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The effect of age and gender on bladder cancer: a critical review of the literature

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While patient age and gender are important factors in the clinical decision-making for treating urothelial carcinoma of the bladder (UCB), there are no evidence-based recommendations to guide healthcare professionals. We review previous reports on the influence of age and gender on the incidence, biology, mortality and treatment of UCB. Using MEDLINE, we searched for previous reports published between January 1966 and July 2009. While men are three to four times more likely to develop UCB than women, women present with more advanced disease and have worse survival rates. The disparity among genders is proposed to be the result of a differential exposure to carcinogens (i.e. tobacco and chemicals) as well as reflecting genetic, anatomical, hormonal, societal and environmental factors. Inpatient length of stay, referral patterns for haematuria and surgical outcomes suggest that inferior quality of care for women might be an additional cause of gender inequalities. Age is the greatest single risk factor for developing UCB and dying from it once diagnosed. Elderly patients face both clinical and institutional barriers to appropriate treatment; they receive less aggressive treatment and sub-therapeutic dosing. Much evidence suggests that chronological age alone is an inadequate indicator in determining the clinical and behavioural response of older patients to UCB and its treatment. Epidemiological and mechanistic molecular studies should be encouraged to design, analyse and report gender- and age-specific associations. Improved bladder cancer awareness in the lay and medical communities, careful patient selection, treatment tailored to the needs and the physiological and physical reserve of the individual patient, and proactive postoperative care are particularly important. We must strive to develop transdisciplinary collaborative efforts to provide tailored gender- and age-specific care for patients with UCB.

KEYWORDS

immunotherapy, age, gender, recurrence, survival, bladder cancer, prognosis, urothelial carcinoma, chemotherapy, elderly

INTRODUCTION

Urothelial carcinoma of the urinary bladder (UCB), the fourth most common cancer in men and the ninth most common in women in the USA, results in significant morbidity and mortality [1]. Based on rates from 2004 to 2006, one in 41 people born today will be diagnosed with UCB at some time during their lifetime [1]. Currently, it is estimated that there are >500 000 living men and women in the USA who have a history of UCB. Most patients with UCB are diagnosed based on gross or microscopic haematuria. At initial diagnosis, ≈70% of patients have cancers confined to the epithelium or subepithelial connective tissue. These cancers are usually managed with endoscopic resection and selective use of intravesical therapy. The recurrence rate for these tumours is 50–70%, while 10–15% progress to muscle invasion over a 5-year period [2,3]. Disease recurrence can be local or in the upper urinary tract even after several years, necessitating life-long surveillance. About 30% of patients have muscle-invasive cancer at initial diagnosis; of this population, half have distant metastasis within 2 years, and 60% die within 5 years, despite aggressive treatment [4–6].

While clinicians recognize the importance of demographic heterogeneity in the management of patients with UCB, there are only minimal evidence-based recommendations that adjust for patient age and gender. Indeed, the association and influence of age and gender on the incidence, staging, prognosis and survival in UCB is poorly investigated and understood. Recent epidemiological and translational research has shed some light on the complex relationship between age and gender and UCB. In this review we discuss previous reports on the effect of age and gender on the incidence, biology, mortality and treatment of UCB.

GENDER AND UCB

The incidence and severity of diseases vary between the genders and might be related to differences in carcinogenic exposures, routes of entry, enzymatic processing of environmental substances, and cellular and physiological responses [7]. UCB is the fourth most common cancer in men after prostate, lung and colorectal cancers, accounting for 6.6% of all cancer cases [8]. Between 1988 and 2008, the number of UCBs diagnosed annually in the USA increased by >50%, and at a 25% faster rate in men than in women [8]. However, while UCB affects more men

than women, the prognosis of men with UCB is better than that of women. In fact, although men are nearly three to four times more likely to develop the disease than women, they are only twice as likely to die from UCB, comprising 3% of all cancer deaths in men and 1.5% in women in the USA [8]. Thus the ratio of UCB-specific mortality to incidence is lower for men than for women.

While men are at higher risk than women for developing UCB, women present with more advanced disease. A retrospective study of the Netherlands Cancer Registry spanning the period 1989–1994 identified 20 541 patients diagnosed with UCB of whom 80% were male and 20% female [9,10]. Male patients were more likely to be diagnosed with non-muscle-invasive UCB (71% vs 63%), but the disparity in gender distribution across stages diminished with advancing pathological stage (25% vs 21% for pT1 and 2.8% vs 3.9% for pT4 for men and women, respectively). However, the occurrence of metastatic disease was similar amongst genders (2.7% vs 2.8% for men vs women).

A study of 615 patients with newly diagnosed UCB between 1997 and 2000 in 17 Spanish hospitals [11] found a 6.7-times greater risk of diagnosing UCB in men than women for both non-muscle-invasive and muscle-invasive disease. Women were somewhat older at the time of diagnosis, with a mean (SD) age of 68 (9) vs 66 (10) years ($P = 0.01$). Women were more likely than men to have multifocal (50% vs 29%, $P = 0.005$) and larger tumours (5.2 vs 3.8 cm, $P = 0.03$). Interestingly, women had an almost five-fold increase in the probability of receiving intravesical therapies after transurethral resection than their male counterparts.

There is no uniform theory to explain the differential presentation and behaviour of UCB between genders. Excessive environmental exposure to carcinogens such as tobacco and industrial chemicals in men has been suggested as an explanation. However, a previous study showed that the gender-related differential risk of developing UCB persisted even after controlling for these factors [12]. Little effort has been spent on exploring other environmental factors or biological pathways that could underlie the differences in UCB incidence and a cancer's intrinsic biological potential between genders. Indeed, studies have focused more on disease aetiology than on disease heterogeneity, and gender is usually little more than a covariate in statistical analyses. Recently, several alternative hypotheses have been proposed that include genetic, anatomical, hormonal, societal and environmental factors.

One explanation for the differential behaviour of UCB between genders has related to sex steroids and their receptors. An epidemiological study showed that postmenopausal women have a greater risk of developing UCB than premenopausal women [13]. Animal studies showed that the incidence of spontaneous and chemically induced UCB is significantly greater in male than in female rats [14–16], and treatment of male rats with androgen deprivation reduce the development of chemically induced UCB [14,15,17]. In humans, the androgen receptor (AR) has been detected in normal bladder epithelium and in bladder tumours from men and women [18,19]. Only a few authors found no AR expression in the rat and human urinary bladder [18,20]. Moreover, experiments using AR antagonists, small interfering RNA against the AR, and androgen deprivation suggested the importance of the AR signalling pathway in the development and progression of UCB [15,21]. However, mechanisms that regulate the activity of the AR in UCB cells remain unknown. Moreover, the prognostic significance of AR expression in human UCB needs further investigation.

Recent studies suggested that oestrogen receptor β (ERβ) expression, the main subtype of ER expressed in the bladder urothelium, might be important in UCB carcinogenesis [22,23]. The expression of ERβ in the normal urothelium of the female bladder is expected, as the upper part of the vagina and a part of the bladder (trigone and posterior bladder neck) have a common embryonic origin [24]. To date, only one study has reported ERβ expression in humans with UCB [25]. The biologic and prognostic significance of ERβ expression remains a subject of ongoing investigations.

The different outcomes between men and women with UCB might also be due to inequalities in healthcare. Analysis of data from a population-based dataset of >15 000 patients who had a radical cystectomy (RC) (the USA Nationwide Inpatient Sample; study period 1988–2000) showed that duration of hospital stay, a possible surrogate marker for the quality of surgical and postoperative care, was significantly longer in women than men [26]. Suboptimal treatment might relate to patient, physician and/or system factors. For example, certain patients might decline the best treatment options available, especially when urinary diversion requiring a stoma, or sexual dysfunction, occurs. However, system-level problems such as provider bias, knowledge or training, health plans, and access to healthcare might influence presentation and referral patterns. Thus, provider diagnostic and therapeutic choices might be influenced by gender, and physicians might not provide the best treatment because of lack of knowledge or training, and the potentially more extensive work required to care for female patients with UCB [27]. In support of this hypothesis, investigators reported a 65% higher likelihood that men would be referred to a urologist than women by their primary provider for new onset or recurrent haematuria [28]. Possibly a presumptive diagnosis of UTI in women could be responsible. A delay in urological referral for haematuria could result in a delay in diagnosis of potentially life-threatening UCB. All too often, UCB is not even in the differential diagnosis when women present to primary-care physicians complaining of haematuria or a change in voiding symptoms. Frequently, women are treated with antibiotics without urine analysis, urine cultures, or cytology.

Recently, three well-designed studies reported that female gender is associated with a worse clinical outcome after cystectomy. Using a large, multicentre dataset comprising 3357 patients (673 women, 20%), the first study identified female gender as a poor risk feature in competing-risk analyses that adjusted for the effects of standard clinicopathological characteristics [29]. Using data from nine Surveillance, Epidemiology and End Results (SEER) registries, the second study found that women presented with more advanced disease and were more likely to die from UCB than their male counterparts, after controlling for the effects of available features such as tumour stage and grade [30]. Using data from 19 021 male and 6693 female patients with UCB diagnosed between 1991 and 1999 from the SEER-Medicare database, the third study found that among those diagnosed with stage IV disease, women had significantly lower 5-year survival rates than men, adjusting for age, race, number of comorbidities and 'ecological' socioeconomic status (hazard ratio 1.36; 95% CI 1.21–1.52) [31]. However, there were no significant

gender differences in 5-year survival rates among those diagnosed with stage I, II or III UCB after adjusting for the effects of sociodemographic characteristics. These findings suggest that differences in sociodemographic characteristics account for much of the gender differences in survival, although none of the characteristics examined explained the persistent gender survival disparity among those diagnosed with stage IV disease.

In an updated analysis from the SEER database of >101 000 patients diagnosed with UCB between 1990 and 2003 [32], investigators found that survival was poorest in African-American women. In addition, data on patient age and distribution of tumour characteristics corroborated previous reports that women present when significantly older and with larger proportions of higher-stage tumours and non-urothelial carcinomas than men. However, differences in these prognostic variables explained only up to 30% of the excess mortality among women vs men. This suggests that delay in diagnosis, possibly evidenced by advanced stage at diagnosis, did not emerge as the most significant contributor to the excess mortality hazard in women.

Thus, while conducting educational programmes aimed at the public and healthcare providers to improve early diagnosis of UCB might reduce disease mortality in women, this might not be sufficient to close the gap between the genders in mortality. Differences in treatment and hormonally mediated differences in bladder cancer biology might be other contributing factors to the worse outcome of women than men. The study showed that excess hazard for death from bladder cancer during the first 3–4 years of follow-up was ≈80% higher among women than men. Although the proportion of more aggressive non-urothelial cancer types was also twice as high in women than men, these cancers only accounted for a small minority of all of the bladder cancers. Muscle-invasive disease was present in 25% of Caucasian women, 22% of Caucasian men, 43% of African-American women, and 30% of African-American men. There were statistically significant differences for comparisons by gender in both racial groups.

The studies on inpatient length of stay, referral patterns for haematuria and surgical outcomes also suggested that a trend toward inferior quality of care for women might be an additional possible cause of the gender inequalities. Epidemiological and mechanistic molecular studies should be encouraged to design, analyse, and report gender-specific associations to aid in understanding gender differences in the incidence, progression and metastasis of UCB.

AGE AND UCB

Age is now widely accepted as the greatest single risk factor for developing UCB. While UCB can occur at any age, it is generally a disease of middle-aged and elderly people. In fact, with the median age at diagnosis being ≈70 years [33], UCB is primarily considered a disease of the elderly. Because of the close link between age and incidence of UCB, UCB can be expected to become an enormous challenge with the growth in the ageing population in the years ahead. Men and women aged ≥65 years represent ≈12% (36.8 million) of the USA population, a number expected to double by the year 2030 [34–42]. Unfortunately, evidence-based practice guidelines regarding the short- and long-term management of UCB are sparse for this group. Moreover, it is inappropriate to extrapolate from studies on younger populations, because elderly adults are physiologically, psychologically and socially different from younger adults [43]. For many older adults, cancer joins the ranks of other age-related chronic diseases, but the post-treatment burden of the disease (e.g. loss of physical function, permanent disability, fatigue, insomnia, depression, anxiety and economic loss) is relatively unknown or at best poorly defined in this population [42].

ASSOCIATION OF AGE WITH INCIDENCE AND PROGNOSIS OF UCB

Age is a strong and independent risk factor for the development of UCB [33]. Various demographic studies have shown that individuals aged ≥65 years have 11 times the incidence of cancer in general and a 15-times greater cancer mortality rate than individuals aged <65 years [33]. The incidence of UCB increases from ≈142 per 100 000 men and 33 per 100 000 women aged 65–69 years, to 296 per 100 000 men and 74 per 100 000 women when aged ≥85 years.

Recent data obtained by the California Cancer Registry revealed that the peak incidence of UCB occurs at 85 years old [44]. This is 20 years after the general retirement age and implies a longer than usual latent period in carcinogenesis. Moreover, there is a 10-year peak difference between lung or bronchial cancer and UCB, two malignancies that share some of the same carcinogens (i.e. tobacco and industrial exposure). This has been hypothesized as the result of the lungs being the first organs to come into contact with these carcinogens, and the bladder being exposed last and in a more diluted potency. Thus, the bladder might require a longer exposure for the induction of cellular mutations by carcinogens. Diminishing pulmonary function and the chronic effects of cigarette smoking on the lungs might increase the cumulative amount of systemically absorbed carcinogens.

Several theories have been proposed to explain the interactions between carcinogenesis in general and the ageing process. First, as individuals age, they experience cumulative environmental exposure to carcinogens (particularly with cigarette smoking and exposure to carcinogens in the workplace or in highly polluted living conditions). Second, ageing allows time for the development and accumulation of cellular events that can lead to neoplastic transformation. The existence of a lag time between these exposures, the cellular events and the clinical expression of malignancy might account for the first appearance of UCB in an older population. Third, ageing might be accompanied by a decreased ability to fully empty the bladder, potentially prolonging the contact time for exposure to carcinogens excreted in the urine. Furthermore, because of bothersome voiding symptoms, people might drink less as they get older. Over time, this would increase the urinary concentration of carcinogens to which the elderly are exposed. An additional contributor to increasing the urinary concentration of carcinogens might be the reduced ability to detoxify potential carcinogens as the result of organ system deterioration with ageing.

In recent years, there has been a small but steadily growing recognition that the link between ageing and cancer is more complex than the simple passage of time to which age-dependence of cancer has traditionally been ascribed. Research on changes in the growth

regulatory function of genes and proteins with advancing age and cancer has led to a better understanding of biological relationships between cancer development and ageing, and has introduced new possibilities for intervention [45]. Certain genes might be activated while others are suppressed with advancing age. This can lead to an increase in oncogene activity, leading to the genesis of a cancer cell, or a decrease in tumour-suppressor gene activity with an inability to suppress or clear an organ of transformed neoplastic cells. Further, an aged cell might have a decreased capacity for repair of mutations in its DNA. In UCB, many genes have been found to fulfil the roles of both oncogenes and tumour-suppressor genes [46–48]. These might then be associated with the development of different types of UCB with individualized and distinctive intrinsic biological potentials [46,48].

As with incidence, mortality from UCB is also higher in the elderly. The ratio of cancer-specific mortality to incidence for men and women in the USA aged 65–69 years is 14% and 18%, respectively, whereas for men and women age 80–84 years it is 30% and 37%, respectively (SEER, 1973–97) [33]. There have been several studies on the biological and clinical aggressiveness of UCB in young vs old patients, but these have been relatively inconclusive. The higher mortality in the elderly has several possible explanations. In patients aged <40 years, UCB tends to be well differentiated and therefore behave in a more indolent fashion [49–51]. While some researchers observed lower rates of disease recurrence and progression with better survival in younger patients [49–56], others have reported that the natural history of UCB in the younger groups resembles that in older patients [57–61]. Differences in outcomes between the elderly and their younger counterparts might be due to a combination of a relatively more advanced stage at diagnosis (due to social and biological reasons) and the administration of less aggressive and effective therapies in the elderly (avoidance or delay of radical treatment or chemotherapy).

AGE AND TREATMENT OF UCB

Treatments for non-muscle-invasive UCB (clinical ≤T1) are generally well-tolerated by the elderly. Surgical procedures and the anaesthetic support they require are not particularly intrusive or disruptive. Neither creates major fluid shifts or pressures imposed on the cardiovascular, pulmonary, renal or liver system. Even when they require repeated endoscopic resection with or without intravesical instillation of chemotherapeutic or immunotherapeutic agents, the risks of side-effects and complications are low. Most of the agents are not absorbed systemically and therefore do not produce significant systemic effects to which the elderly might be more vulnerable. Moreover, in certain elderly patients whose comorbid conditions can create an excessive risk for anaesthesia, treatments for some tumours can be deferred without increasing the risk to the patient, as many low-grade tumours are at low risk of progression and therefore will not threaten survival. However, the potential complications of intravesical therapy might not be as well-tolerated in elderly individuals whose urinary, vascular, cardiac and immunological functions and pulmonary reserve are decreased [62–67]. Even minor complications such as high fevers, increased urinary frequency, discomfort on urination, haematuria, clot retention and the need for repeated catheterization can be more problematic for the elderly than the young patient. Therefore, some investigators caution against using intravesical therapy in the elderly, and even avoid this therapy in patients aged ≥80 years, which might contribute to the poor disease-specific outcomes as well [68].

In addition to leading to a higher rate of complications, age might also affect the efficacy of intravesical therapy, especially immunotherapy. One investigator reported a 10% absolute difference in freedom from disease at 5 years after intravesical treatment with BCG for patients aged >70 years (27%) vs those aged <70 years (37%) [69]. This was confirmed by a second study which reported a 22% lower absolute disease-free rate for patients aged ≥80 years treated with BCG plus interferon, compared with similarly treated patients aged 60–70 years [70]. Together with higher complication rates, this suggests that older patients should either be treated with alternative regimens or should be considered for earlier RC.

When muscle-invasive UCB is diagnosed in the elderly, considerations of selective treatments become more complicated. The standard treatment for muscle-invasive UCB is RC with bilateral lymphadenectomy [4,5] with or without perioperative systemic chemotherapy [71–77]. Each of these treatments creates substantial challenges to the various organ systems in the body, both individually and in aggregate, and potentially even more so for the elderly, in whom gradual diminution of physiological capabilities to withstand the rigors of these treatments has occurred over time. These same events could compromise the ability required to respond to these treatments. In addition, decreased physiological reserve could compromise the recoverability of the different organ systems and of the host as a whole to these treatments. Comorbid conditions and the fundamental 'frailty' that accompany the ageing process might also compromise the delivery of treatments to their full dosages and capabilities. In addition, potential side-effects and complications of treatments might themselves create morbidities and mortality in an already weakened patient with cancer and a reduced ability to respond to the additional treatments and challenges.

Elderly patients are less likely to be treated with extirpative surgery than their younger counterparts [78,79]. Fore example, an analysis of patients from the SEER database reported that only 55% of patients aged 55–59 years whose cancers indicated the need for RC actually had this surgery [78]. The percentage of those treated with RC further decreased with advancing patient age, with only ≈25% of patients aged 70–79 years undergoing RC. This suggests that RC is all too often withheld or delayed in elderly patients who could benefit from it. Reasons for this are multifactorial and can only be hypothesized. They include a delay in diagnosis, the overuse of non-surgical alternatives for an inappropriately long period, the relative inexperience of many surgeons leading them to avoid RC, or a perceived or real belief that many patients simply will not tolerate surgery because of age or comorbidity.

Elderly patients face both clinical and broader institutional barriers to appropriate treatment, are less likely to have their cancer staged [80,81], and might receive less aggressive treatment and subtherapeutic dosing because of comorbid conditions or perceptions of less physiological reserve, inability to withstand the more rigorous therapeutic approaches, or greater underlying risk of having side-effects and complications. For example, older patients with UCB are less likely to receive extended lymph node

dissection or adjuvant chemotherapy [55]. Moreover, older patients might not be referred to comprehensive cancer centres or offered participation in clinical trials because of these perceptions and considerations.

RC and urinary diversion present individual challenges to any patient, especially an elderly one. The procedures themselves require the relative health and normal physiological reserves of each organ system to recover fully and rapidly. Incorporating a urinary reservoir or conduit to assume the function of the bladder in storing and eliminating urine will compound these issues. These procedures result in a perioperative morbidity rate of 30–60%, even at major referral centres with substantial experience [5,6,82–84]. Each of these procedures challenges the patient not only in initial recovery, but over the long-term. These considerations might be particularly significant in the elderly individual who is already weakened both by an aggressive cancer and compromised by deterioration of multiple organ systems. Fortunately, both morbidity and mortality rates have declined dramatically due to significant improvements in perioperative care [4,82,85].

The reported mortality rate in elderly patients treated with RC is 0–11% [84]. A low mortality rate was reported even when specifically evaluating patients both aged >75 years and with significant comorbidities, as measured using the American Society of Anesthesiology physical status classification [86]. A study in 2008 found that age is not associated with 90-day mortality or early postoperative complications in a data set of 314 patients treated with RC [87]. Conversely, several studies reported a significant relationship between age at RC and perioperative complication rate. The Health Care Utilization Project, involving 13 964 patients who had RC, showed that increasing age was independently associated with in-hospital mortality after RC (odds ratio 1.05; 95% CI 1.03–1.07) [88]. Similarly, a study of 2538 RC patients from the American College of Surgeons National Surgical Quality Improvement Program found that increasing age was independently associated with an increased risk of any postoperative complication after RC (odds ratio 1.3; 95% CI 1.2–1.5) [89]. Reasons for the differences between such studies are unknown, but might be related to differences in study populations, definitions and recording of clinical outcomes (i.e. complications), patient selection and study designs. Perioperative mortality or 30-day mortality/morbidity that is reported by many studies is not sufficient to capture all treatment-related mortality/morbidity. Expanding the definition of perioperative mortality to at least 90 days is necessary to reflect the true health-related quality-of-life effect of RC. Using data from 5510 patients treated with partial or RC within four SEER registries between 1984 and 2004, one study showed that, at 30, 60 and 90 days after RC, the perioperative mortality rates were relatively low at 1.1%, 2.4% and 3.9%, respectively [90]. Interestingly, age, stage and histological subtype represented statistically significant and independent predictors of 90-day mortality.

The combined data show that chronological age alone is not sufficient to predict the worst outcomes observed in elderly patients treated with RC. More importantly, the cumulative data suggests that chronological age should not preclude definitive surgical therapy.

Quality of life after RC is an important consideration. Differences in body image and urinary, sexual and social function after RC are still undefined. Elderly patients are offered primarily an ileal conduit, while the ileal neobladder is usually reserved for younger and healthier patients [5,6,91]. One study found an insignificant trend towards a higher rate of complications in 85 elderly patients with an ileal neobladder compared to elderly patients with an ileal conduit [92]. Another study of patients with ileal neobladders found that advanced age does not preclude a good daytime continence level. However, decreased long-term reservoir capacity, higher rate of nocturia, and worse continence status were noted in elderly patients with ileal neobladders [93]. In another study, the continence status at the 5-year follow-up approached 100% in patients aged <50 years, vs 90% for those aged >60 years [94]. While this still represents a very high overall level of continence in the older population, possible explanations for the decreased overall level in the elderly include worsening external urethral sphincter function [94] and decreased urethral sensitivity with advancing age [95]. Similarly, as expected, age and pre-surgical erectile function are the best predictors of recovery of erectile function after RC [96]. Even when older patients do have RC, they are less likely to have a pelvic lymph dissection, and if they have the latter, the extent is more limited than that in younger patients.

Adding to the complexity and risk for older individuals is the perioperative use of systemic chemotherapy. Although perioperative chemotherapy has been suggested to improve cancer-specific survival in patients with muscle-invasive UCB [71–77], it can also have a deleterious effect on various organ systems, with potential side-effects that delay surgery and from which an older patient might not fully recover. The systemic agents used can compromise the immune system and its ability to respond to infection, and the cardiac, renal, hepatic and pulmonary functions in their ability to respond to various physiological challenges during surgery and in the recovery period afterward. Furthermore, any pre-existing compromise to these systems through comorbid conditions or through the physiological deterioration that has occurred with ageing might limit the application of full-dose treatment, thereby limiting the potential benefit offered by chemotherapy administered in conjunction with surgical treatment.

Ongoing treatment for comorbid conditions such as diabetes, pulmonary disease and heart disease can also result in various drug interactions when chemotherapy is introduced. Chronic diseases, e.g. renal or liver disease, might alter the pharmacokinetics and pharmacodynamics of chemotherapeutic agents. These changes, as well as alterations in drug absorption, distribution, metabolism and excretion, can result in greater exposure to toxicities among older patients with cancer [97,98]. Consequently, older adults might be less likely than younger patients to receive optimal doses of chemotherapy because of toxicities and complications [55,99,100]. Treatment trials seldom adjust for individual or multi-organ comorbid conditions [98,101,102]. Notwithstanding all of these considerations, radical surgery and systemic chemotherapy is feasible, safe and effective in the treatment of adequately selected elderly patients with UCB.

CONCLUSIONS

In recent years, rates of UCB in women gradually increased because smoking and exposure to chemicals has become more common in women. Nevertheless, UCB is still predominantly a disease of men. While some

authors have investigated the potential relationship between sex hormones and UCB development and progression, there is, at present, no convincing evidence for their role. There is no doubt that men are diagnosed more commonly with UCB and that women present at a more advanced stage. Whether women patients harbour biologically more aggressive cancers than men remains an unanswered question. Until research at the molecular level can help to resolve genetic or proteomic differences in UCB, clinicians must change system-related factors that cause gender-specific inequalities in UCB care.

The decision to undergo treatment for cancer is a compromise between loss of function and independence on one side, and extension of life on the other, a compromise complicated by a host of concomitant issues such as comorbid medical conditions, functional declines and 'frailty', family dynamics, and social and psychological issues. With an ageing population and increased life-expectancy, greater attention must be devoted to the development of UCB in the elderly. Interest must be expanded in the concomitant age-associated illness burden of older people diagnosed with UCB. Healthcare professionals must deal with the concurrent health problems of the elderly, as cancer occurs frequently in the presence of one or more other chronic diseases or health problems. These chronic diseases and conditions can increase the risk of adverse effects from various treatment interventions. Thus, a priority in managing UCB is to integrate concurrent conditions in decision-making regarding treatment and multispeciality perioperative care.

The critical factor for the success of treatment for muscle-invasive UCB in the elderly is patient selection. Elderly patients, when treated adequately, tolerate and respond well to cancer treatment [103]. The treatment and management decisions for older patients should be guided by treatments for comorbid conditions, organ function, frailty and cognitive status. Each age cohort brings a wide range of comorbid conditions, depressive affects, physical, social and cognitive limitations, and other indicators of frailty and associated indications of organ decrements and geriatric syndromes. It is important to understand how variations in each of these indicators accompanies and successively changes in older patients. While perioperative morbidity and mortality are increased in the elderly patient, chronological age should not be viewed as a barrier to treatment [55]. It is imperative that healthcare practitioners and researchers from disparate disciplines collectively focus efforts towards gaining a better understanding of what the consequences of UCB and its treatments are for older adults, and how to appropriately meet the multifaceted medical and psychosocial needs of this growing population.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ.** Cancer Statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225–49
2 **Prout GR Jr, Barton BA, Griffin PP, Friedell GH.** Treated history of noninvasive grade 1 transitional cell carcinoma. The National Bladder Cancer Group. *J Urol* 1992; **148**: 1413–9
3 **Pagano F, Bassi P, Galetti TP *et al.*** Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. *J Urol* 1991; **145**: 45–50
4 **Shariat SF, Karakiewicz PI, Palapattu GS *et al.*** Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the bladder cancer research consortium. *J Urol* 2006; **176**: 2414–22
5 **Stein JP, Lieskovsky G, Cote R *et al.*** Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001; **19**: 666–75
6 **Madersbacher S, Hochreiter W, Burkhard F *et al.*** Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003; **21**: 690–6
7 **Anonymous.** Exploring the biological contributions to human health: does sex matter? *J Womens Health Gend Based Med* 2001; **10**: 433–9
8 **Jemal A, Siegel R, Ward E *et al.*** Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71–96
9 **Mungan NA, Aben KK, Schoenberg MP *et al.*** Gender differences in stage-adjusted bladder cancer survival. *Urology* 2000; **55**: 876–80
10 **Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA.** Gender differences in stage distribution of bladder cancer. *Urology* 2000; **55**: 368–71
11 **Winter CC, Puente E, Wall RL.** Bladder involvement with lymphoma. *Urology* 1979; **14**: 151–3
12 **Hartge P, Harvey EB, Linehan WM *et al.*** Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst* 1990; **82**: 1636–40
13 **McGrath M, Michaud DS, De Vivo I.** Hormonal and reproductive factors and the risk of bladder cancer in women. *Am J Epidemiol* 2006; **163**: 236–44
14 **Okajima E, Hiramatsu T, Iriya K, Ijuin M, Matsushima S.** Effects of sex hormones on development of urinary bladder tumours in rats induced by N-butyl-N-(4-hydroxybutyl) nitrosamine. *Urol Res* 1975; **3**: 73–9
15 **Miyamoto H, Yang Z, Chen YT *et al.*** Promotion of bladder cancer development and progression by androgen receptor signals. *J Natl Cancer Inst* 2007; **99**: 558–68
16 **Boorman GA.** Animal model of human disease: carcinoma of the ureter and urinary bladder. *Am J Pathol* 1977; **88**: 251–4
17 **Imada S, Akaza H, Ami Y, Koiso K, Ideyama Y, Takenaka T.** Promoting effects and mechanisms of action of androgen in bladder carcinogenesis in male rats. *Eur Urol* 1997; **31**: 360–4
18 **Zhuang YH, Blauer M, Tammela T, Tuohimaa P.** Immunodetection of androgen receptor in human urinary bladder cancer. *Histopathology* 1997; **30**: 556–62
19 **Boorjian S, Ugras S, Mongan NP *et al.*** Androgen receptor expression is inversely correlated with pathologic tumor stage in bladder cancer. *Urology* 2004; **64**: 383–8
20 **Ruizeveld de Winter JA, Trapman J, Vermey M, Mulder E, Zegers ND, van der Kwast TH.** Androgen receptor expression in human tissues: an immunohistochemical study. *J Histochem Cytochem* 1991; **39**: 927–36
21 **Chen F, Langenstroer P, Zhang G, Iwamoto Y, See WA.** Androgen dependent regulation of bacillus Calmette-Guerin induced interleukin-6 expression in human transitional

carcinoma cell lines. *J Urol* 2003; **170**: 2009–13
22 **Pelletier G.** Localization of androgen and estrogen receptors in rat and primate tissues. *Histol Histopathol* 2000; **15**: 1261–70
23 **Makela S, Strauss L, Kuiper G *et al.*** Differential expression of estrogen receptors alpha and beta in adult rat accessory sex glands and lower urinary tract. *Mol Cell Endocrinol* 2000; **170**: 219–29
24 **Saez S, Martin PM.** Evidence of estrogen receptors in the trigone area of human urinary bladder. *J Steroid Biochem* 1981; **15**: 317–20
25 **Shen SS, Smith CL, Hsieh JT *et al.*** Expression of estrogen receptors-alpha and – beta in bladder cancer cell lines and human bladder tumor tissue. *Cancer* 2006; **106**: 2610–6
26 **Taub DA, Hollenbeck BK, Cooper KL *et al.*** Racial disparities in resource utilization for cystectomy. *Urology* 2006; **67**: 288–93
27 **Schulman KA, Berlin JA, Harless W *et al.*** The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 1999; **340**: 618–26
28 **Johnson EK, Daignault S, Zhang Y, Lee CT.** Patterns of hematuria referral to urologists: does a gender disparity exist? *Urology* 2008; **72**: 498–502
29 **Svatek RS, Shariat SF, Dinney C *et al.*** Evidence-based gender related outcomes after radical cystectomy: results of a large multicenter study (abstract #1744). *J Urol* 2009; **181**: 629
30 **Jeldres C, Isbarn H, Capitanio U *et al.*** Gender is an important predictor of cancer-specific survival in patients with urothelial carcinoma after radical cystectomy (abstract #1761). *J Urol* 2009; **181**: 635
31 **Datta GD, Neville B, Datta NS, Earle C.** Gender disparities in bladder cancer survival: an assessment of socio-demographic factors. *AACR Meeting Abstracts* 2006: B38
32 **Scosyrev E, Noyes K, Feng C, Messing E.** Sex and racial differences in bladder cancer presentation and mortality in the US. *Cancer* 2009; **115**: 68–74
33 **Messing EM.** Urothelial tumors of the bladder. In Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA eds, *Campbell-Walsh Urology*, Ninth Edition, Chapter 75. Philadelphia: Saunders-Elsevier, 2008: 2407–46
34 **Centers for Disease Control and Prevention.** Available at: http://www.cdc.gov/aging. Accessed September 2009
35 **Kent MM, Mather M.** What drives US population growth? *Population Bull* 2002; **57**: 1–40
36 **Kinsella K, Velkoff VA.** *An Aging World.* 2005 US Census Bureau. Series P95/005-1. Washington, DC: US Government Printing Office, 2005
37 **UBoCw.** Available at: http://www.census.gov Accessed September 2009
38 **Yancik R, Ries LA.** Cancer in older persons: an international issue in an aging world. *Semin Oncol* 2004; **31**: 128–36
39 **Yancik R, Ries LA.** Cancer in older persons. Magnitude of the problem – how do we apply what we know? *Cancer* 1994; **74**: 1995–2003
40 **Yancik R, Ries LA.** Aging and cancer in America. Demographic and epidemiologic perspectives. *Hematol Oncol Clin North Am* 2000; **14**: 17–23
41 **Edwards BK, Howe HL, Ries LA *et al.*** Annual report to the nation on the status of cancer 1973–99, featuring implications of age and aging on U.S: cancer burden. *Cancer* 2002; **94**: 2766–92
42 **Hewitt M, Rowland JH, Yancik R.** Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci* 2003; **58**: 82–91
43 **Boss GR, Seegmiller JE.** Age-related physiological changes and their clinical significance. *Western J Med* 1981; **135**: 434–40
44 **Schultzel M, Saltzstein SL, Downs TM, Shimasaki S, Sanders C, Sadler GR.** Late age (85 years or older) peak incidence of bladder cancer. *J Urol* 2008; **179**: 1302–5
45 **Campisi J.** Aging and cancer cell biology, 2008. *Aging Cell* 2008; **7**: 281–4
46 **Shariat SF, Karam JA, Lerner SP.** Molecular markers in bladder cancer. *Curr Opin Urol* 2008; **18**: 1–8
47 **Ehdaie B, Theodorescu D.** Predicting tumor outcomes in urothelial bladder carcinoma: turning pathways into clinical biomarkers of prognosis. *Expert Rev Anticancer Ther* 2008; **8**: 1103–10
48 **Wu XR.** Urothelial tumorigenesis: a tale of divergent pathways. *Nat Rev Cancer* 2005; **5**: 713–25
49 **Benson RC Jr, Tomera KM, Kelalis PP.** Transitional cell carcinoma of the bladder in children and adolescents. *J Urol* 1983; **130**: 54–5
50 **Fitzpatrick JM, Reda M.** Bladder carcinoma in patients 40 years old or less. *J Urol* 1986; **135**: 53–4
51 **Linn JF, Sesterhenn I, Mostofi FK, Schoenberg M.** The molecular characteristics of bladder cancer in young patients. *J Urol* 1998; **159**: 1493–6
52 **Madgar I, Goldwasser B, Nativ O, Hanani Y, Jonas P.** Long-term followup of patients less than 30 years old with transitional cell carcinoma of bladder. *J Urol* 1988; **139**: 933–4
53 **Witjes JA, Debruyne FM.** Bladder carcinoma in patients less than 40 years of age. *Urol Int* 1989; **44**: 81–3
54 **Resorlu B, Beduk Y, Baltaci S, Ergun G, Talas H.** The prognostic significance of advanced age in patients with bladder cancer treated with radical cystectomy. *BJU Int* 2009; **103**: 480–3
55 **Nielsen ME, Shariat SF, Karakiewicz PI *et al.*** Advanced age is associated with poorer bladder cancer-specific survival in patients treated with radical cystectomy. *Eur Urol* 2007; **51**: 699–706
56 **Shi B, Zhang K, Zhang J, Chen J, Zhang N, Xu Z.** Relationship between patient age and superficial transitional cell carcinoma characteristics. *Urology* 2008; **71**: 1186–90
57 **Johnson DE, Hillis S.** Carcinoma of the bladder in patients less than 40 years old. *J Urol* 1978; **120**: 172–3
58 **Kurz KR, Pitts WR, Vaughan ED Jr.** The natural history of patients less than 40 years old with bladder tumors. *J Urol* 1987; **137**: 395–7
59 **Kutarski PW, Padwell A.** Transitional cell carcinoma of the bladder in young adults. *Br J Urol* 1993; **72**: 749–55
60 **Wan J, Grossman HB.** Bladder carcinoma in patients age 40 years or younger. *Cancer* 1989 1; **64**: 178–81
61 **Yossepowitch O, Dalbagni G.** Transitional cell carcinoma of the bladder in young adults: presentation, natural history and outcome. *J Urol* 2002; **168**: 61–6
62 **Malkowicz SB.** Management of superficial bladder cancer. In Walsh PC, Retik AB, Darracott Vaughan E, Wein AJ eds, *Campbell's Urology*, Eighth Edition. Philadelphia: Saunders-Elsevier, 2002: 2789–92

63 **Gonzalez JA, Marcol BR, Wolf MC.** Complications of intravesical bacillus Calmette-Guerin: a case report. *J Urol* 1992; **148**: 1892–3

64 **Leebeek FW, Ouwendijk RJ, Kolk AH *et al.*** Granulomatous hepatitis caused by Bacillus Calmette-Guerin (BCG) infection after BCG bladder instillation. *Gut* 1996; **38**: 616–8

65 **Marans HY, Bekirov HM.** Granulomatous hepatitis following intravesical bacillus Calmette-Guerin therapy for bladder carcinoma. *J Urol* 1987; **137**: 111–2

66 **Orikasa K, Namima T, Ota S *et al.*** Acute eosinophilic pneumonia associated with intravesical bacillus Calmette-Guerin therapy of carcinoma in situ of the bladder. *Int J Urol* 2003; **10**: 622–4

67 **Rawls WH, Lamm DL, Lowe BA *et al.*** Fatal sepsis following intravesical bacillus Calmette-Guerin administration for bladder cancer. *J Urol* 1990; **144**: 1328–30

68 **Heiner JG, Terris MK.** Effect of advanced age on the development of complications from intravesical bacillus Calmette-Guerin therapy. *Urol Oncol* 2008; **26**: 137–40

69 **Herr HW.** Age and outcome of superficial bladder cancer treated with bacille Calmette-Guerin therapy. *Urology* 2007; **70**: 65–8

70 **Joudi FN, Smith BJ, O'Donnell MA, Konety BR.** The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. *J Urol* 2006; **175**: 1634–9

71 **Grossman HB, Natale RB, Tangen CM *et al.*** Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; **349**: 859–66

72 **von der Maase H, Sengelov L, Roberts JT *et al.*** Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate vinblastine doxorubicin plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005; **23**: 4602–8

73 **Anonymous.** Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol* 2005; **48**: 189–99

74 **Anonymous.** Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005; **48**: 202–5

75 **Pectasides D, Pectasides M, Nikolaou M.** Adjuvant and neoadjuvant chemotherapy in muscle invasive bladder cancer: literature review. *Eur Urol* 2005; **48**: 60–7

76 **Schultz PK, Herr HW, Zhang ZF *et al.*** Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. *J Clin Oncol* 1994; **12**: 1394–401

77 **Sonpavde G, Petrylak DP.** Perioperative chemotherapy for bladder cancer. *Crit Rev Oncol Hematol* 2006; **57**: 133–44

78 **Prout GR Jr, Wesley MN, Yancik R, Ries LA, Havlik RJ, Edwards BK.** Age and comorbidity impact surgical therapy in older bladder carcinoma patients: a population-based study. *Cancer* 2005; **104**: 1638–47

79 **Hollenbeck BK, Miller DC, Taub D *et al.*** Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. *Urology* 2004; **64**: 292–7

80 **Muss HB, Biganzoli L, Sargent DJ, Aapro M.** Adjuvant therapy in the elderly: making the right decision. *J Clin Oncol* 2007; **25**: 1870–5

81 **Balducci L.** Aging, frailty, and chemotherapy. *Cancer Control* 2007; **14**: 7–12

82 **Shabsigh A, Korets R, Vora KC *et al.*** Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2008; 2008 July 18 [Epub ahead of print]

83 **Donat SM, Shabsigh A, Savage C *et al.*** Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. *Eur Urol* 2008; 2008 Jul 14 [Epub ahead of print]

84 **Froehner M, Brausi MA, Herr HW, Muto G, Studer UE.** Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol* 2009; **56**: 443–54

85 **Rosario DJ, Becker M, Anderson JB.** The changing pattern of mortality and morbidity from radical cystectomy. *BJU Int* 2000; **85**: 427–30

86 **Farnham SB, Cookson MS, Alberts G, Smith JA Jr, Chang SS.** Benefit of radical cystectomy in the elderly patient with significant co-morbidities. *Urol Oncol* 2004; **22**: 178–81

87 **Fairey A, Chetner M, Metcalfe J *et al.*** Associations among age, comorbidity and clinical outcomes after radical cystectomy: results from the Alberta Urology Institute radical cystectomy database. *J Urol* 2008; **180**: 128–34

88 **Konety BR, Dhawan V, Allareddy V, Joslyn SA.** Impact of hospital and surgeon volume on in-hospital mortality from radical cystectomy: data from the health care utilization project. *J Urol* 2005; **173**: 1695–700

89 **Hollenbeck BK, Miller DC, Taub D *et al.*** Identifying risk factors for potentially avoidable complications following radical cystectomy. *J Urol* 2005; **174**: 1231–7

90 **Isbarn H, Jeldres C, Zini L *et al.*** A population based assessment of perioperative mortality after cystectomy for bladder cancer. *J Urol* 2009; **182**: 70–7

91 **Stroumbakis N, Herr HW, Cookson MS, Fair WR.** Radical cystectomy in the octogenarian. *J Urol* 1997; **158**: 2113–7

92 **Sogni F, Brausi M, Frea B *et al.*** Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer. *Urology* 2008; **71**: 919–23

93 **Madersbacher S, Mohrle K, Burkhard F, Studer UE.** Long-term voiding pattern of patients with ileal orthotopic bladder substitutes. *J Urol* 2002; **167**: 2052–7

94 **Hautmann RE, Miller K, Steiner U, Wenderoth U.** The ileal neobladder: 6 years of experience with more than 200 patients. *J Urol* 1993; **150**: 40–5

95 **Hugonnet CL, Danuser H, Springer JP, Studer UE.** Decreased sensitivity in the membranous urethra after orthotopic ileal bladder substitute. *J Urol* 1999; **161**: 418–21

96 **Kessler TM, Burkhard FC, Perimenis P *et al.*** Attempted nerve sparing surgery and age have a significant effect on urinary continence and erectile function after radical cystoprostatectomy and ileal orthotopic bladder substitution. *J Urol* 2004; **172**: 1323–7

97 **Cohen HJ.** The cancer aging interface: a research agenda. *J Clin Oncol* 2007; **25**: 1945–8
98 **Lichtman SM, Wildiers H, Chatelut E *et al.* International Society of Geriatric Oncology Chemotherapy Taskforce.** Evaluation of chemotherapy in older patients – an analysis of the medical literature. *J Clin Oncol* 2007; **25**: 1832–43
99 **Surbone A, Kagawa-Singer M, Terret C, Baider L.** The illness trajectory of elderly cancer patients across cultures: SIOG position paper. *Ann Oncol* 2007; **18**: 633–8
100 **Terret C, Zulian G, Droz JP.** Statements on the interdependence between the oncologist and the geriatrician in geriatric oncology. *Crit Rev Oncol Hematol* 2004; **52**: 127–33
101 **Terret C, Zulian GB, Naiem A, Albrand G.** Multidisciplinary approach to the geriatric oncology patient. *J Clin Oncol* 2007; **25**: 1876–81
102 **Extermann M, Aapro M, Bernabei R. *et al.*** Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol* 2005; **55**: 241–52
103 **Kemeny MM.** Surgery in older patients. *Semin Oncol* 2004; **31**: 175–84

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Abbreviations: **UCB**, urothelial cancer of the bladder; **RC**, radical cystectomy; **AR**, androgen receptor; **ERβ**, oestrogen receptor β; **SEER**, Surveillance, Epidemiology and End Results.