aerobic fitness before RC can improve quickly and lessens perioperative inflammatory processes, improves treatment tolerance, and enhances wellbeing. In older patients, the optimal intensity and duration of exercise is unclear. However, starting exercise at an intensity of around 50% of the heart rate reserve, corresponding to a target heart rate of 110 beats per minute, is recommended for patients over 70.

Optimisation of physical fitness and nutritional state are the cornerstones of effective prehabilitation but should not delay surgery once RC has been decided on.

Blood management and thromboprophylaxis

The incidence of preoperative anaemia can be >75% in cancer patients. For surgical patients, a preoperative haemoglobin (Hb) concentration of <13 g/dL is suboptimal, independent of sex. Most MIBC patients have iron deficiency anaemia with a low ferritin concentration (<100 ng/mL). In addition, due to nutritional deficiency, a low ferritin concentration is often present even in non-

anaemic patients. Blood loss during RC is expected to be >500mL, and iron storage may be insufficient to restore perioperative Hb loss.

Preoperative anaemia should be corrected, generally through an i.v. iron formulation. This leads to a more rapid and complete response than the oral formulation. In older adult malnourished patients, vitamin B12 and folic acid are also recommended.⁵³ Whether preoperative erythropoietin improves outcome remains unclear. In Europe, it is approved only for orthopaedic surgery with moderate to elevated blood loss. In the U.S. it is indicated for all major non-cardiac surgery.

Intraoperative transfusion of red blood cells (RBCs) leads to poorer cancer-related outcomes after RC.⁵⁴ It is not clear whether transfusion is causally related to poor outcome or simply a reflection of higher risk disease. A perioperative Hb level that is too low increases short-term major complications. A Hb target of around 8 mg/dL (for fit patients) and 9 (for the frail) seems appropriate to lower major short-term complication.⁵⁵

Intraoperative blood loss was lower in patients with pelvic venous pressure less than 5 mm Hg (which is not correlated to central venous pressure).⁵⁶ This was achieved more frequently in patients treated with a norepinephrine-low volume strategy than with liberal use of intravenous fluid. Continuous norepinephrine administration resulted in lower blood loss and rate of transfusions.⁵⁷ Furthermore, pelvic venous pressure decreased significantly after removing abdominal packing and abdominal lifting during RC.

With regard to thromboprophylaxis, using low molecular weight heparins for four weeks after discharge reduces the rate of thromboembolic events by approximately 70% in patients with and without perioperative chemotherapy.⁵⁸

Anaesthesia management

Changes in body composition, renal function and drug metabolism make older patients more vulnerable to drug mismanagement or overdose.⁵⁹ Reduced plasma volume and intracellular water significantly increase the initial volume of distribution of drugs like propofol, requiring a lower dose.^{60,61} Intraoperative management should aim for normothermia since hypothermia increases oxygen demand and may result in coagulopathy and infection.⁶¹ The use of short acting anaesthetics is recommended and use of long-acting opioids discouraged.^{62,63} Too deep anaesthesia (i.e. bispectral index value < 45 assessed by neuromonitoring) should be avoided. Due to their impaired autonomic nervous system, older patients are highly preload-dependent and stroke volume

optimization may be beneficial. The administration of saline solution (NaCl 0.9%) should be avoided in favour of a physiologic balanced solution such as Plasmalyte.⁶⁴

Surgical aspects

Extent of radical surgery

RC consists of the removal of the bladder, the prostate and the seminal vesicles in men, and the urethra, uterus, adnexa and anterior third of the vaginal wall in women.⁶⁵ A bilateral pelvic lymph node dissection (PLND) including the external, obturator and internal lymph node region usually up to the crossing of the common iliac artery with the ureters is recommended.⁶⁶ However, the cranial extent of PLND is still under debate and final results of randomised trials are pending.

Among unselected patients undergoing RC with an extended pelvic lymph node dissection, the 5- and 10-year recurrence-free survival rates were 68% and 66% after a median follow-up of 10.2 years. Current guidelines support the use of RC in older adult patients.⁶⁷ However, survival rates decrease with age. A systematic review of forty-two studies found that none directly addressed the use of geriatric assessment.⁶⁸ Given the retrospective nature of most studies, it is difficult to find meaningful guidance on clinical decision-making in an individual patient. Comprehensive assessment of both tumour and patient characteristics is needed on a case-by-case basis.

Urinary diversion

In older adult patients, retrospective studies show that complications after RC and urinary diversion often relate to bowel surgery and lymph node dissection.⁶⁵ For this reason, there is increasing awareness of the need to restrict the extent of surgery.⁶⁹ Although specialised centres can safely perform continent diversions in carefully selected older patients,^{70,71} the majority receive an ileal conduit as the preferred type of urinary diversion. Moreover, patients with severe comorbidities benefit from avoidance of bowel surgery and a quicker procedure, leading to ureterocutaneostomy that might be bilateral. In a series of 111 patients aged ≥ 80 years, 79% received an ileal conduit, and 15% a cutaneous ureterostomy, while only 4.5% received a neobladder. The surgical reintervention rate was low (13%).⁷² Major complication rates in the early and late periods were only 14% and 11%, respectively.

Postoperative management

Enhanced Recovery After Surgery (ERAS) pathways aim to improve postoperative outcome by optimising both anaesthesiologic and surgical care. Older RC patients may therefore derive a marked benefit. Although we do not have protocols specific to older patients, randomised trials – with a median patient age around 70 years -- have investigated ERAS after RC.^{73,74} Significant improvements in time to flatulence, bowel movement and quality of life were seen at day 3, 7 and discharge. Wound healing disorders, fever, thrombosis, demand for analgesics, and time spent in intensive care were less for patients on ERAS protocols.⁷³ ERAS patients were also had significantly less disturbed sleep and interference with functioning.⁷⁴

Postoperative delirium

Postoperative delirium is frequent, being experienced by up to 29% of patients.⁷⁵ Lower preoperative Mini-Mental Status Examination score and older age were significantly associated with delirium, as were cognitive impairment or dementia, depression, alcohol abuse, poor visual acuity, hearing impairment, and anticholinergic medication. Postoperative delirium is associated with increased mortality, length of stay on ICU, increased cost, and long-term loss of cognitive function. Perioperative steps to reduce the incidence of delirium include the intraoperative use of dexmetomidine, avoidance of excessively deep anaesthesia, avoidance of psychoactive substances such as the benzodiazepines, restricted administration of opioids perioperatively, and ensuring adequate hydration.

Conclusions regarding RC in older adult patients

- Adoption of an ERAS protocol including prehabilitation helps improve postoperative outcomes: This involves:
 - Preoperative nutrition: administration of high quality protein foods and immunonutrients prior to RC reduces the risk of perioperative complications in malnourished patients.
 - Treating preoperative anaemia requires administration of i.v. iron. This reduces the need for RBC transfusion and thus reduces postoperative mortality, morbidity and costs.
 - Making the patient fit for surgery: implementation of a fitness program including endurance training.

- Thromboprophylaxis using low-molecular weight heparin derivatives for four weeks after discharge reduces the relative risk of thromboembolic events.
- Avoiding bowel surgery for reconstruction of the lower urinary tract reduces perioperative complications but at the cost of a potentially bilateral ureterostomy.
- There are no clear data on whether nodal dissection can safely be avoided in older patients without compromising oncological outcome.
- Well-designed studies are urgently needed to determine which subgroups of older adult patients benefit from RC in terms of survival and quality of life and which groups are at particular risk from complications.

Neoadjuvant and adjuvant chemotherapy

According to guidelines, older adult patients who are sufficiently fit should be considered for perioperative systemic therapy in addition to local treatment. While the best evidence is for neoadjuvant chemotherapy, its adjuvant use can also be discussed.

Retrospective series show that advanced age is associated with decreased use of perioperative chemotherapy.⁷⁶⁻⁸⁰ Older adult patients who are fit for definitive local therapy should be evaluated for the feasibility of cisplatin-based neoadjuvant chemotherapy,⁸¹⁻⁸³ but the priority should be definitive local therapy.

Standard cisplatin-based regimens include MVAC (methotrexate, vinblastine, adriamycin, cisplatin), high-dose-intensity MVAC and GC (gemcitabine, cisplatin). Classic MVAC is more toxic than high-dose-intensity MVAC plus GCSF.⁸⁴ Although there has been no direct comparison and numbers are small, MVAC appears more likely than GC to cause haematological toxicity in patients ≥ 70 years.⁸⁵

Older adult patients eligible for cisplatin by standard criteria vary greatly in health status and functional reserve. So it may help to use tools that predict severe toxicity. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) is one of them.⁸⁶ However, only 7% of those included in the validation study had BC. Another (the CARG score), developed by Hurria et al, is primarily based on geriatric assessment to predict chemotherapy toxicity in older adult patients.⁸⁷ Again, few BC patients were included in the validation study.

Outcome data on older adult patients are limited, both in trials and retrospective series. However, in the subgroup analysis of the MVAC trial, the benefit of neoadjuvant chemotherapy was also seen in patients ≥ 65 . Dash et al showed that -- depending on the formula used to calculate creatinine clearance -- 50-83% of patients aged 70 years and older were cisplatin-ineligible in the preoperative setting, and 30-67% ineligible in the postoperative setting.⁸⁸ Other factors such as the Clavien Grade 3-4 complication rate after RC are also relevant.⁸⁹ Despite there being no increase in surgical complications with neoadjuvant treatments in trials, we must consider the potential impact of chemotherapy on older adult patients with less functional reserve. The risk is that neoadjuvant therapy will impair their ability to undergo surgery.

Carboplatin is not equivalent to cisplatin⁹⁰ and should not be used for BC in either the neoadjuvant or adjuvant settings.

For patients with advanced BC (pT3/pT4 or pN+) who did not receive neoadjuvant chemotherapy, adjuvant treatment can be discussed if they are fit enough to receive cisplatin-based combinations.^{91,92}

While the benefit of neoadjuvant chemotherapy for MIBC has been confirmed in meta-analyses, its benefit in patients undergoing chemo-radiation is supported by less evidence.^{93,94}

Trimodality therapy

Trimodality therapy (TMT) and RC have not been compared head to head. Evidence about relative outcomes depends on retrospective series, with many confounding factors. Hence both TMT and RC are considered potentially curative first-line options in MIBC, and preference differs between clinicians and geographical areas. As with radical cystectomy, TMT should also be offered in specialist centres.

Trimodality treatment entails a maximal TURBT followed by radiotherapy (RT) with one of several radiosensitisers. Cisplatin was first used in a Canadian randomised study showing improved local control, though the study did not have adequate power to confirm a survival benefit.⁹³ However, cisplatin is nephrotoxic, and many older adult patients do not have sufficient renal function to tolerate it.

Radiosensitisation with hypoxia modification using the bladder carbogen nicotinamide protocol (BCON)⁹⁴ or systemic chemotherapy with fluorouracil/mitomycin C or gemcitabine^{95,96} improves outcomes (mainly progression free survival and local control) compared to radiotherapy alone and is standard of care in the UK.⁹⁷ The phase III BCON trial showed RT with carbogen and nicotinamide significantly improved 3 year recurrence-free survival from 43% to 54% and 3 year OS from 46% to 59% compared to RT alone.⁹⁸ The BC2001 trial showed that fluorouracil and mitomycin-C given concomitantly with RT significantly improved 2 year locoregional disease-free survival from 54% to 67% when compared with RT.⁹⁵ Christodolou et al have published an age-specific analysis of the BCON study and GemX (RT with concurrent gemcitabine) showing that outcomes for patients over 75 years are comparable to those in younger patients, with similar disease-specific survival and progression-free survival in both groups.⁹⁸

In BCON, BC2001 and the RTOG studies, RT is to the bladder alone. There is no evidence of any additional benefit from pelvic lymph node irradiation, but there is a risk of increased toxicity.

Median rates of salvage cystectomy in patients failing TMT have been reported to be 25-30%,⁹⁹ with recent series reporting lower rates of 15-20%.¹⁰⁰ Complete resection of all visible bladder tumour has been shown repeatedly to be an independent predictor of long-term bladder preservation¹⁰¹ and the need for salvage cystectomy.¹⁰²

Patients who do not respond to TMT or have muscle invasive recurrent disease are considered for salvage cystectomy if appropriate. This salvage procedure is associated with an increased healing complications such as fascial dehiscence, ureteral and anastomotic stricture, stoma/loop revisions compared to upfront cystectomy.¹⁰³ Unfortunately, there are no predictive biomarkers to aid clinicians or patients when deciding between radical surgery or TMT. The best outcomes for radical treatment with TMT are in fit patients with small unifocal tumours, no hydronephrosis, carcinoma in situ or diverticulae. The only absolute contraindication for TMT is previous pelvic RT. Increasingly, patient preference is an important consideration.

Alternative bladder-preserving techniques with curative intent

Radical TURBT only

Large radical cystectomy series show pT0 rates in up to 18.9% of patients without neoadjuvant chemotherapy.^{104,105} This suggests that in these patients a radical TURBT-only approach could be curative. However, 20% of pT2 tumours have lymph node metastasis at radical cystectomy,¹⁰⁵ and a potential therapeutic effect of a lymphadenectomy is missed in a TURBT-only approach. In addition, only 22% of MIBCs had no residual tumour on re-TURBT.¹⁰⁶ However in highly selected patients with MIBC and after complete radical TURBT, CSS of 81.9%, 79.5% and 76.7% at 5, 10 and 15 years, and PFS of 75.5%, 64.9% and 57.8%, have been reported¹⁰⁷ and might therefore be considered as a potentially curative alternative.

Partial cystectomy +/- lymphadenectomy

If a patient is suitable for a surgical approach, partial cystectomy can be considered in selected patients. A solitary muscle-invasive tumour, located outside the trigone, that allows complete excision with adequate margins with reasonable residual bladder volume, and a biopsy-proven absence of carcinoma in situ in the remaining bladder and absence of hydronephrosis are generally considered prerequisites.

A pelvic LND should be offered. This allows more accurate staging as well as having potential oncologic benefit without significantly increasing surgical morbidity. In recent studies, the rate of partial cystectomies ranges between 4-10% and has been decreasing. A similar trend is found in patients older than 74 years, while the number of RCs increased from 14% (2003) to 24% (2012).¹⁰⁸ For partial cystectomies, 5-year RFS ranges from 39-67%¹⁰⁹⁻¹¹⁰ with 10-year metastasis-free survival of 61% and CSS of 58%. No significant differences were seen compared with radical cystectomies in selected populations.¹¹¹ Similarly, no differences were found between the two procedures in matched-pair analysis of the SEER database.¹¹²

Follow-up

Follow-up of MIBC in older patients is not standardized and mainly based on expert opinion. Patients treated with curative intent who have good performance status and a life expectancy of more than five years should receive a regular uro-oncological follow up as recommended by the EAU 2018 guidelines.¹¹³

Metastatic bladder cancer in older adult patients

Since no treatment is curative in this setting but there is the possibility of improving survival and symptoms, the goals of therapy and the options for palliative care should be discussed with patients and their caregivers from the outset.

The general hurdles to conventional systemic treatment are the high incidence of comorbidities such as chronic cardiovascular and kidney disease, and the higher likelihood of frailty (PS ≥ 2 or dependency in ADL or IADL).¹¹⁴⁻¹¹⁶ To be more specific, the main obstacle is the greater chance of being ineligible (“unfit”) for current first-line cisplatin-based regimens. However, a patient above 70 with adequate renal function and no major comorbidities can tolerate cisplatin-based chemotherapy as well as younger patients and achieve comparable clinical outcomes.¹¹⁷ With the introduction of checkpoint inhibitors for the treatment of BC, therapeutic options have broadened for cisplatin unfit patients and those with relapse or progression.

Evaluation

Patients with congestive heart failure, cerebrovascular disease, grade 2 or above peripheral neuropathy, or severe hearing impairment are usually excluded from cisplatin. Cisplatin is also contraindicated in patients with impaired renal function according to the Galsky criteria.¹¹⁸ Though the GFR threshold is debated, the cut-off is generally at an estimated GFR below 60 mL/min. According to SIOG, cisplatin dose reduction is not an option.¹¹⁹ How best to evaluate renal function in the older adult is also debated since in patients >70 years, calculated creatinine clearance tends to underestimate GFR; and some authors advocate creatinine clearance measurement by 24-hour urine collection.¹²⁰ In routine practice, older adult patients should have a comprehensive medical evaluation before starting systemic treatment in general and cisplatin in particular.

Ten to 25% of patients aged over 65 years are characterised as frail on geriatric assessment.¹²¹ Even with skilled interventions, such individuals rarely become fit for either cisplatin or carboplatin. This is mainly due to the rapid growth of metastatic urothelial cancer and hence deterioration of PS. Such patients generally receive best supportive care.

With the advent of checkpoint inhibitors, immunotherapy (IO) agents may be considered when evaluating older adult urothelial cancer patients for systemic treatment (see cautions below).

First line

Standard of care in older adult patients fit for cisplatin is cisplatin-based combination chemotherapy with gemcitabine plus cisplatin or ddMVAC.⁸⁵ Of note, more hematological toxicity was seen with MVAC in patients ≥ 70 years. If patients are ineligible for cisplatin, carboplatin combined with gemcitabine is an alternative recommended by the guidelines.

The IOs atezolizumab (anti-PDL-1 antibody) and pembrolizumab (anti-PD-1 antibody) are a valid alternative for cisplatin-ineligible patients and were recently added to the guidelines. In the IMVIGOR 210 trial of first-line atezolizumab in advanced or metastatic urothelial carcinoma, the median age of patients enrolled was 73 years; and subgroup analysis showed no heterogeneity of response by age.¹²² In the KEYNOTE 052 trial of pembrolizumab in cisplatin-ineligible advanced urothelial cancer, 34% of patients were aged 80 years and above. A post hoc analysis found that antitumour activity in patients aged ≥ 65 years and ≥ 75 years and with poor PS was consistent with that in the overall population.¹²³ Toxicity in the older adult subgroup, irrespective of performance status and renal function, was also similar to that in the overall study population.¹²⁴⁻⁷

Checkpoint inhibitors are not directly nephrotoxic,¹²⁴⁻¹²⁷ and their advent is perceived as a positive development for older adult BC patients, many of whom have poor renal function. Of note, in 2018 regulatory agencies restricted the first-line use of atezolizumab and pembrolizumab to patients with PD-L1 positive tumours.¹²⁸ This recommendation was independent of age. This follows IDMC information from the Keynote-361 and IMvigor130 trials suggesting a reduced survival with IO compared with chemotherapy in patients with low levels of PD-L1.

Second line

EAU guidelines suggest rechallenge after >12 months with a cisplatin combination in patients who are eligible and whose tumours may still be cisplatin sensitive.¹¹³ This is also an option for older adult patients who are sufficiently fit. Vinflunine is the only chemotherapy specifically approved (by the EMA) for patients progressing on or after platinum.

Pembrolizumab, atezolizumab and nivolumab are FDA and EMA-approved for patients previously treated with platinum-based chemotherapy.¹²⁹⁻¹³¹ Durvalumab and avelumab are also approved by the FDA for this indication.^{132,133}

The only positive phase III data are with pembrolizumab, which improves OS compared to chemotherapy for patients with metastatic or locally advanced urothelial carcinoma with disease progression after platinum. No difference in efficacy was evident with age.¹³⁴

Other treatments are being evaluated. The molecular characterization of tumours has led to the development of targeted therapies. Recent trials with FGFR inhibitors, anti-VEGF therapies and antibody drug conjugates (ADC) have shown interesting response rates also in older adult patients on trial. The FDA has granted accelerated approval for the ADC Enfortumab Vedotin in December 2019) for the treatment of locally advanced or metastatic urothelial cancer that has progressed on chemotherapy and immunotherapy. There is no specific information about older adults on this drug. The FGFR inhibitor erdafitinib is approved by the FDA for patients with locally advanced or metastatic urothelial carcinoma which has susceptible fibroblast growth factor receptor (FGFR)3 or FGFR2 genetic alterations and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. The specific toxicities of these drugs and drug interactions must be carefully assessed, especially in older adult patients.

Palliation

Early palliative care should be included in the management of advanced bladder cancer patients. In the palliative setting, TURBT or radiotherapy should be used to control symptomatic bleeding, pain or lower urinary tract obstruction. In locally advanced disease, cystectomy with urinary diversion should only be performed if there is no other option for relief of symptoms.⁸²

Radiotherapy is used for symptomatic and local control even in the context of metastatic disease. However, the bladder cannot be retreated. Haematuria, pain and dysuria can respond well to hypofractionated palliative radiotherapy with minimal side effects.¹²⁷ A randomised control trial of 21 Gray in 3 fractions over one week compared to 35 Gray in 10 fractions over two weeks showed comparable outcomes, confirming that palliative hypofractionated radiotherapy can be delivered safely, effectively and provide long term local control.¹³⁵

Summary

The treatment of older adult BC patients who may have limited life expectancy and comorbidities that complicate standard treatment poses many dilemmas. Unlike prostate cancer, BC is rarely indolent. However, the question of if and how to treat remains.

In principle, treatment of NMIBC in the older adult should not differ from that in younger patients. Use of intravesical treatments should be offered independent of patients' age, although follow-up procedures might be tailored to a less rigid scheme, especially in low risk disease.

MIBC is an aggressive disease and should be treated aggressively if the patients' condition permits, and if that is their wish.¹³⁶ At all ages and all disease stages, it is important to discuss with the patient the risks and benefits of radical or conservative treatment and each treatment modality.

In general, radical cystectomy for MIBC is an acceptable treatment in the older adult but may be associated with significant peri-operative morbidity. In addition to surgical experience and appropriate selection of patients and type of urinary diversion, a geriatric assessment should be conducted to assess the risk of perioperative complications. This may encourage optimisation of the patient's condition, and hence increase the range of management options. Whether this improves ultimate outcome remains to be confirmed by controlled trials. Alternatively, trimodality therapy combining an extensive TURB; and radiotherapy combined with radiosensitising chemotherapy is an alternative. The overall results for patients without hydronephrosis and a completely macroscopically resected lesion seem to be in line with those obtained with radical cystectomy.

Progression of metastatic disease typically leads quickly to clinical symptoms, and clear radiographic evidence of progression is a potential trigger for active treatment with the goal of increasing survival but also of delaying symptoms and achieving general palliation. This may involve administration of chemotherapy, radiation and, more recently, immunotherapy. Checkpoint inhibitors are now a second-line option for all patients and a first line option for biomarker-selected cisplatin-ineligible patients.

There is a lack of clinical trial data on the treatment of older adult bladder cancer patients. To help guide choice of treatment, efforts should be made to enroll such patients in controlled trials and in

studies of routine practice. Studies should include at least a minimum of geriatric data (i.e. G-CODE) to provide a representative description of the older adult patients treated.¹³⁷

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