Université de Montréal

A detailed assessment of adverse perioperative outcomes of the elderly treated with radical cystectomy for bladder cancer

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Ce mémoire intitulé:

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Dr. Pierre I. Karakiewicz, directeur de recherche
Dr. Julie Franc-Guimond, membre du jury

Résumé

Objectifs:
Les données provenant des centres de soins tertiaires suggèrent que le taux de mortalité péri-opératoire (MPO) après cystectomie notés pour les patients âgés (septuagénaires et octogénaires) n'excède pas celle des patients plus jeunes. Toutefois, les données provenant de la communauté démontrent un phénomène inverse. Spécifiquement, la MPO est plus élevés chez les ainés. Dans cette thèse nous allons présenter une réévaluation contemporaine du taux de MPO après cystectomie.

Méthodes:
Entre 1988 et 2006, 12722 cystectomies radicales pour le carcinome urothéliale de la vessie ont été enregistrées dans la banque de données SEER. Le taux de MPO a été évalué dans les analyses de régression logistique univariées et multivariées à 90 jours après cystectomie radicale. Les covariables incluaient: le sexe, l'ethnie, l'année de chirurgie, la région d'origine du patient ainsi que le grade et le stade de la tumeur.

Résultats:
Parmi tous les patients, 4480 étaient des septuagénaires (35.2%) et 1439 étaient des octogénaires (11.3%). Le taux de MPO à 90 jours était de 4% pour la cohorte entière vs. 2% pour les patients moins de 69 ans vs. 5.4% pour les septuagénaires vs. 9.2% pour les octogénaires. Dans les analyses de régression logistiques multivariées, les septuagénaires (OR=2.80; <0.001) et les octogénaires (OR=5.02; <0.001) avaient reçu un taux de MPO plus augmenté que les patients moins de 70 ans après une cystectomie radicale.

Conclusion:
Cette analyse épidémiologique basée sur les donnés le plus contemporaines démontre que l'âge avancée représente un facteur de risque pour un taux de MPO plus élevé.

Mots-clés: âge, mortalité périoperatoire, mortalité, cancer de la vessie, carcinome urothélial, cystectomie radicale,

Abstract

Objective
Data from tertiary care centers suggest that the perioperative mortality (POM) after radical cystectomy (RC) is not different in septuagenarian or octogenarian patients, compared to younger individuals. Conversely, population-based data state otherwise. We revisited this topic in a large contemporary population-based cohort.

Methods
Between 1988 and 2006, 12722 radical cystectomies were performed for urothelial carcinoma of the urinary bladder (UCUB) in 17 Surveillance, Epidemiology and End Results (SEER) registries. Of those 4480 were aged 70-79 and 1439 were 80 years and older. Univariable and multivariable logistic regression models tested 90-day mortality (90dM) after radical cystectomy. Covariates consisted of gender, race, year of surgery, SEER registry, histological grade and stage.

Results
Of all 12722 patients, 4480 (35.2%) were septuagenarian and 1439 (11.3%) were octogenarian. The overall 90dM rate was 4% for the entire population, 2% for patients aged 69 years or younger, 5.4% for septuagenarian patients and 9.2% for octogenarian patients. In multivariable logistic regression analyses, septuagenarian (OR= 2.80; <0.001) and octogenarian (OR= 5.02; <0.001) age increased the risk of 90dM after RC.

Conclusions
In this population-based analysis, POM was between 3 and 5-fold higher respectively in septuagenarian and octogenarian patients which is higher in tertiary care centers. This information needs to be included in informed consent considerations, specifically if RC will not be performed at a tertiary care center.

Keywords : age, perioperative, mortality, bladder cancer, urothelial carcinoma, radical cystectomy

List of abbreviations

CCI: Charslon Cormorbidity Index

CGA: Comprehensive geriatric assessment

CSM: Cancer-specific mortality

OCM: Other-cause mortality

POM: perioperative mortality

RC: Radical Cystectomy

SEER: Surveillance Epidemiology and End Results

TURBT: Trans-urethral resection of bladder tumor

UCUB: Urothelial carcinoma of the urinary bladder

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To my beloved Sophie, who has supported me throughout this venture, I am forever indebted to you.

and to my miracle baby boy Samuel Jacob, without you nothing matters.

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Objective

The objective of this study is to assess the effect of advanced age on 90-day perioperative mortality after radical cystectomy using a large population-based cohort.

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Review of the Literature

Bladder cancer is the second most common genitourinary malignancy, with over 60,000 new cases annually in the United States and more than 13,000 deaths from the disease per year [1]. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database has demonstrated that since 1975, there has been a 40% increase in urothelial cancer of the urinary bladder (UCUB) incidence[2]. This can be attributed to the latent effects of tobacco abuse, industrial carcinogens and our aging society [1]. Despite its increasing incidence, the death rate from bladder cancer is declining.

Risk factors that have been associated with bladder cancer include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, indwelling catheters or schistosomiasis), and chemotherapeutic exposure such as cyclophosphamide [3-7]. Other risk factors include; pelvic irradiation, occupational exposure to chemicals from the aromatic amines family and chronic phenacetin use [8-11].

Staging

The American Joint Commission on Cancer in combination with the International Union Cancer Consortium meets on a regular basis to determine the tumor, nodes, and metastases (TNM) staging classifications. The 2009 staging system is shown below (Figure #1). Non-invasive bladder cancer (pTa and CIS) are defined as the absence of invasion of the basement membrane. Muscle invasive disease (T2) is sub-divided into pT2a and pT2b, depending on the degree of invasion of the muscularis propria, where pT2a invades the superficial half and pT2b invades the deeper half of the bladder muscle. pT3 disease constitutes invasion outside the bladder into the peri-adipose tissue. This is further subdivided into microscopic invasion (pT3a) or macroscopic invasion (pT3b). Extra-vesical extension of the tumor is defined as pT4 disease. It can invade any of the following structures; prostatic stroma, seminal vesicles, uterus, vagina (pT4a). Any invasion of the pelvic wall or abdominal wall is categorized as pT4b disease.

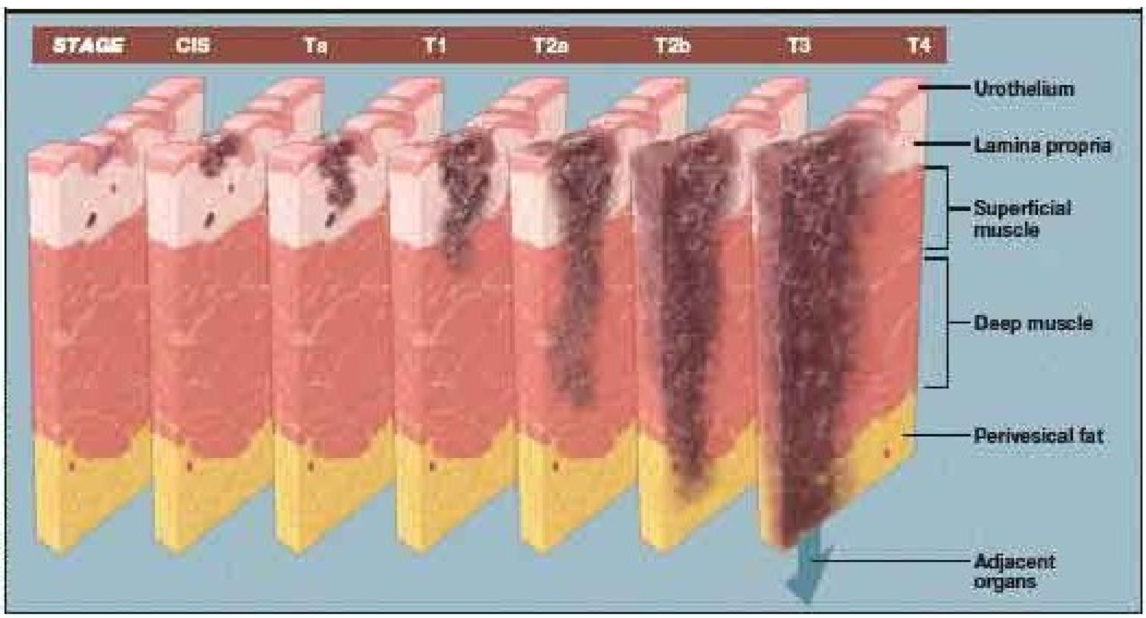


Figure 1: Bladder cancer staging

(Reproduced from http://www.urocentersc.com/conditions/bladder-cancer)

Radical Cystectomy for UCUB

Radical cystectomy (RC) for UCUB is considered the gold standard for local control and survival of muscle invasive tumors. The aim of the procedure is to remove all of the cancer in the bladder, pelvis and regional lymph nodes with negative surgical margins [12]. The first publication of long-term outcomes using the techniques of radical surgery with wide local excision and lymph node removal was authored by Whitmore et al., and demonstrated a 5-year survival rate of 21-49% [13]. Since that landmark study, there have been great advances in perioperative care that have drastically reduced surgical mortality. Recent large studies have demonstrated 10-year cancer survival rates in patients with pathologic T2 disease of 65-78% [14, 15].

RC can be performed for several reasons. The indications to bladder cancer are [16]:

1) As a primary modality of treating muscle-invasive bladder cancer
2) As a salvage procedure after the failure of bladder sparing modalities
3) After the failure of intra-vesical therapy for high risk Ta/T1/ CIS.

Since RC has become the gold standard treatment of organ-confined UCUB, the use of RC has sharply increased. There are many factors that can explain the increasing temporal trend in survival after RC. Advances in perioperative care are reducing the morbidity and mortality associated to this procedure. Involvement of sub-specialist oncology teams in larger urological departments is significant [16]. Furthermore, multi-disciplinary team work has facilitated the evaluation treatment and follow-up of the RC candidate.

The surgical essentials of RC include a lower midline abdominal incision and an exploratory examination of abdominal contents to exclude disseminated disease. The urachal remnant is encircled and divided near the level of the umbilicus. The peritoneum is incised and the vas deferens is identified and divided. The ureters are identified at the crossing of iliac vessels bilaterally and are dissected and ligated. A pelvic lymph node dissection is then performed extending to the proximal common iliac artery superiorly, the cooper ligament inferiorly and the genito-femoral nerve laterally [12]. With the completion of the pelvic lymph node dissection, the vesical pedicles are ligated and divided.

In men, an incision of the endopelvic fascia and pubo-prostatic urethral ligaments is used. The dorsal vein complex is ligated and the membranous urethra is transected [16]. The prostate is then mobilized and the specimen is excised. Different forms of urinary diversions are performed depending on clinical and surgical indications.

In women, traditional cystectomy involves anterior pelvic exenteration with removal of the bladder as well as the adjoining cervix, uterus and anterior vaginal wall. Female patients with stage T1 UCUB are candidates for female organ preservation including the vaginal vault. Female patients without bladder neck involvement are candidates for orthotopic neobladder construction [12].

After completion of the procedure the patient is transferred to the recovery room. Post-operative laboratory studies should include complete blood count as well as a metabolic panel. Complications after RC are common. In a series from a large tertiary care center, 64% of RC patients experienced one perioperative complication at 90 days of surgery [17]. Additionally, long-term complications are equally as frequent. Roughly one in third of patients will experience one or several serious long-term complications within 10 years after

RC [18]. Attention to clinical parameters is necessary to limit the morbidity and mortality of this complex procedure.

The Surveillance, Epidemiology and End Results (SEER) Database

The SEER database is an important data source for analyses in urologic oncology. The SEER program was first initiated after the Second World War and eventually put forth by President Nixon's administration. Its purpose was to collect cancer statistics on a national level. Its data collection began January 1st 1971 in the states of Iowa, New Mexico, Connecticut, Utah, Hawaii and the metropolitan areas of Detroit and San Francisco/Oakland. Over the years other regions were added to the registry. After the year 2000, SEER represents approximately 25% of all cancers cases diagnosed in the United States and covers roughly 25% of the US population [2]. This database provides vital information on a large number of cancer cases with firm assurance of confidentiality and quality control [19]. This database contains information on demographics, clinical pathological factors, treatment and survival for patients diagnosed with cancer in areas of the SEER surveillance. Research projects can perform epidemiological analyses on each individual cancer case by including the year of diagnosis, region of residence, demographic factors (ie: race, ethnicity, gender, marital status) detailed pathological data, initial treatment and information on survival. The SEER program is considered the standard for data quality around the world. Quality control involves case finding audits, reliability studies, re-abstraction studies, electronic field edits and training programs for SEER registry personnel [20, 21].

The SEER database is not devoid of limitations. Lack of central histology review is an important shortcoming whereby only pathological information from the treating institutions report is included and cannot be as accurate or consistent as those recorded in tertiary care reference centers. Conversely, pathology included in the SEER database reflects community practice patterns. Lack of information on disease recurrence and progression are another example of some limitations. Moreover, lack of comorbidity, functional status and quality life measures represent additional considerations. Only partial information on systemic chemotherapy is available. Use of intravesical therapy cannot be examined. This is particularly important with regards to UCUB, where intravesical and systemic therapy play a major role [19].

Oncogeriatrics

Men and women aged 65 years and older represent approximately 12% (36.8 million) of the U.S. population, a figure that will double by the year 2030 having a significant impact on the burden of cancer on our society [22-25]. The SEER database has demonstrated that in the years 1998-2002, 56% of all new cancers will be diagnosed in the elderly [26]. By 2030, approximately 70% of all cancers will be diagnosed in older patients [27]. These cancer and aging trends are a major public health concern and the American Society of Clinical Oncologists (ASCO) has already actively explored strategies to increase the number of physicians trained in oncology-oriented societies [28].

It is now widely accepted that age is the largest single risk factor for the development of cancer and that cancer is primarily a disease of the elderly [29]. There is a paucity in the literature dealing with this sub-group. In addition, it is unfitting to use oncological outcomes in younger patients and extrapolate to the elderly since there are clear differences in their bio-psycho-social profile. Shariat et al., in their elaborate review of cancer and the elderly patient have proposed theories explaining carcinogenesis and the aging process [30]. Firstly older individuals have been exposed longer to potential carcinogens and therefore have an increased risk for the potential accumulation of cellular events that can lead to neoplastic transformation. Secondly, the elderly are at increased risk for the accumulation of carcinogens over time, like the effect of smoking with additional exposure of occupational toxins. Thirdly, the long lag time of manifestation of the disease phenotype may account for the increased incidence of cancer in the elderly. The decreased ability to detoxify potential offending agents can also be additional risk factor. Furthermore, the increased contact time with carcinogens with specific tissue, like in the case of the bladder urothelium due to urinary stasis in the context of lower urinary tract obstruction in older men can be an additional factor for the increased risk of bladder cancer [30].

These theories have been substantiated with genetics research demonstrating that aging and cancer are intimately connected to the activity of specific genes and the cellular responses to potentially oncogenic insults [29]. Specifically, certain truncated forms of p53 that reduce its activity, have been shown to increase the risk of cancer while at the same time being a protective factor for increased longevity [31]. Conversely, the increased activity of the tumor-suppressor gene p16/INK4a, while decreasing the risk of cancer mortality has been shown to lead to decreased function in several varieties of age-sensitive stem cells [31]. This body of evidence have demonstrated the relationship between cancer risk and aging.

A gradual deterioration in the physiologic reserve or functional capacity is the characteristic hallmark of aging. This has a direct effect on the choice of cancer therapy and their toxicity profile [32]. Cardiovascular, respiratory, gastro-intestinal and renal deterioration in the form of a reduction of cardiac output, decreased pulmonary reserve, increased mucosal friability and decreased nephron reserve respectively, can all impair the ability of an elderly patient to tolerate cancer therapy. As such, this can lead to a decreased functional status, resulting frailty, poor quality of life, and poor oncological outcomes [32].

With the collaboration of oncologists and geriatricians a more comprehensive multidisciplinary evaluation has been developed of the elderly patient incorporating the individual's functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and a review of the patient's medications.

Traditionally the oncologist's assessment of the functional status has relied on the Karnofsky or the eastern Cooperative Oncology Group (ECOG) performance status. "Comorbidity" is defined as a concurrent medical problem that is a competing source of morbidity or mortality in the setting of a developing malignancy. Comorbidities have demonstrated to impact treatment tolerance and also have been shown to impact the behavior of the cancer itself. [33]. Many results demonstrate that comorbidity status is an independent predictor of disease-free and overall survival in older patients with bladder cancer [34-37]. Therefore, routine assessment of comorbidity should be included in the evaluation of elderly cancer patients.

Cognition is another important consideration in elderly patients. The impact of mild cognitive impairment on the diagnosis, treatment choice, treatment toxicity and risk of further cognitive decline as a consequence to cancer therapy is not negligible [38]. For example, studies in colon and breast cancer have shown that older patients suffering from dementia were more likely to be diagnosed with more advanced clinical stage and less likely to receive curative therapy and less likely to receive adjuvant chemotherapy [39, 40]. On the other hand, Moffitt et al., has demonstrated that when a specialized geriatric oncology program is implicated in the treatment of elderly individuals, cognitively impaired individuals received similar treatments compared to non-impaired patients [38]. Their survival duration was about a third of that of the un-impaired patients. Studies of cognitive changes associated with cancer therapy demonstrate that such changes can be minimal and affect only a subset of patients [41, 42].

The geriatric literature supports the finding that depressive symptoms and socially isolated older adults have poor oncologic outcomes [43, 44]. The preliminary results of the PACE (Preoperative Assessment of Cancer in the Elderly) study reported that patients with depressive symptoms (evaluated by the Geriatric Depression Scale) had an increased risk of 30-day postoperative morbidity [45]. An assessment of an older patient's social support and psychological state has becoming crucial for the care of oncology patients.

Bladder cancer and the elderly

Age has been widely accepted as the greatest single risk factor for the development of UCUB [46]. In fact the median age at diagnosis is 70 years of age whereby UCUB can be considered a disease of the elderly [47]. Recent studies have considered differences in clinco-pathological presentation in elderly individuals compared to their younger counterparts. Younger patients (<40 years old) tend to develop well differentiated non-invasive UCUB whereas older patients develop more invasive pathology with an un-differentiated pattern [48].

Many studies have demonstrated that individuals ages 65 years and older have an 11-fold increase in the incidence of bladder cancer in general and a 15-fold increased risk of bladder cancer mortality when compared to their younger counterparts [30]. A contemporary study using the California Cancer Registry analyzed 55,159 cases of invasive bladder cancer between 1988 and 2004. They determined a late peak in the incidence of UCUB of 85 years or older. Specifically, the rate of annual increase in the percent of bladder cancer in octogenarians rose 10 times as rapidly as their younger counterparts [49].

There are several hypotheses that could explain the late presentation of UCUB. The accumulation of toxins (ie: cigarette smoking, occupational exposure) in the bladder as well as failure to completely empty the bladder due to lower urinary tract pathology increasing contact time with the toxin and the bladder urothelium. Others suggest that a decreased pulmonary function in the elderly can diminish the ability of the lungs to clear the carcinogen and therefore may increase the amount of carcinogen absorbed in the bloodstream. This along with a decreased metabolism can be responsible for the late peak of UCUB incidence.

Mortality from bladder cancer is the highest in elderly individuals particularly in patients 80 years and older, accounting for the third most common cause of cancer death in men older than 80 years [46]. The reason for the higher mortality in the elderly is still debated. Some studies have shown lower rates of recurrence and progression with better survival in younger patients [37, 50, 51]. Other studies have shown similar disease progression in younger and older patients [52, 53]. Age related differences in UCUB outcomes can be twofold. Firstly, the tumor biology can be more aggressive in older patients compared to their younger counterparts. Secondly, that physician practices may tend to offer less aggressive and effective therapies and recommend curative therapy to younger individuals [46].

UCUB treatment in the elderly for non-muscle invasive disease

Non-muscle invasive UCUB accounts for approximately 75-80% of bladder cancer cases [54]. Tumor stage Ta (infiltration of the urothelium), accounts for the majority of non-muscle invasive UCUB with a percentage of 60%. Conversely, tumor stage T1 and CIS account for 30% and 10% respectively. Recent studies have demonstrated that the actual prevalence of non-muscle invasive UCUB is ten times its incidence creating a major economic burden on health care systems [55]. Avritscher and colleagues estimated that the lifetime cost of bladder cancer and the contribution of its complications was between $99,270 and $120,684 [56]. This study concluded that the management of bladder cancer and its complications is one of the most expensive human cancer to treat [56].

The two most important prognostic factors are stage and grade. Trans-urethral resection of bladder tumor (TURBT) is considered the first and gold standard treatment option for non-muscle invasive UCUB. TURBT should be made to include the detrusor muscle in the specimen to ensure to rule out the presence of muscle-invasive disease and minimize the risk of under-staging.

Patients after TURBT can be treated with either intra-vesical chemotherapy or immunotherapy. This treatment modality can be either therapeutic (treatment of CIS, or residual non-visible tumor), prophylactic (prevention of recurrence and progression of disease) or adjuvant in the immediate post-operative setting [57].

Treatment for non-muscle invasive UCUB is generally well tolerated in older patients. Most intravesical therapy is not absorbed systemically and therefore can be given to elderly patients even with significant comorbid conditions. However, there are some recent analyses that have demonstrated that immunotherapy could be less effective in the elderly population. Specifically, Herr et al., and Joudi et al., have shown that septuagenarians and octogenarians were less likely to sustain a response and remain free of tumor recurrence during a 5-year period with intravesical BCG [58, 59].

BCG sepsis, a rare but important complication of this therapy can be exaggerated in the elderly. Several reports have detailed that advanced age is considered a risk factor for serious complications related to intravesical BCG. Specifically, Heiner et al., concluded that the complication rate was statistically significantly higher in patients older than 70 years of age than their younger counterparts (48.6% vs. 17.6%) [60, 61].

UCUB treatment in the elderly for muscle invasive disease

The Society of Geriatric Oncology considers patients with a chronologic age of 65 years to be elderly [62]. The median age at radical cystectomy (RC) has been >65 years in both tertiary care centers (66 years) and population-based analyses (69 years).[15, 63] Moreover, as many as 25% of RC procedures are performed in even older patients, namely septuagenarians and octogenarians [64]. A major abdominal surgery, such as RC, can be associated with a non-negligible perioperative mortality (POM) risk in elderly patients [63]. Because of its irreversible nature, it is imperative to provide an accurate estimate of that risk to elderly patients who are candidates for RC.

Some would suggest that in a selected sub-group of patients a course of neo-adjuvant chemotherapy may be indicated [65, 66]. These treatment strategies offer significant complications for the elderly population which have lower physiological reserve. Comorbidities and overall "frailty" that have been associated with the aging process might also compromise the actual delivery of these therapeutic options. Furthermore, the complications of these treatment options could be compounded by an already reduced ability to respond and fully recover.

Prout et al., demonstrated that even when accounting for comorbid conditions patients aged 75 years and older were less likely to undergo RC compared to patients aged 55-64 years with muscle-invasive UCUB ($p<0.001$)

[64]. This suggests that RC in some cases has been delayed or withheld in patients who could benefit. In addition, Nielson et al., demonstrated that older patients were less likely to undergo extended lymph node dissection and receive post-operative chemotherapy (all $p<0.05$) than their younger counterparts [67]. Reasons for these age related discrepancies are numerous but can include a delay in diagnosis, the use of nonsurgical alternatives for an inappropriate long period of time, the relative inexperience of many surgeons leading them to avoid performing this procedure in the elderly and the perception that elderly patients will simply not tolerate the procedure despite a comprehensive geriatric assessment [30]. It seems that after a critical review of the literature, carefully selected elderly patients can tolerate RC offering the best chance for disease control and survival.

The existing urologic data have failed to show a consensus regarding the estimates of POM risk. In brief, data from tertiary care centers have suggested that POM in the elderly is not unacceptably greater than that for their younger counterparts [68]. In contrast, population-based rates have indicated otherwise [69]. Because of the lack of agreement, we decided to revisit the topic of POM using a large contemporary population-based cohort of patients who had undergone RC for urothelial carcinoma of the urinary bladder (UCUB) from 1988 to 2006. Our hypothesis was that RC for the elderly might predispose to greater POM.

METHODS

Study Population

Within the Surveillance, Epidemiology, and End Results (SEER)-17 registry database, we identified 14 240 patients who had undergone RC for non-metastatic (M0) UCUB (“International Classification of Diseases, 9th revision,” codes C670-679 and 812 and 813 histologic codes) from 1988 to 2006. The SEER population represents a 26% sample of the U.S. population and is considered representative of the entire U.S. population in terms of demographics, cancer incidence, and mortality rate [2]. The 17 registries included Alaska, California (excluding San Francisco, San Jose-Monterey, and Los Angeles), Connecticut, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, rural Georgia, San Francisco Oakland-Standard Metropolitan Statistical Area, San Jose-Monterey, Seattle (Puget Sound), and Utah and the metropolitan areas of Atlanta, Georgia, and Detroit, Michigan. All those with non-urothelial histologic findings were excluded (n = 1518). Thus, 12 722 patients with known clinical and pathologic characteristics were included in the analyses. The disease stage was categorized using the SEER stage distribution (localized vs regional). According to the SEER definitions, “localized” refers to tumors regardless of size that are confined to the urinary bladder, and “regional” refers to tumors that have invaded the regional lymph nodes or have extended directly from the bladder into surrounding tissues or organs.

The study endpoint consisted of the 90-day mortality. Thus, deaths from any cause that occurred within 90 days of surgery were considered as events. The all-cause of death was determined using the cause of death recode information provided by the SEER database. Except for the deceased patients, any patient who had had follow-up of 90 days was excluded from our analyses.

Statistical Analysis

The chi-square test and the independent sample t test were used to compare the proportions and mean values, respectively. The overall mortality-free and cancer-specific mortality-free survival rates of the entire population and stratified according to the different age groups were assessed using the Kaplan-Meier method. We used the Statistical Package for Social Sciences life-table method to determine the 90-day POM rate within the entire cohort. We tested the effect of the age groups (<70 vs. 70-79 vs. ≥80), sex, race (white vs. non-white), year of surgery (1988-1995 vs. 1996-2000 vs. 2001-2003 vs. 2004-2006), grade (low vs. high vs. unknown), stage (localized vs. regional), and SEER registry on the recorded 90-day mortality rates in univariate and multivariate logistic regression models.

All statistical tests were performed using S-PLUS Professional, version 1.0 (Mathsoft, Seattle, WA) and the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL). Moreover, all tests were 2 sided, with the significance level set at $p<0.05$.

RESULTS

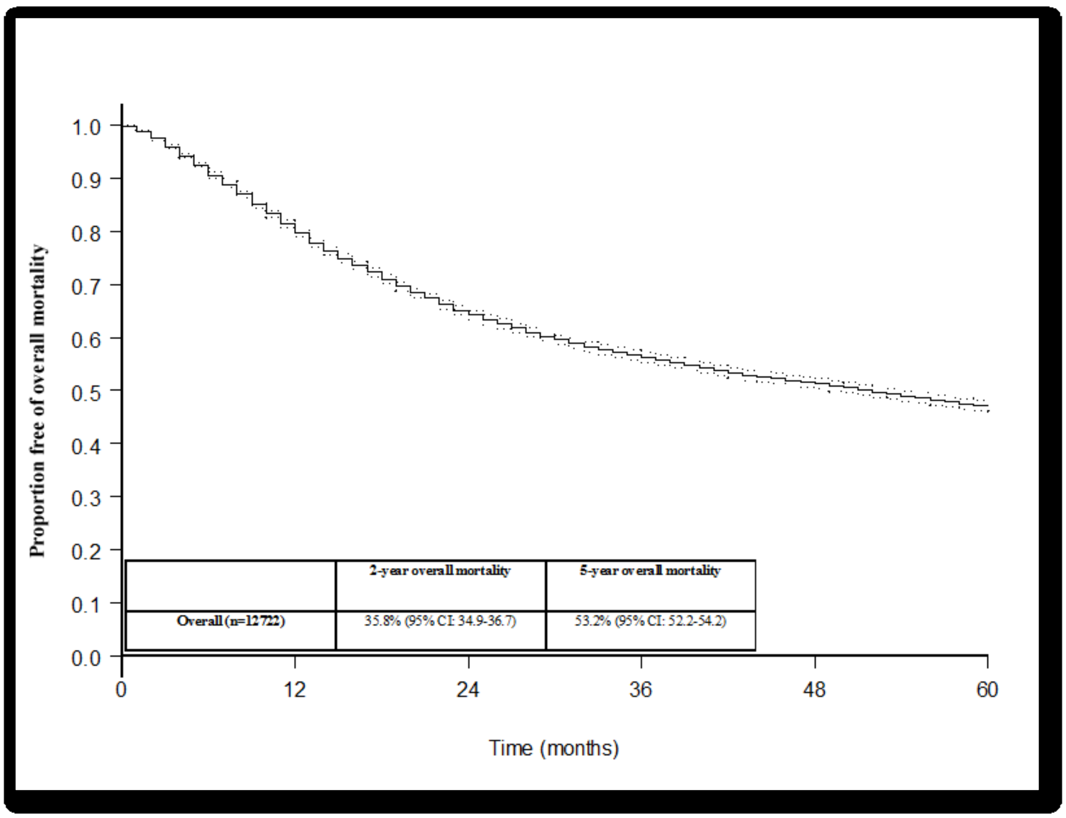
Of the 12 722 patients who underwent RC for UCUB, 4480 (35.2%) were septuagenarians and 1439 (11.3%) were octogenarians. The overall mean age was 67.4 years (median 69, range 17-100). Most of the patients were male (74.8%) and white (90.0%). Most patients underwent RC in the most contemporary year quartile (26.2%), and most had presented with a high histologic grade (grade 3-4, 89.1%) and a regional (non-localized) stage (84.8%).

Table 1 lists the clinical and pathologic features of the overall population and of the subgroups stratified according to age (<70, 70-79, and ≥80 years). The septuagenarian and octogenarian patients were more likely to be women (26.3% and 33.1%, respectively; p <0.001), and these 2 groups of patients were more likely to have undergone RC in the most contemporary year quartile of 2004-2006 (24.6% and 32.6%, respectively; p< 0.001). The septuagenarian and octogenarian patients had greater proportions of grade 3 or 4 UCUB (89.3% and 91.2%, respectively; p=0.003) and greater rates of locally advanced stage (85.8% and 88.4%, respectively; p<0.001) than the younger patients.

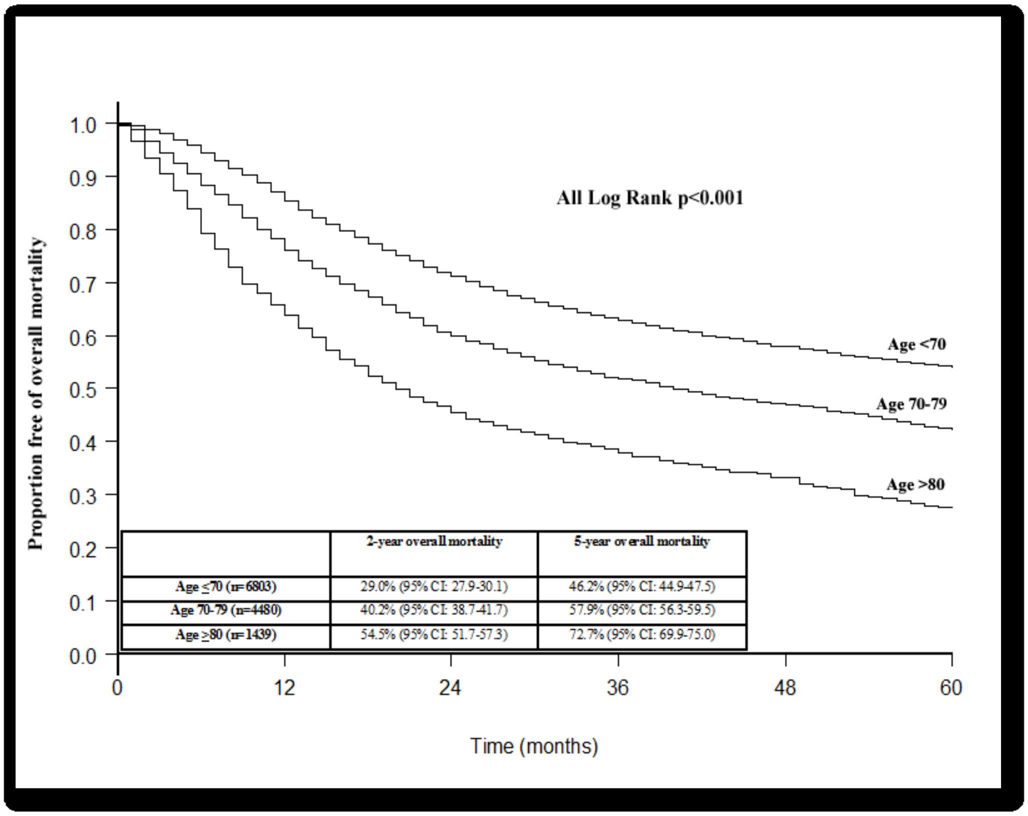
Table 1. Descriptive characteristics of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder.

Variables	Overall population n=12722	Age <70 n=6803 (53.5%)	Age 70-79 n=4480 (35.2%)	Age ≥80 n=1439 (11.3%)	ANOVA/ X^2 (p-value)
Age (years)					
Mean (median)	67.4 (69.0)	59.9 (61.0)	74.2 (74.0)	82.9 (82)	-
Range	17-100	17-69	70-79	80-100	
Gender					
Male	9518 (74.8)	5256 (77.3)	3300 (73.7)	962 (66.9)	p<0.001
Female	3204 (25.2)	1547 (22.7)	1180 (26.3)	477 (33.1)	
Race					
Caucasian	11444 (90.0)	6053 (89.0)	4069 (90.8)	1322 (91.9)	p<0.001
Non-Caucasian	1278 (10)	750 (11.0)	411 (9.2)	117 (8.1)	
Year of Surgery					
1988-1995	3049 (24.0)	1772 (26.0)	1070 (23.9)	207 (14.4)	
1996-2000	3117 (24.5)	1605 (23.6)	1175 (26.2)	337 (23.4)	p<0.001
2001-2003	3224 (25.3)	1667 (24.5)	1131 (25.2)	426 (29.6)	
2004-2006	3332 (26.2)	1759 (25.9)	1104 (24.6)	469 (32.6)	
Tumor Grade					
Low (grade 1+2)	1057 (8.3)	604 (8.9)	370 (8.3)	83 (5.8)	p=0.003
High (grade 3+4)	11335 (89.1)	6024 (88.5)	3999 (89.3)	1312 (91.2)	
Unknown	330 (2.6)	175 (2.6)	111 (2.5)	44 (3.1)	
Disease Stage					
Localized	1939 (15.2)	1134 (16.7)	637 (14.2)	167 (11.6)	p<0.001
Regional	10784 (84.8)	5669 (83.3)	3843 (85.8)	1272 (88.4)	
SEER registries					
California excl SF/SJM/LA	1705 (13.4)	872 (12.8)	594 (13.3)	239 (16.6)	
Alaska	9 (0.1)	7 (0.1)	2 (0)	0 (0)	
Atlanta (Metropolitan)	393 (3.1)	263 (3.9)	109 (2.4)	21 (1.5)	
Connecticut	1142 (9.0)	594 (8.7)	407 (9.1)	141 (9.8	
Detroit (Metropolitan)	1325 (10.4)	733 (10.8)	477 (10.6)	115 (8.0)	
Hawaii	291 (2.3)	167 (2.5)	93 (2.1)	31(2.2	
Iowa	977 (7.7)	531 (7.8)	361 (8.1)	85 (5.9)	p<0.001
Kentucky	512 (4.0)	287 (4.2)	169 (3.8)	56 (3.9)	
Los Angeles	1747 (13.7)	910 (13.4)	604 (13.5)	233 (16.2)	
Louisiana	400 (3.1)	234 (3.4)	133 (3.0)	33 (2.3)	
New Jersey	966 (7.6)	505 (7.4)	352 (7.9)	109 (7.6)	
New Mexico	382 (3.0)	201 (3.0)	147 (3.3)	34 (2.4)	
Rural Georgia	14 (0.1)	11 (0.2)	2 (0)	1 (0.1)	
San Francisco Oakland-SMSA	955 (7.5)	478 (7.0)	348 (7.8)	129 (9.0)	
San Jose-Monterey	438 (3.4)	234 (3.4)	151 (3.4)	53 (3.7)	
Seattle (Puget-Sound)	1127 (8.9)	605 (8.9)	402 (9.0)	120 (8.3)	
Utah	339 (2.7)	171 (2.5)	129 (2.9)	39 (2.7)	

The overall mortality rate for the entire population was 20.4%, 35.8%, 53.2%, and 67.0% at 1, 2, 5, and 10 years after RC, respectively (Figure 2). The overall mortality rate was 24.0%, 40.2%, 57.9%, and 74.5% for the septuagenarians, 36.1%, 54.5%, 72.7%, and 90.9% for the octogenarians, and 14.7%, 29.0%, 46.2%, and 58.3% for those <70 years old (all log-rank p<0.001) for the corresponding years (Figure 3).

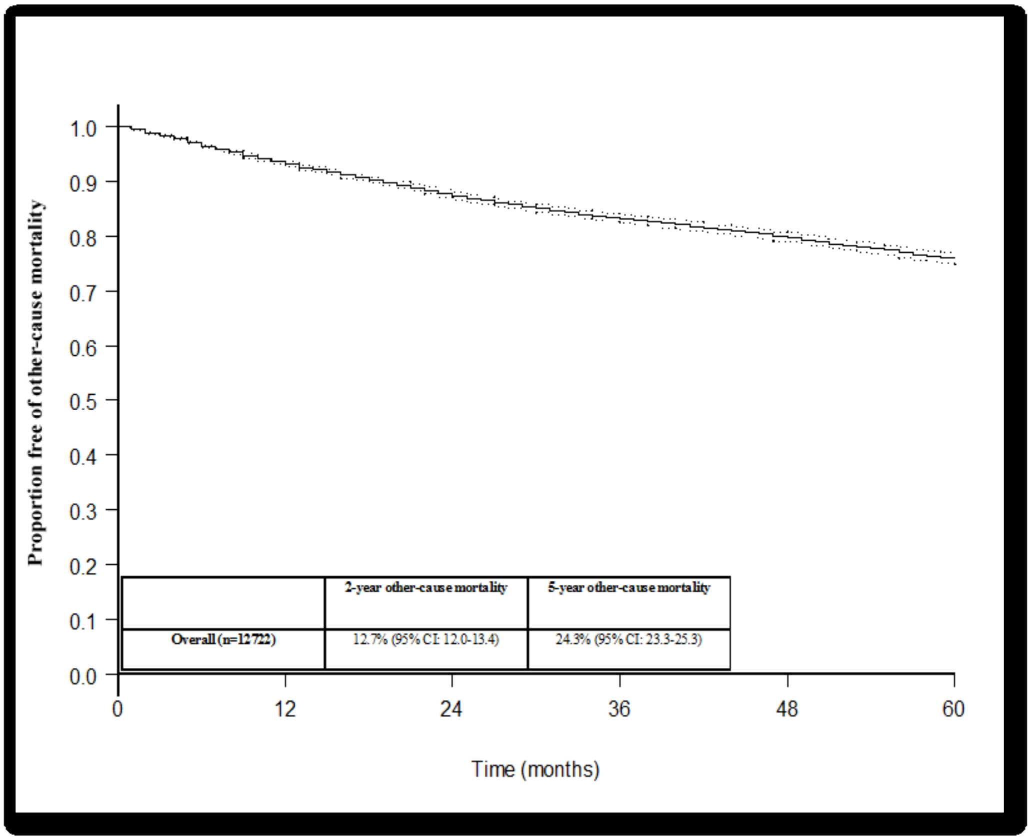


<u>Figure 2:</u> Kaplan-Meier derived overall survival of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder

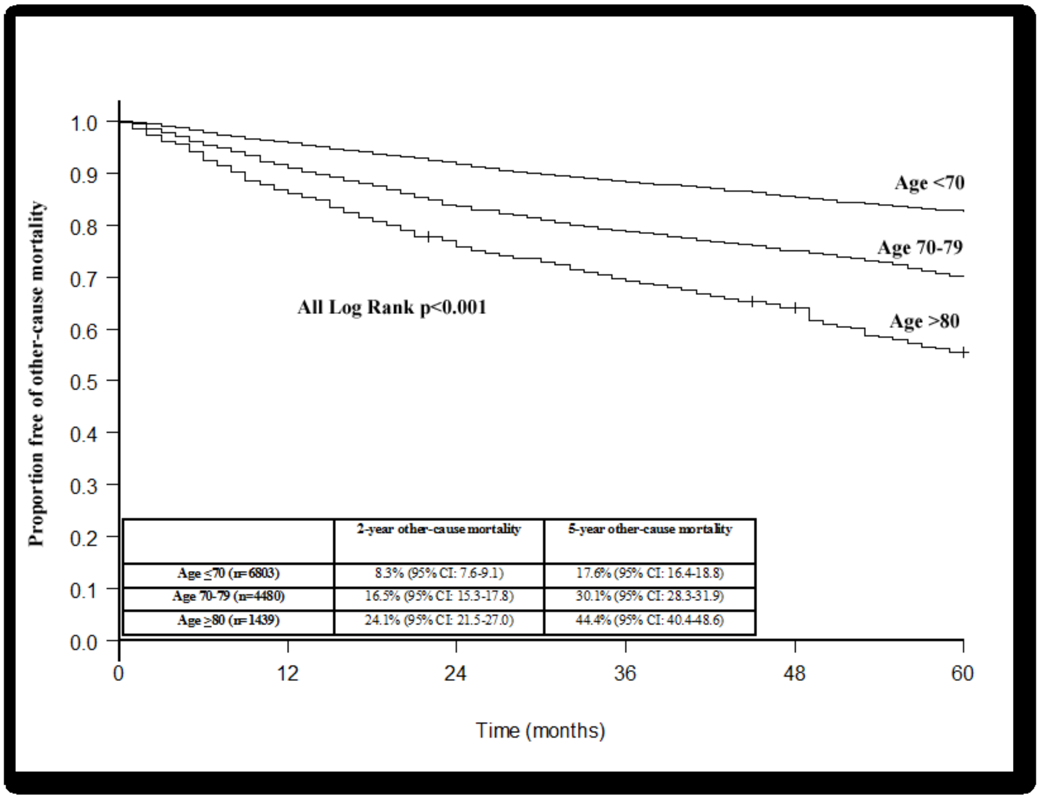


<u>Figure 3:</u> Kaplan-Meier derived overall survival of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder according to age strata

The other-cause mortality rate for the entire population was 6.9%, 12.7%, 24.3% and 42.3% at 1,2 5 and 10 years after RC (Figure 4). The other-cause mortality rate was 19.0%, 16.5%, 30.1% and 53.5% for the septuagenarians, 14.0%, 24.1%, 44.5% and 78.4% for the octogenarians, and 4.3%, 8.3%, 17.6% and 31.4% for those <70 years old (all log-rank p<0.001) for the corresponding year (Figure 5).



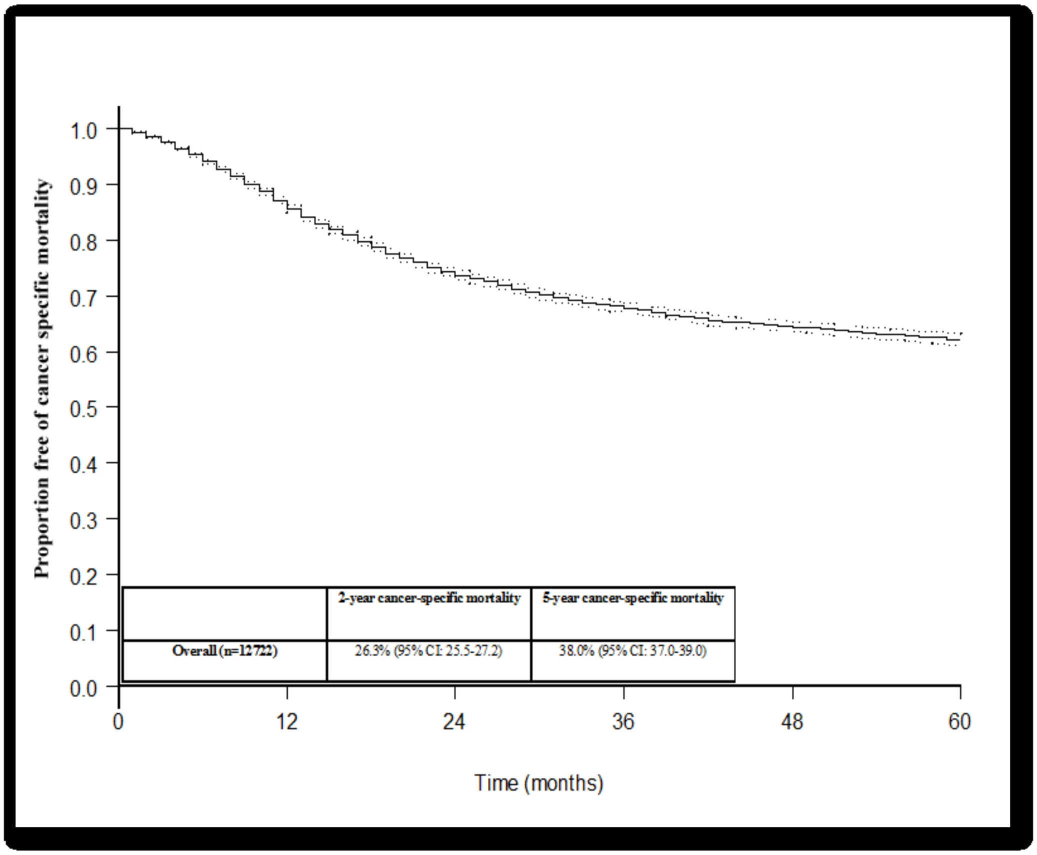
<u>Figure 4:</u> Kaplan-Meier derived free of other-cause mortality of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder



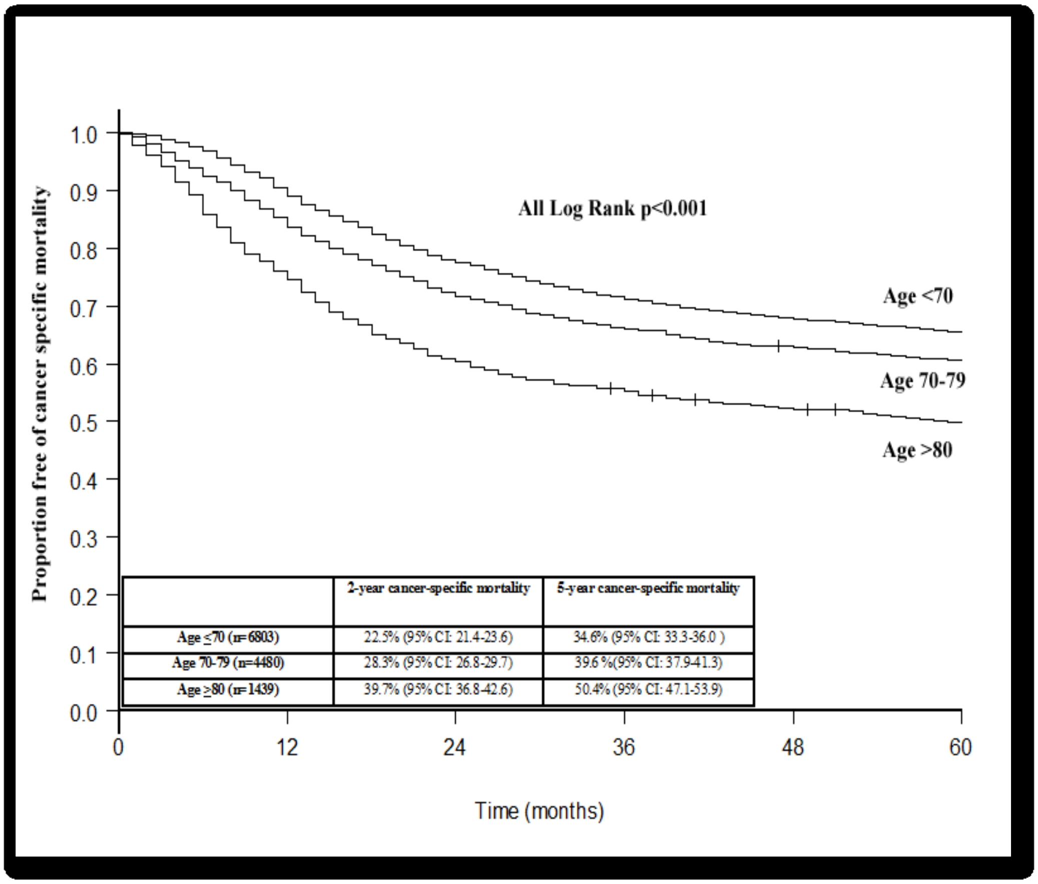
	2-year other-cause mortality	5-year other-cause mortality
Age ≤70 (n=6803)	8.3% (95% CI: 7.6-9.1)	17.6% (95% CI: 16.4-18.8)
Age 70-79 (n=4480)	16.5% (95% CI: 15.3-17.8)	30.1% (95% CI: 28.3-31.9)
Age ≥80 (n=1439)	24.1% (95% CI: 21.5-27.0)	44.4% (95% CI: 40.4-48.6)

<u>Figure 5:</u> Kaplan-Meier derived free of other-cause mortality of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder according to age strata

The cancer-specific mortality rate was 14.4%, 26.3%, 38.0%, and 42.7% at 1, 2, 5, and 10 years after RC, respectively (Figure 6). The overall cancer-specific mortality rate was 16.4%, 28.3%, 39.6%, and 44.8% for the septuagenarians 25.5%, 39.7%, 50.4%, and 59.4% for the octogenarians, and 10.9%, 22.5%, 34.6% and 40.0% for those <70 years old (all log-rank p<0.001) for the corresponding years (Figure 7).



<u>Figure 6:</u> Kaplan-Meier derived free of cancer-specific mortality of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder



	2-year cancer-specific mortality	5-year cancer-specific mortality
Age ≤70 (n=6803)	22.5% (95% CI: 21.4-23.6)	34.6% (95% CI: 33.3-36.0)
Age 70-79 (n=4480)	28.3% (95% CI: 26.8-29.7)	39.6 %(95% CI: 37.9-41.3)
Age ≥80 (n=1439)	39.7% (95% CI: 36.8-42.6)	50.4% (95% CI: 47.1-53.9)

<u>Figure 7:</u> Kaplan-Meier derived free of cancer-specific mortality of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder according to age strata

Table 2 lists the 90-day mortality rates according to age category, sex, race, year of surgery, histologic grade and stage, and SEER registry. The overall 90-day POM rate was 4.0% (n=512). Of these 512 patients, 142 (27.7%), 180 (35.2%), and 190 (37.1%) had an event at 30, 60, and 90 days after RC, respectively. For the septuagenarian and octogenarian patients, the overall 90- day mortality rate was 5.4% and 9.2%, respectively, compared with

2.0% for their younger counterparts. This resulted in an unadjusted odds ratio of 2.9 and 5.0 for the septuagenarians and octogenarians, respectively, relative to their younger counterparts ($p<0.001$; Table 3). Moreover, the octogenarian patients were 1.8-fold more likely to die within 90 days of RC than their septuagenarian counterparts ($p<0.001$). Additional stratification revealed a tendency toward lower POM rates in the more contemporary year of surgery (4.0% for 1988-1995 vs. 3.7% for 2004-2006; chi-square trend $p<0.001$). Even more pronounced decreases in the POM rates according to the year of surgery were recorded for the septuagenarian and octogenarian patients. For example, the POM rate decreased for septuagenarians from 6.2% to 4.9% between the most historic and the most contemporary year quartiles (chi-square trend $p<0.001$). Similarly, the POM rate decreased for the octogenarian patients from 12.1% to 8.5% in the same period (chi-square trend $p<0.001$).

Table 2: 90-Day mortality rates of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder.

Variables	Overall population n=12722 % (95% CI): n	Age <70 n=6803 % (95% CI): n	Age 70-79 n=4480 % (95% CI): n	Age ≥80 n=1439 % (95% CI): n
Overall	4.0 (3.7-4.4); 512	2.0 (1.7-2.3); 135	5.4 (4.8-6.2); 244	9.2 (7.7-10.9); 133
Gender				
Male	3.7 (3.3-4.1); 354	1.7 (1.3-2.1); 91	5.5 (4.8-6.3); 182	8.4 (6.7-10.3); 81
Female	4.9 (4.2-5.8); 158	2.8 (2.1-3.8); 44	5.3 (4.1-6.7); 62	10.9 (8.2-14.0); 52
Race				
Caucasian	4.1 (3.7-4.5); 467	1.9 (1.6-2.3); 117	5.5 (4.8-6.2); 223	9.6 (8.1-11.3); 127
Non-Caucasian	3.5 (2.6-4.7); 45	2.4 (1.4-3.8); 18	5.1 (3.1-7.7); 21	5.1 (1.9-10.8); 6
Year of Surgery				
1988-1995	4.0 (3.4-4.8); 123	1.8 (1.2-2.5); 32	6.2 (4.8-7.8); 66	12.1 (8.0-17.3); 25
1996-2000	4.1 (3.5-4.9); 129	2.3 (1.6-3.2); 37	5.5 (4.3-7.0); 65	8.0 (5.3-11.4); 27
2001-2003	4.2 (3.6-5.0); 136	2.2 (1.5-3.0); 36	5.2 (4.0-6.8); 59	9.6 (7.0-12.8); 41
2004-2006	3.7 (3.1-4.4); 124	1.7 (1.1-2.5); 30	4.9 (3.7-6.3); 54	8.5 (6.2-11.4); 40
Disease Stage				
Localized	2.6 (1.9-3.3); 50	1.0 (0.5-1.7); 11	3.0 (1.8-4.6); 19	12.0 (7.5-17.9); 20
Regional	4.3 (3.9-4.7); 462	2.2 (1.8-2.6); 124	5.9 (5.1-6.6); 225	8.9 (7.4-10.6); 113
Tumor Grade				
Low (grade 1+2)	3.3 (2.3-4.6); 35	1.7 (0.8-3.0); 10	4.9 (2.9-7.6); 18	8.4 (3.5-16.6); 7
High (grade 3+4)	4.1 (3.7-4.5); 464	2.0 (1.7-2.4); 121	5.5 (4.8-6.3); 221	9.3 (7.8-11.0); 122
Unknown	3.9 (2.1-6.6); 13	2.3 (0.6-5.7); 4	4.5 (1.5-10.2); 5	9.1 (2.5-21.7); 4
SEER registries				
California excl SF/SJM/LA	4.4 (3.5-5.5); 75	1.6 (0.9-2.6); 14	5.6 (3.9-7.7); 33	11.7 (7.9-16.5); 28
Alaska	0; 0	0; 0	0; 0	0;0
Atlanta (Metropolitan)	2.3 (1.1-4.3); 9	1.5 (0.4-3.8); 4	3.7 (1.0-9.1); 4	4.8 (0.1-23.8); 1
Connecticut	3.4 (2.4-4.6); 39	1.9 (0.9-3.2); 11	5.2 (3.2-7.8); 21	5.0 (2.0-10.0); 7
Detroit (Metropolitan)	3.6 (2.7-4.8); 48	1.5 (0.7-2.7); 11	5.7 (3.8-8.1); 27	8.7 (4.2-15.4); 10
Hawaii	5.2 (2.9-8.4); 15	4.2 (1.7-8.4); 7	6.5 (2.4-13.5); 6	6.5 (0.7-21.4); 2
Iowa	3.3 (2.6-4.6); 32	1.5 (0.6-2.9); 8	4.4 (2.5-7.1); 16	9.4 (4.2-17.7); 8
Kentucky	3.9 (2.4-6.0); 20	0.7 (0.08-2.5); 2	6.5 (3.3-11.3); 11	12.5 (5.2-24.1); 7
Los Angeles	3.9 (3.1-5.0); 69	2.5 (1.6-3.8); 23	4.5 (3.0-6.4); 27	8.2 (5.0-12.4); 19
Louisiana	7.0 (4.7-10.0); 28	3.0 (1.2-6.1); 7	10.5 (5.9-17.0); 14	21.2 (9.0-38.9); 7
New Jersey	4.9 (3.6-6.4); 47	3.2 (1.8-5.1); 16	4.5 (2.6-7.3); 16	13.8 (7.9-21.7); 15
New Mexico	5.6 (3.6-8.6); 22	3.0 (1.1-6.3); 6	7.5 ((3.8-13.0); 11	14.7 (5.0-31.1); 5
Rural Georgia	0; 0	0; 0	0; 0	0; 0
San Francisco Oakland-SMSA	3.7 (2.6-5.1); 35	2.3 (1.1-4.1); 11	5.5 (3.3-8.4); 19	3.9 (1.3-8.8); 5
San Jose-Monterey	4.6 (2.8-7.0); 20	2.1 (0.6-4.9); 5	6.6 (3.2-11.8); 10	9.4 (3.1-20.7); 5
Seattle (Puget-Sound)	3.0 (2.1-4.2); 34	1.0 (0.4-2.2); 6	5.2 (3.3-7.9); 21	5.8 (2.4-11.6); 7
Utah	5.6 (3.4-8.6); 19	2.3 (0.6-5.9); 4	6.2 (2.1-11.9); 8	17.9 (7.5-33.5); 7

Table 3: Univariable and multivariable logistic regression analyses of 90-day mortality of 12,722 patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder

Variables	Univariable OR; p-value	Multivariable OR; p-value
Age	<0.001	<0.001
70-79 vs. <70	2.85; <0.001	2.80; <0.001
≥80 vs. <70	5.03; <0.001	5.02; <0.001
Gender		
Female vs. Male	1.34; 0.003	1.20; 0.062
Race		
Non-Caucasian vs. Caucasian	0.86; 0.3	0.88; 0.4
Year of Surgery	0.8	0.031
1996-2000 vs. 1988-1995	1.031; 0.8	0.85; 0.2
2001-2003 vs. 1988-1997	1.05; 0.7	0.74; 0.039
2004-2006 vs. 1988-1997	0.92; 0.5	0.65; 0.004
Tumor Grade	0.5	0.8
High vs. Low	1.25; 0.2	1.11; 0.6
Unknown vs. Low	1.20; 0.6	1.19; 0.6
Disease Stage		
Regional vs. Localized	1.69; 0.001	1.54; 0.005
SEER Registries	0.045	0.006
Alaska vs. California excl SF/SJM/LA	0; 0.9	0; 0.9
Atlanta(Metropolitan) vs. California excl SF/SJM/LA	0.51; 0.6	0.55; 0.1
Connecticut vs. California excl SF/SJM/LA	0.77; 0.2	0.68; 0.07
Detroit(Metropolitan) vs. California excl SF/SJM/LA	0.82; 0.3	0.78; 0.2
Hawaii vs. California excl SF/SJM/LA	1.18; 0.6	1.21; 0.5
Iowa vs. California excl SF/SJM/LA	0.74; 0.2	0.68; 0.09
Kentucky vs. California excl SF/SJM/LA	0.88; 0.6	0.96 0.9
Los Angeles vs. California excl SF/SJM/LA	0.894; 0.5	0.82; 0.3
Louisiana vs. California excl SF/SJM/LA	1.64; 0.031	1.91; 0.006
New Jersey vs. California excl SF/SJM/LA	1.11; 0.6	1.172; 0.4
New Mexico vs. California excl SF/SJM/LA	1.33; 0.3	1.21; 0.5
Rural Georgia vs. California excl SF/SJM/LA	0; 0.9	0; 0.9
San Francisco Oakland-SMSA vs. California excl SF/SJM/LA	0.83; 0.4	0.70; 0.1
San Jose-Monterey vs. California excl SF/SJM/LA	1.04; 0.9	0.96; 0.9
Seattle (Puget-Sound) vs. California excl SF/SJM/LA	0.68; 0.06	0.62; 0.027
Utah vs. California excl SF/SJM/LA	1.29; 0.3	1.143; 0.6

Additionally, POM varied with disease stage, with patients with more advanced disease having greater POM. In the overall population, the patients with localized UCUB had a POM rate of 2.6% compared with 4.3% for patients with locally advanced UCUB ($p<0.001$). The increase in POM according to stage was from 1.0% to 2.2% and 3.0% to 5.9% for those aged <70 years and those aged 70-79 years, respectively (all $p<0.003$). In contrast, in octogenarian patients, an increase in POM according to UCUB stage was not observed (12.0% and 8.9% for localized and locally advanced UCUB, respectively; $p=0.1$).

Overall, 59% of patients who succumbed to POM at 90 days died of CSM, 35% died of (OCM), and 6% died of other cancer-related mortality. In those who died of other-cause mortality, most died of heart disease (14.6%), cerebrovascular disease (2.1%), septicemia (1.8%), or other, unspecified, causes (9.8%). Similar rates were recorded across all age groups.

In the multivariate analyses, septuagenarian and octogenarian age increased the risk of POM, as shown by respective odds ratios of 2.8 and 5.0 ($p<0.001$). This implies that septuagenarians were 2.8 times more likely to die within 90 days of RC ($p<0.001$) and octogenarians were 5.0 times more likely to die within 90 days after RC, relative to their younger counterparts ($p<0.001$). When the analyses were repeated with septuagenarian patients as the reference category, the adjusted odds ratio for 90-day mortality for octogenarian patients was 1.8 ($p<0.001$). The patients who underwent RC in 2001-2003 were 26% less likely to die within 90 days and patients in 2004-2006 were 35% less likely to die within 90 days of RC compared with those patients who underwent RC in the earliest year quartile (1988-1997). The effect of tumor stage also remained statistically significant after all adjustments (odds ratio 1.5 for locally advanced disease vs. localized p=.005).

Finally, statistically significant differences were recorded for 2 of the 17 examined SEER registries. Specifically, POM was statistically significantly higher in Louisiana (odds ratio 1.9; p=0.006) and statistically significantly lower in Seattle (odds ratio 0.6; p=0.0027) than in the reference registry of California. To rule out the potential influence of the degree of urbanization between each SEER registry, we grouped them into metropolitan, urban, and rural areas, as defined by the county attributes provided by the SEER database, which rely on the rural-urban continuum codes as described by the U.S. Department of Agriculture. The comparisons between metropolitan and urban or rural areas were not significantly different statistically in the multivariate analyses (p=0.3; data not shown). Specifically, rural counties (odds ratio 1.29) were not an independent predictor of an increased risk of POM.

DISCUSSION

Despite the existence of several reports that suggest little differences in POM between elderly and younger patients, we decided to examine the POM rates according to age in a large population-based cohort. The rationale for performing this type of analysis stemmed from the small sample sizes of most previous contributions. For example, 11 investigators relied on series that had included <100 septuagenarians [70-80]. Similarly, 17 investigators relied on <50 octogenarian patients to assess the POM risk [70, 71, 73-87]. These sample size limitations precluded a valid assessment of POM and precluded valid conclusions about either a more elevated or a similar POM risk in elderly RC patients relative to younger RC patients. Thus, uncertainty exists regarding the relationship between POM and age. Because of this uncertainty, we decided to specifically focus on the POM of septuagenarian and octogenarian patients, and we compared the POM rates for these 2 patient groups with the rates recorded for younger patients.

Our analysis relied on the SEER-17 database. Our results demonstrated a 2.0%, 5.4%, and 9.2% POM rate for patients <70 years old and septuagenarian and octogenarian patients, respectively. In the multivariate analyses, septuagenarian and octogenarian patients demonstrated a 2.8-fold ($p<0.001$) and 5.0-fold ($p<0.001$) increase in POM, respectively, relative to younger patients, even after adjustment for all available covariates. Taken together, these findings have clearly confirmed that POM is greater in elderly patients after RC. Our findings apply to the SEER population and are not representative of tertiary care centers, such as the University of Texas M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, Kenneth Norris Jr. Cancer Center, or other similar institutions, in which very large numbers of RCs are performed.

The present analysis relied on 4480 septuagenarian and 1439 octogenarian patients (for a total of 5919 elderly patients), and comparisons were made to 6803 patients who were <70 years old. Thus, the sample size was at least 10-fold greater than that reported in all other studies, except for the elegant analyses of Konety et al., [69], in which 6690 elderly patients (≥70 years old) were assessed. Thus, our analysis focused on septuagenarian and octogenarian patients and did so with an adequate sample size. Moreover, unlike in the study by Konety et al., [69], in which patients aged ≥70 years old were grouped, our analyses distinguished between the POM rates of septuagenarian and octogenarian patients and showed an important difference between these 2 groups (5.4% vs 9.2% and odds ratio of 2.8 vs 5.0, respectively; all $p<0.001$). This was not reported by Konety et al., [69] In addition, Konety et al., [69] reported the in-hospital mortality, which might have underestimated the POM. In contrast, our study addressed POM during the initial 90 days after surgery, regardless of the length of stay. Finally, our study has provided a more contemporary assessment of POM (1988-2006) compared with the report by Konety et al., (1988-1999) [69]. Therefore, we have provided important novel elements that had not been previously reported.

The Impact of Comorbidities on Perioperative Mortality in the elderly

As mentioned previously, long-standing questions exist on the safety and efficacy of RC in the elderly suffering from muscle invasive and high risk non-muscle invasive UCUB. It is imperative to the surgeon to balance the risks of conservative management to the adverse perioperative outcomes in the elderly. Morgan et al., performed a retrospective cohort study from a single tertiary care center and developed a predictive tool to estimate the individualized risk estimation of 90-day POM [88]. In their multivariate analysis, adjusting for Charlson comorbidity index (CCI), age and pre-operative albumin were independent predictors POM at 90 days. Age and pre-operative albumin were associated with a 2.3 fold and 2.5 fold increase in POM (all $p<0.01$) [88]. A pre-operative nomogram to predict 90 day POM in patients 75 years and older was developed containing the following variables; age, CCI, muscle involvement and pre-operative albumin. The overall accuracy of the model was between 71% and 75% [88]. Other studies have substantiated the concept that nutritional deficiency, as measured by pre-operative weight loss, body mass index, and serum albumin are all strong predictors of 90-day POM and poor survival [89].

A similar analysis from our institution by Lughezzani et al., addressed comorbidities in the elderly and UCUB outcomes by using the SEER database to identify patients treated with RC [33]. Our analysis attempted to establish a graphical tool capable of illustrating the likelihood of CSM relative to OCM. This analysis attempted to discriminate elderly individuals who will benefit most from extirpative therapy. Analysis employed smoothed Poisson regression models to obtain estimated of cancer-specific mortality (CSM) and other-cause mortality (OCM) rates at specific time points after radical cystectomy. Age and disease stage were the predominant determinants of OCM and CSM, respectively. Moreover, age was also an independent predictor of CSM even when adjusting for disease stage. Patients ≥80 years irrespective of disease stage had an important effect of CSM [33]. Lughezzani concluded that CSM drives the overall mortality in patients with locally advanced pathological stage ($pT_{3-4}N_0$ or $pT_{1-2}N_{1-3}$) irrespective of patient age. Conversely, in patients with localized disease, OCM plays a substantially more important role [33].

A German single center study retrospectively analyzed perioperative morbidity and mortality after RC. 830 RCs were performed from 1993 to 2010, in which 365 patients (44%) were ≥70 years old [90]. They focused on health status prior to RC in order to correlate the effect of concomitant disease and age on the surgical outcome of RC. Novotny confirmed that elderly RC patients were more likely to have hypertension, coronary artery disease, diabetes, renal insufficiency and cerebrovascular disease. Specifically, 22% of elderly patients had three or more concomitant systemic diseases compared to 12% of younger patients ($p<0.001$). The overall perioperative morbidity was 25.7% and 21.5% compared to 31.0% for younger patients and elderly patients respectively. The most frequent medical complication was deep vein thrombosis and paralytic ileus. These rates are similar to those previously reported [91, 92]. In a multivariable logistic regression analysis, age, ASA score and specific comorbidities (chronic obstructive pulmonary disease, hypertension, coronary artery disease) were all independent predictors for post-operative morbidity (all $p<0.01$). It is most probable that comorbidities have an indirect effect on physiologic processes that are directly related to adverse outcomes after RC. For example, alterations in bowel function in patients suffering from vasculopathy and neuropathy associated with advanced diabetes [90]. Furthermore, other studies have confirmed that when adjusting for comorbidities age still remains an independent predictor of morbidity after RC [80, 93, 94].

Age and the fundamental frailty of this population should be considered itself an important factor when predicting morbidity after RC. Age has been correlates with the occurrence of any post-operative complication and is shown to be a risk factor for post-operative disability [95]. Age alone should not affect the consideration of RC, since elderly patients derive a survival advantage from extirpative therapy compared to those treated conservatively [93]. Moreover, advanced age mandates more diligent attention to pre-operative medical optimization [96].

Volume and Outcome Studies for Radical Cystectomy

There has been growing evidence indicating the relationship between hospital and/or surgeon volume outcomes for treatment of various diseases [34, 69, 97-100]. Birkmeyer and colleagues were the initial group to establish a role of both hospital and surgeon volume on the outcome of cystectomy on the basis of Medicare claims in the late 1990s [101, 102]. A very crucial debate raises the question should cancer care be centralised in specialized high volume reference centers? Some studies have suggested that high volume surgeons have more experience and better outcomes, proving the practice makes perfect theory [103, 104]. There is also evidence that high volume centers and high volume surgeons have the ability to stratify patients at risk, identify early signs of complications and reduce serious outcomes. The geriatric oncology population is an example where careful perioperative planning is crucial.

The analysis of Konety et al., attempted to determine the influence of hospital and surgeon volume on various outcome measures, including in-hospital mortality, length of stay and total hospital charges. Patient information was gathered using the Health Care Utilization Project-Nationwide Inpatient Sample (NIS) from 1988 to 1999. Konety and colleagues concluded that hospital volume appeared to have a significant effect on post-operative mortality after RC in older patients (OR=1.07; $p<0.001$) [69]. This study revealed three important advantages of RC at a high volume center; decreased POM, shortened length of stay and cost savings

Elting and colleagues between 1999 and 2001 identified 1302 patients in the state of Texas and evaluated POM and morbidity with respect to hospital volume [100]. Annual hospital volume of each center was divided into tertiles where low volume moderate volume and high volume and centers performed; <4 RCs, 4-10 RCs and >10 RCs annually respectively. POM was significantly more common among the elderly (2.5% vs. 4.5% for patients <75 years and >75 years respectively; $p=0.02$). Among the elderly both complications and mortality were more common in low volume hospitals. Specifically the POM rate in the elderly was 3.8% for low volume centers compared to 0.9% for high volume centers ($p=0.03$). The authors found overall POM and length of stay were statistically significantly related to annual hospital volume (all $p<0.04$). In their multivariable model patient age and high volume hospital were correlated with POM. Of note despite its statistical significance in univariable models, comorbidity status failed to reach independent predictor status in multivariable models.

The concept of failure to rescue is an important element when analyzing outcomes after surgical procedures. This concept is defined as the ability to prevent mortality after a post-operative complication has occurred. Some would suggest that failure to rescue is a better measure of quality of care than all-cause impatient mortality, which may contain inherent confounding factors [105, 106]. Elting et al., reported that high nurse-to bed ratio was associated with a

60% lower risk of failure to rescue (p=0.03). High nurse to occupied bed ratio was also found to an independent predictor of POM (OR=0.43; p-0.04). This finding is clinically apparent where improved patient monitoring by health care professionals can help identify post-operative complications and be able to treat them early preventing treating complications in a more advanced or disseminated state [100].

Clinical Implications

Our results have the following clinical implications. First, we have reported greater POM rates for septuagenarian and octogenarian patients than were previously reported from tertiary care centers [68]. This difference might relate to the ability to properly select surgical candidates, as was probably done at the tertiary care centers. With this premise, high-risk patients would be referred for other modalities, such as bladder preservation protocols [64]. Therefore, the inherent risk of POM might be truly lower at tertiary care centers than it is at other institutions, such as those included in the present analysis. The differences in surgical volume, hospital volume, and various processes related to RC at high-volume tertiary care centers represent a potential explanation for this phenomenon [69, 100].

Second, our results should be used in the informed consent process for patients who are candidates for RC outside of tertiary care centers. The POM rate of 5.4% and 9.2% for septuagenarians and octogenarians, respectively, should be contrasted with the POM rate of 2% for younger patients. If RC represents the only treatment option, all possible and necessary steps should be undertaken to maximally reduce the risk of POM before RC.

Third, it is important to realize that the POM rates have been improving with time. For example, the effect of the year of surgery on POM became increasingly protective in the more recent periods. This implies that urologic surgeons within the community have been improving their ability to preselect and optimize RC candidates. This observation was also likely related to improvements in all other processes related to the perioperative and postoperative care of RC patients, such as preoperative screening for comorbidities, anesthesia, convalescence, and others.

Fourth, our analysis has also validated previously reported observations in which the pathologic stage at RC was a predictor of POM [63]. Even after controlling for all other covariates, locally advanced UCUB conferred a 1.5-fold greater CSM rate compared with localized UCUB. Previously, Isbarn et al., [63] showed that the pathologic T stage represented the second most significant and second most powerful predictor of POM. Thus, the pathologic stage should also be considered in the RC informed consent process.

Finally, our results have also shown that variability exists with regard to the POM rates in the 17 examined SEER registries. After multivariate adjustment for all available covariates, only 2 inter-registry differences remained statistically significant. The POM rate observed in patients from

Louisiana was virtually twofold greater relative to California, which represented the reference registry (P=0.006). In Louisiana, 28 POM events were recorded in 400 patients. In contrast, in Seattle, 34 POM events were reported in 1127 patients, for a highly statistically significant protective effect for those who resided in Seattle (odds ratio 0.62; p=0.003). The variability in POM according to geographic localization after RC has not been previously reported. Therefore, these differences warrant additional attention to ensure that in some geographic areas patients are not predisposed to greater POM than in other areas. It is possible that the greater mortality in those registries represented very high-risk patients or extremely complex cases that had been referred for RC at tertiary care centers.

Limitations

Despite its values and strengths, our study did have limitations. As with all other studies that have examined the same endpoint (POM), our study was not prospective [15, 63, 68, 69, 100, 107]. However, because of the endpoint that was examined, it is unlikely that a large proportion of misclassifications in mortality occurred or would have been avoided in a prospective design. Moreover, as with all other studies, including that by Konety et al., [69], that focused on the relationship between age and POM, our study did not benefit from central pathology review [15, 68]. Additionally, no information was available on the preoperative comorbidity status, which could have been quantified using the CCI or the American Society of Anesthesiologists physical status classification system [34, 100]. Ideally, comorbidity should be examined along with other variables in future analyses. Information regarding diversion type and history of urinary diversion also could not be included in the present analysis. Although no valid data exist suggesting that the diversion type affects mortality, it is possible that the longer surgery duration and more complex postoperative course might affect POM [74, 108]. Other variables, such as intraoperative blood loss and the number of hypotensive episodes, could also affect POM. These were also not included in the present study owing to their unavailability in the SEER database. Last, but not least, it should be emphasized that POM represents only one of the important endpoints after RC. Another endpoint is disease-specific mortality. Previous data from the SEER database have suggested that elderly patients with muscle-invasive UCUB who have undergone RC might be able to derive important benefits from RC, just as do their younger counterparts [64, 109].

CONCLUSIONS

In the present population-based analysis, POM showed a three and five-fold increase in septuagenarian and octogenarian patients, respectively, relative to patients aged ≤69 years. These important increases in the risk of POM should be communicated to elderly RC candidates, especially those with existing important comorbidities. The consideration of these rates does not imply that RC should no longer be considered as the ideal treatment option. However, the POM rates we have reported should be communicated to patients to sensitize them about the non-negligible risk associated with the proposed surgery. The present data cannot be used to quantify the magnitude of change in short-term mortality relative to a treatment alternative. Future studies should consider other variables that could modify the risk of POM after RC. These include comorbidities, American Society of Anesthesiologists score, length of stay, surgery duration, blood loss, and identification of the underlying complication that initiated the cascade of events that led to POM.

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