Bladder Cancer 1 (2015) 123–131
DOI 10.3233/BLC-150018
IOS Press

Review

The Role of Population-Based Observational Research in Bladder Cancer

Andrew G. Robinson[a,*], Jason P. Izard[a,b] and Christopher M. Booth[a,c]
[a]*Department of Oncology, Queen's University, Kingston, ON, Canada*
[b]*Department of Urology, Queen's University, Kingston, ON, Canada*
[c]*Department of Public Health Sciences, Queen's University, Kingston, ON, Canada*

Abstract. While clinical trials have led to many advances in the treatment of bladder cancer, important gaps in knowledge persist. Population-based studies have made important contributions to what is known about bladder cancer and can contribute unique insights to practice and policy. In addition to evaluating effectiveness of interventions in routine practice, population-based studies can identify gaps between evidence and practice, and generate knowledge that cannot be gained from clinical trials. In this review we will highlight how population-based research has informed practice, policy, and the research agenda for bladder cancer.

Keywords: Population-based, effectiveness, utilization, bladder, metastatic, early, muscle invasive, chemotherapy, radiation-therapy, surgery

INTRODUCTION

Bladder cancer is common, and is responsible for a significant burden of malignancy in an aging population [1]. In an ideal world, unambiguous clarity of evidence would exist to guide clinicians in making recommendations for the individual patient, and to guide policy-makers in making recommendations for the health system. The pinnacle of clarity in evidence-based medicine is the large randomized controlled trial (RCT). The act of randomization inherent to the RCT minimizes confounding and bias that plagues other forms of clinical research [2]. As such, RCTs remain the gold standard to establish efficacy of cancer therapy. When a clinician sees a patient for whom evidence exists from large RCTs, treatment decisions are easily made. Unfortunately, many patients with bladder cancer are both dissimilar to those enrolled in clinical trials, and present with questions that have not, or cannot, be answered by clinical trials. Thus, clinicians and policy makers must rely on other forms of evidence to inform decision-making. Other forms of evidence may include case studies, case series describing experience and outcomes of single institutions. While these are valuable records of experience, reports of single institution outcomes are prone to referral bias, selection bias, and publication bias.

Population-based studies are complementary to RCTs and can provide insight into questions that RCTs cannot address including: quality of care delivered in routine practice, effectiveness of interventions in the "real world", and gaps between practice and evidence (Table 1). By including all patients within the population of interest, these studies are less prone to selection bias and referral bias that plague traditional institution-based cohort studies. However, population-based studies are not free from confounding and bias;

*Correspondence to: Andrew Robinson, Department of Oncology, Queen's University, 25 King Street West, Kingston, ON, K7L 5P9, Canada. Tel.: +1 613 544 2631; Fax: +1 613 546 8209; E-mail: robinsa4@kgh.kari.net.

ISSN 2352-3727/15/€27.50/$35.00

their insights should be viewed as complementary to knowledge that comes from RCTs. In particular, ascribing differential outcomes to different treatments used in routine practice is fraught with challenges due to unmeasured or residual cofounding.

In this review, we will consider how population-based observational research has contributed to the knowledge base for bladder cancer. We will consider three disease settings: non-muscle invasive bladder cancer (NMIBC), muscle invasive non-metastatic bladder cancer (MIBC), and metastatic/advanced bladder cancer (ABC). A review of the relevant clinical questions, and insights generated from observational research (Table 2) will highlight the relevance of population-based studies in bladder cancer, and identify priorities for future research.

NON-MUSCLE INVASIVE BLADDER CANCER

Non-muscle invasive urothelial bladder cancer (NMIBC) represents approximately 77% of newly diagnosed patients with bladder cancer in North America [3]. It is a heterogeneous category of tumors with a wide spectrum of recurrence and progression rates dependent on various prognostic factors [4–6].

As this represents the most common presentation of bladder cancer, it also represents the area of bladder cancer management for which there is the largest wealth of clinical trials upon which to base practice. Questions that have been answered either directly (i.e. as the primary endpoint) or indirectly (i.e. as analysis of the rich databases generated from clinical trials) include: what factors affect the risk of recurrence and progression in NMIBC; and, what treatments reduce recurrence and progression in NMIBC Questions not answered by RCT's include: what is optimal follow-up for patients; and are there gaps in follow up or treatment of patients.

Risk of recurrent NMIBC

Sylvester et al. conducted a retrospective analysis of seven EORTC bladder cancer trials in an effort to quantify the risk of recurrence and progression and to identify factors which predispose patients with Ta and T1 disease to these outcomes [4]. The authors generated a scoring system which incorporated the number of tumors present, the number of prior recurrences, the tumor size, the tumor grade, the presence of CIS and the T stage into a predictive model. Depending on the risk factors present, their model predicted an overall 5 year risk of recurrence ranging from 31–78% with the 5 year probability of progression ranging from 1 to 45%. A lower risk of recurrence and progression is estimated by utilizing the CUETO predictive tables which are derived from the results of 4 Spanish randomized control trials involving patients receiving intravesical BCG therapy [7]. The CUETO model incorporates the same factors as the EORTC tables in addition to age and gender to generate expected 5 year recurrence rates ranging from 21–68% and 5 year rates of progression ranging from 4–34% [8].

On a population level, Wyszynski et al. used the New Hampshire State Cancer Registry to identify and follow 726 patients with NMIBC diagnosed over a 7 year period [9]. The overall risk of recurrence was 55% with a median follow-up of 5.6 years. In their multivariate model, they identified smoking history and BMI as being associated with both an accelerated time to recurrence and an increased risk of recurrence. The risk of progression in this cohort was only 5% overall. However, 74% of patients had low grade tumors.

Management and surveillance of NMIBC

The cornerstone of management to reduce recurrence rates in NMIBC involve intravesical instillations. A meta-analysis of 2,548 patients from 13 RCTs demonstrated that a single dose of peri-operative chemotherapy within 24 hours of transurethral resection of a bladder tumour (TURBT) leads to a 38% improvement in recurrence free interval and a 12% absolute risk reduction in recurrence within 1 year [10]. Six different drugs were used in the 13 studies with mitomycin C (5 of 13 studies) and epirubicin (4 of 13 studies) being used most commonly.

Immunotherapy with BCG has been shown to be an effective treatment in reducing the risk of recurrence and progression compared to TURBT alone [11, 12]. Lamm et al. demonstrated in a RCT that maintenance instillations of BCG were superior to induction BCG alone by improving recurrence free survival from 41 months to 60 months [13]. Patients receiving maintenance BCG also experienced a longer time to worsening disease or death. However, only 16% of these patients were able to receive the entire maintenance regimen. In a meta-analysis of studies comparing BCG to mitomycin C, Bohle and Bock reported that BCG was superior to mitomycin in preventing disease progression [14]. This effect was limited to studies that included BCG maintenance.

With recurrence rates that are variable depending on patient and disease characteristics, both the National

Table 1
Relative strengths and limitations of three study designs in bladder cancer

	Randomized controlled trials	Institutional case series	Population-based observational studies
Strengths	Excellent internal validity	Provide insight into what "can" be achieved.	Good external validity.
	Provide precise measures of efficacy and acute toxicity under ideal conditions.	Detailed data regarding patient (i.e. performance status, renal function) and treatment (i.e. decision-making, drug dosing, intra-operative findings) are often available.	Provide insight into delivery of care in routine practice to all patients – including elderly and those with comorbidity.
	Confounding is mitigated through randomization.	Often uniform practice patterns.	Provide information to identify gaps in care.
	Prospective registration may reduce publication bias.		Can provide effectiveness of new therapies in the general population.
	Detailed prospective data capture enables multiple rich analyses (i.e. patients-reported outcomes and correlative science)		Large samples allow the opportunity to study rare diseases.
			Provides insight into short and long term toxicity in routine practice.
			Can address questions that cannot or will not be evaluated in a RCT.
Limitations	External validity is limited.	Questionable external validity.	Limited internal validity.
	Provide evidence of efficacy (treatment effect under ideal circumstances), but not effectiveness (benefit in routine practice).	Large numbers imply a long time period, so external validity is questionable.	Vulnerable to unmeasured and/or residual confounding.
	Very difficult where modalities of therapy are very different.	Vulnerable to referral bias, selection bias, and publication bias.	Identification of comparative benefit is prone to cofounding by indication.
	Patients, providers, and health systems in RCTs are not representative of routine practice.	No requirement for registration or to submit protocol beforehand.	Databases often lack detail regarding performance status, comorbidity, patient preference, and treatment delivery
	May detect clinically modest effect that does not apply to larger group of patients.		No requirement for prospective registration of study.
	May use surrogate endpoints that are not valid measures of patient benefit.		

Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) recommend risk adapted approaches to surveillance in patients with NMIBC. Both organizations recommend an intense surveillance cystoscopy schedule for patients with a high risk of recurrence with urinary cytology every 3 months for the first 2 years and then less frequently thereafter (EUA), and every 3–6 months for high risk patients the first two years (NCCN) [15, 16]. These recommendations are based largely on expert opinion. Population-based research has shown variable uptake of these recommendations. Hollenbeck et al. used the Surveillance, Epidemiology, and End Results (SEER) Medicare dataset to describe intensity of treatment and surveillance in relation to outcome among 20,713 patients with early stage bladder cancer [17]. Patients treated by high-intensity providers received more endoscopic evaluations, more frequent urinary cytology and more radiographic imaging than patients treated by low-intensity providers. Despite this degree of variation, median survival was similar across all provider categories. Although high intensity providers treated more patients with high risk features, after adjusting for grade and stage of disease, being treated

Table 2
Insights from population-based research into the management and outcome of bladder cancer

Disease setting	Key findings from population-based research
Non-muscle invasive bladder cancer	Significant gaps exist between guidelines and practice for surveillance and use of intravesical therapy.
	Intense follow-up may be associated with improved outcomes in high grade NMIBC.
Muscle invasive bladder cancer	There are significant gaps between evidence and practice in the care of patients with MIBC; many patients with localized MIBC do not receive cystectomy or radical radiotherapy and most patients do not receive neoadjuvant/adjuvant chemotherapy.
	Age, comorbidity, and socioeconomic status are associated with variation in care. Practice also varies considerably based on geography and provider.
	Time to treatment may be related to survival with adjuvant therapy.
	Hospital and surgeon cystectomy volume is associated with patient outcome.
	Lymph node harvest at time of cystectomy is associated with long-term survival.
	Most patients with MIBC treated with cystectomy are not referred to a medical oncologist.
	Any difference in survival between cystectomy and radiotherapy for MIBC is likely to be small.
	Confirms finding from RCT's that adjuvant cisplatin-based chemotherapy is associated with improved survival.
Metastatic bladder cancer	The uptake of palliative chemotherapy for patients with metastatic bladder cancer is very low.

by a high intensity provider had a similar risk of death compared to a low intensity provider. In contrast to these results, an analysis of the same dataset for those patients with high grade NMIBC reveals an increased risk of death in patients who receive less than 4 cystoscopies and less than 4 urinary cytologies in the first 2 years after their diagnosis [18]. This work suggests that uptake of guidelines is variable, and that intensity of follow-up may be associated with outcome in some clinical populations.

Patterns of care for NMIBC

Although much of what we know about how to treat NMIBC is derived from randomized control trials, how that knowledge has been translated into clinical practice is largely demonstrated through population-based studies. The majority of these studies have highlighted a lack of compliance to guidelines and recommended treatment strategies.

Schrag et al. analyzed the SEER Medicare dataset to measure adherence to NCCN guideline surveillance strategies [19]. They found only 40% of patients received the minimum number of surveillance cystoscopies and 18% of patients underwent a cystoscopic examination in less than 2 of the 5 6-month intervals that composed their 3 year follow-up. Huang et al. utilized the SEER Patterns of Care project to examine the use of intravesical chemotherapy on a population-based level [20]. Despite Level I evidence demonstrating its effectiveness, only 42% of high risk patients received some form of intravesical therapy. Increased stage and grade were associated with higher utilization of intravesical therapy. However, race and geographic location were also significantly associated with receipt of therapy. Low use of intravesical therapy is corroborated by Madeb et al. who used MEDSTAT Commercial Claims Encounters and Medicare Supplemental Coverage Claims to show that less than 1% of patients with newly diagnosed bladder cancer received a dose of intravesical chemotherapy within 1 day of TURBT [21].

Chamie et al. amalgamated the AUA, EAU and NCCN guidelines to generate a series of quality metrics and then measured adherence to these metrics with the SEER Medicare dataset [18]. Only one case out of their sample of 4790 subjects was compliant with all metrics. Adherence with these metrics was associated with age, race, year of diagnosis and stage and grade of tumor. They found that those patients who received $\geq$4 cystoscopies, $\geq$4 urinary cytologies and first BCG treatment within 90 days had improved survival compared to those with <4 cystoscopies, <4 urinary cytologies and no BCG therapy.

MUSCLE INVASIVE BLADDER CANCER

For patients with localized muscle invasive bladder cancer, two major decisions need to be made: 1) whether radiation or cystectomy is best initial local treatment for this patient; and, 2) whether this patient should receive adjuvant or neoadjuvant chemotherapy. Clinical trials have not answered the first question. However, evidence from clinical trials does support utilization of neoadjuvant, and to a lesser extent adjuvant, chemotherapy [22–30]. Other decisions include in the

management of MIBC include: which chemotherapy to use; how extensive should surgery be; where should surgery to be done; what fractionation of radiation should be used; and, what post-therapy surveillance should be used.

Patterns of care for MIBC

Population-based studies are useful to describe patterns of care which may identify gaps between clinical evidence and clinical practice. For MIBC, the two main aspects of care addressed by these studies relate to use of cystectomy or radiotherapy (RT) and utilization of chemotherapy.

David et al. demonstrated in a series of patients from 1998 to 2003 that only 11% of T3 tumours in the National Cancer Database received peri-operative chemotherapy [31]. There was a slight increase in 2003 in this study, with 16% of patients receiving peri-operative chemotherapy. Porter et al. also reported in 2011 on SEER population data on patients with bladder cancer diagnosed between 1992 and 2002 and showed a very low utilization of chemotherapy [32]. Booth et al., in a study from Ontario, examined peri-operative chemotherapy utilization in 2944 patients from 1994 to 2008, and showed that even in the time period 2004 to 2008, only 22% of patients with MIBC received neoadjuvant or adjuvant chemotherapy [33].

While these population-based studies may show a low utilization of peri-operative therapy, they do not answer why this is, and have some inherent flaws. The Porter et al. study is notable for being published in 2011, with SEER data for patients who were diagnosed until 2002. The David data was more current when published – published in 2007 with treatment data until 2003, but a note is made that it is unclear if the data in 2003 was fully updated in the database. The Booth paper did show 22% of patients with muscle invasive bladder cancer from 2004 to 2008 had received peri-operative chemotherapy, but does not comment on the fact that gemcitabine was not funded for neoadjuvant or adjuvant bladder cancer treatment during this time period in Ontario.

Each of these studies show that age and comorbidity are associated with chemotherapy utilization. The Ontario data demonstrate that most patients who undergo cystectomy for MIBC are not referred to a medical oncologist [34]. As such, upstream decision-making by urologists is an important target in future knowledge translation to improve use of peri-operative chemotherapy in MIBC. The existing literature demonstrates substantial geographic regions in practice but does not offer insight into the root causes. At the very least, these studies demonstrate that clinical evidence and guidelines are not being translated into clinical practice.

In terms of local therapy, Gray et al. examined the use of local aggressive modality therapy in the treatment of muscle invasive non-metastatic bladder cancer between 2004 and 2008 using the National Cancer Data Base [35]. Their results showed that 29% of these patients received a radical cystectomy alone, 4% partial cystectomy, 13% underwent radical cystectomy with neoadjuvant (2%) or adjuvant (11%) chemotherapy. Radiation therapy was used in 9% of cases – chemoradiotherapy in 5% and radiation alone in 4%. In total, only 53% of cases received potentially curable treatment. Age, socioeconomic status, and type of care institution were significantly associated with modality of therapy.

Population-based research can also provide insight into questions that simply cannot be addressed by clinical trials. In breast cancer and colorectal cancer, population-based data-sets have established that the time interval between surgery and initiation of chemotherapy is associated with survival [36, 37]. Our group recently evaluated this issue among patients with MIBC and found that initiation of adjuvant chemotherapy more than 12 weeks from surgery was associated with inferior overall survival compared to earlier treatment [38]. It is important to highlight that this form of evaluation can be easily confounded; misclassification bias may cause some patients with metastatic disease to be considered adjuvant, and selection bias may explain why patients with delayed chemotherapy have inferior outcomes. However, recognizing these important limitations, the existing literature suggests that if adjuvant therapy is considered, patients should start treatment as soon as soon as they are medically and emotionally fit to do so.

Effectiveness of cystectomy and radiotherapy for local disease

There is a surprising lack of Level I evidence to evaluate the optimal local therapy for MIBC. A meta-analysis of three small trials, involving a total of 439 patients suggested a survival benefit for cystectomy over radiotherapy (RT). However both the internal validity (i.e. the high number of patients who did not receive their intended therapy), and the external validity (i.e. these studies were done prior to aggressive transurethral resection, and before significant advances in surgical and radiation techniques) of the

meta-analysis limits how this evidence may be applied to contemporary clinical practice [39].

Case series from high volume academic centers have described outcomes of both cystectomy and RT. Among 1054 patients treated with cystectomy at the University of Southern California during 1971–1997, Stein reported a 5 year survival of 60% [40]. Similarly, several single institution reports for the use of primary organ sparing procedures also exist, with Rodel et al. accumulating several single institution studies, and reporting a 50–60% survival at 5 years using this technique in 1000 patients treated at various single institutions during the 1970s–1990s [41].

Modern clinical trials have not been successful in the context of localized MIBC. The SPARE study – an ambitious randomized study from the UK examining selective bladder preservation versus cystectomy – enrolled 45 patients over 2.5 years and was closed due to poor accrual [42]. The likelihood that a clinical trial will successfully compare bladder preservation versus upfront cystectomy is unfortunately very low. Recent randomized trials in muscle invasive bladder cancer were designed to evaluate: early versus delayed chemotherapy [43], neoadjuvant chemotherapy [28], and high dose volume versus standard volume radiation [44] were all closed early due to poor accrual.

Population-based data examining the role of radiotherapy and cystectomy surgery may help shed some light on this issue. Unlike single center case series, population-based studies have the advantage of relatively high external validity – particularly if the context of the population and health system are similar to the population for which one is using the data for. The comorbidity profile, age, and socioeconomic profile that limit enrollment on clinical trials also influences decisions regarding optimal treatment, and requires assessment in evaluating a comparison of treatment modalities.

Several population-based reports have evaluated outcomes associated with cystectomy and radical RT in routine practice. Studies from Ontario, Canada ($n = 5259$), Alberta, Canada ($n = 398$), Yorkshire, UK ($n = 398$), and a SEER database analysis ($n = 26{,}851$) have had similar conclusions [45–49]. Utilization of cystectomy has increased over time and unadjusted outcomes appear to favor surgery. However, patients who undergo primary surgical therapy are fundamentally different from those who undergo primary radiation therapy, predominantly with lower comorbidity and lower age. When outcomes are adjusted for age and comorbidity the relative benefit of cystectomy over RT is significantly reduced and in some cases disappears. One advantage of the significant regional variations in practice found in population-based studies is that this variation allows a 'pseudorandomization', where the variable analyzed is not the variable of interest - i.e. radiation or surgery, but an instrumental variable. If surgical therapy were superior to radiation therapy, then it would follow that being treated in an area with a high proportion of patients receiving surgery would be associated with a better outcome. In this case, region of treatment is considered an instrumental variable which remove some of the hidden selection bias and confounding that occurs when comparing one treatment modality to another, but also reduces the power to detect a small difference [49, 50]. Indeed, where this regional variable was used instead of modality of therapy, it was also shown being treated in an area where a high proportion of patients had surgery did not have a significant benefit in terms of survival, providing additional evidence that the difference between surgery and radiation is small at best [48]. As it is unlikely that Level I evidence will emerge in the future, patient selection for each modality will continue to be driven by patient preference, residual bladder function, and operative risk.

Population-based research had also yielded important insights into quality of care for cystectomy. Work from Ontario and the Netherlands have consistently shown that post-operative mortality and long-term survival of patients with bladder cancer is associated with hospital cystectomy volume and surgeon cystectomy volume [51, 52]. Additional work by our group and others has also shown that the extent of node harvest is associated with long term survival, and that there is sub-optimal utilization of pelvic lymph node dissection in routine practice [53–55]. These are but two examples of how health system performance and quality of care can be monitored and improved using population-based observational research.

Effectiveness of peri-operative chemotherapy

RCTs have demonstrated improved survival with neoadjuvant platinum-based chemotherapy [26, 27]. Although absolute benefit varies, a meta-analysis showed an overall survival benefit of approximately 5% [22]. While the quality of the evidence is less robust, meta-analysis suggests that adjuvant chemotherapy is associated with a comparable effect size [22, 23]. Unfortunately, recent RCTs have failed to accrue enough patients to make meaningful conclusions about the benefit of adjuvant therapy [24, 25].

Several population-based studies have described utilization and outcome of peri-operative chemotherapy in routine clinical practice. Our group has described used of chemotherapy among all patients with MIBC treated with cystectomy in Ontario Canada during 1994–2008 ($n = 2944$). We found that contrary to treatment guidelines, only 4% of patients received neoadjuvant chemotherapy, while 18% received adjuvant chemotherapy [33]. A second, large multi-institution study from the US described treatment of 3947 patients, of whom 932 (23%) received adjuvant chemotherapy [32]. In adjusted analyses, both studies suggest that adjuvant chemotherapy improves survival in routine practice. In fact, the effect size observed in these studies (HR OS 0.71; HR CSS 0.73 and 0.83) is remarkably consistent results from the published meta-analyses (HR OS 0.75. 0.74, 0.77) [23, 29, 30]. The majority of patients in the Ontario study were treated with gemcitabine-cisplatin; this regimen was not tested in the earlier clinical trials. However, a recent analysis that pooled data across 28 institutions, suggested that gemcitabine-cisplatin has comparable effectiveness to MVAC [56].

METASTATIC BLADDER CANCER

Palliative chemotherapy and radiation are standard treatments for metastatic bladder cancer. There are surprisingly no clinical trials that have compared best supportive care to palliative chemotherapy. However, clinical trials have demonstrated that multi-agent platinum chemotherapy is associated with improved survival compared to single agent platinum [57]. RCTs have also demonstrated that gemcitabine/cisplatin is a more tolerable and equally efficacious regimen to MVAC, and that gemcitabine/carboplatin offers some palliative benefit for patients intolerant of cisplatin [58, 59]. A small study ($n = 40$) suggested a possible benefit for bone targeted agents such as zoledronic acid in patients with metastatic disease to bone [60].

In applying these therapies to patients in routine practice, the following questions arise: how effective are these therapies in the "real world"; how toxic are these therapies in the "real world"; and, and what is the uptake of these therapies.

Compared to NMIBC and localized MIBC, there is a lack of population-based literature to provide insights into practice and outcomes of metastatic bladder cancer in routine care. Using SEER data, Porter et al demonstrated that approximately 45% of patients with stage IV bladder cancer received chemotherapy in the non-peri-operative setting [32]. This study was limited to patients over the age of 65 only, and is limited in interpretation due to the peculiarity of staging for bladder cancer – stage IV including both patients with distant metastases, and those with local nodal involvement only. Moreover, staging data pertain to stage at diagnosis only. Based on these limitations, it is difficult to use SEER data to describe the utilization of palliative chemotherapy for patients with metastatic disease as the true denominator is missing. Using the Ontario Cancer Registry we have recently explored this issue by using a 'look-back' technique. In this approach we describe the proportion of patients who die of bladder cancer that received chemotherapy in the last 12 months of life [61]. We found that approximately one quarter of such patients receive chemotherapy. Similar to the use of peri-operative therapy, the use of palliative intent chemotherapy for bladder cancer is associated with age, comorbidity, socioeconomic status, and place of residence.

CONCLUSIONS

Cancer of the bladder is relatively common, and occurs in a relatively difficult to treat, aged, population with significant comorbidity. Population-based studies can augment information that is gained from clinical trials, answer questions that clinical trials cannot address, and reveal gaps between evidence and practice in the uptake of established medical therapies.

Understanding and closing gaps in care represent an important priority. Reducing the gap between what is known to benefit patients and what actually happens in the "real world" has far greater potential for public health benefit than a decade of clinical trials testing novel therapies with small incremental gains in median survival. True improvements in the care of patients with bladder cancer will require both RCTs to establish the novel treatments of the future, and population-based observational research to identify how to optimally deploy these treatment advances in order to maximize the benefit to patients.

REFERENCES

[1] Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009;27(3):289-93.

[2] Atkins D, et al. Systems for grading the quality of evidence and the strength of recommendations II: Pilot study of a new system. BMC Health Serv Res 2005;5(1):25.

[3] Scosyrev E, et al. Sex and racial differences in bladder cancer presentation and mortality in the US. Cancer 2009;115(1): 68-74.
[4] Sylvester RJ, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49(3):466-5; discussion 475-7.
[5] Kiemeney LA, et al. Predictability of recurrent and progressive disease in individual patients with primary superficial bladder cancer. J Urol 1993;150(1):60-4.
[6] Millan-Rodriguez F. et al. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol 2000;163(1):73-8.
[7] Fernandez-Gomez J, et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: Multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008;53(5):992-1001.
[8] Fernandez-Gomez J, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: The CUETO scoring model. J Urol 2009;182(5):2195-203.
[9] Wyszynski A, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. Cancer 2014; 120(3):408-14.
[10] Perlis N, et al. Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: An updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol 2013;64(3):421-30.
[11] Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 2002;168(5):1964-70.
[12] Shelley MD, et al. A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int 2001;88(3):209-16.
[13] Lamm DL, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group Study. J Urol 2000;163(4): 1124-9.
[14] Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: Formal meta-analysis of comparative studies on tumor progression. Urology 2004;63(4):682-6; discussion 686-7.
[15] Clark P, Agarwal N, Biagioli M. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Fort Washington, PA: National Comprehensive Cancer Network, 2013.
[16] Babjuk M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. Eur Urol 2013;64(4):639-53.
[17] Hollenbeck BK, et al. Provider treatment intensity and outcomes for patients with early-stage bladder cancer. J Natl Cancer Inst 2009;101(8):571-80.
[18] Chamie K, et al. Quality of care in patients with bladder cancer: A case report? Cancer 2012;118(5):1412-21.
[19] Schrag D, et al. Adherence to surveillance among patients with superficial bladder cancer. J Natl Cancer Inst 2003; 95(8):588-97.
[20] Huang GJ, et al. Predictors of intravesical therapy for nonmuscle invasive bladder cancer: Results from the surveillance, epidemiology and end results program 2003 patterns of care project. J Urol 2008;180(2):520-4; discussion 524.
[21] Madeb R, et al. Treatment of nonmuscle invading bladder cancer: Do physicians in the United States practice evidence based medicine? The use and economic implications of intravesical chemotherapy after transurethral resection of bladder tumors. Cancer 2009;115(12):2660-70.
[22] 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(2):202-5; discussion 205-6.
[23] 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(2):189-199; discussion 199-201.
[24] Paz-Ares ESLG, Esteban E, Saez A, Gonzalez-Larriba J, Anton A, Hevia M, de la Rosa F, Guillem V, Bellmunt J. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. Journal of Clinical Oncology 2010;28(18_suppl). LBA4518.
[25] Cognetti F, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: An Italian, multicenter, randomized phase III trial. Ann Oncol 2012;23(3):695-700.
[26] Griffiths G, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. J Clin Oncol 2011;29(16):2171-7.
[27] Grossman HB, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349(9):859-66.
[28] Kitamura H, et al. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. Ann Oncol 2014;25(6):1192-8.
[29] Leow JJ, et al. Adjuvant chemotherapy for invasive bladder cancer: A 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014;66(1):42-54.
[30] Ruggeri EM, et al. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: A pooled analysis from phase III studies. Cancer 2006;106(4):783-8.
[31] David KA, et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: A report from the National Cancer Data Base. J Urol 2007;178(2):451-4.
[32] Porter MP, et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol 2011;29(3):252-8.
[33] Booth CM, et al. Perioperative chemotherapy for muscle-invasive bladder cancer: A population-based outcomes study. Cancer 2014;120(11):1630-8.
[34] Booth CM, et al. Patterns of referral for perioperative chemotherapy among patients with muscle-invasive bladder cancer: A population-based study. Urol Oncol 2014;32(8):1200-8.
[35] Gray PJ, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: Results from the National Cancer Data Base. Eur Urol 2013; 63(5):823-9.

[36] Biagi JJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: A systematic review and meta-analysis. Jama 2011;305(22): 2335-42.
[37] Lohrisch C, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 2006;24(30):4888-94.
[38] Booth CM. et al. Delivery of perioperative chemotherapy for bladder cancer in routine clinical practice. Ann Oncol 2014;25(9):1783-8.
[39] Shelley MD, et al. A meta-analysis of randomised trials suggests a survival benefit for combined radiotherapy and radical cystectomy compared with radical radiotherapy for invasive bladder cancer: Are these data relevant to modern practice? Clin Oncol (R Coll Radiol) 2004;16(3):166-71.
[40] Stein JP, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol 2001;19(3):666-75.
[41] Rodel CC, Weiss, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol 2006;24(35):5536-44.
[42] Moynihan C, et al. The Patient Deficit Model Overturned: A qualitative study of patients' perceptions of invitation to participate in a randomized controlled trial comparing selective bladder preservation against surgery in muscle invasive bladder cancer (SPARE, CRUK/07/011). Trials 2012;13:228.
[43] Sternberg CN, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or *N*+ M0 urothelial carcinoma of the bladder (EORTC 30994): An intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015;16(1):76-86.
[44] Huddart RA, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: Results of the BC2001 trial (CRUK/01/004). Int J Radiat Oncol Biol Phys 2013;87(2):261-9.
[45] Scrimger RA, et al. Muscle-invasive transitional cell carcinoma of the urinary bladder: A population-based study of patterns of care and prognostic factors. Int J Radiat Oncol Biol Phys 2001;51(1):23-30.
[46] Booth CM, et al. Curative therapy for bladder cancer in routine clinical practice: A population-based outcomes study. Clin Oncol (R Coll Radiol) 2014;26(8):506-14.
[47] Hayter CR, et al. The management and outcome of bladder carcinoma in Ontario 1982–1994. Cancer 2000;89(1):142-51.
[48] Kozak KR, et al. Bladder preservation for localized muscle-invasive bladder cancer: The survival impact of local utilization rates of definitive radiotherapy. Int J Radiat Oncol Biol Phys 2012;83(2):e197-204.
[49] Munro NP, et al. A 10-year retrospective review of a nonrandomized cohort of 458 patients undergoing radical radiotherapy or cystectomy in Yorkshire, UK. Int J Radiat Oncol Biol Phys 2010;77(1):119-24.
[50] Newhouse JP, McClellan M. Econometrics in outcomes research: The use of instrumental variables. Annu Rev Public Health 1998;19:17-34.
[51] Goossens-Laan CA, et al. Survival after treatment for carcinoma invading bladder muscle: A Dutch population-based study on the impact of hospital volume. BJU Int 2012; 110(2):226-32.
[52] Siemens DR, et al. Processes of care and the impact of surgical volumes on cancer-specific survival: A population-based study in bladder cancer. Urology 2014;84(5):1049-57.
[53] Hedgepeth RC, et al. Variation in use of lymph node dissection during radical cystectomy for bladder cancer. Urology 2011;77(2):385-90.
[54] Hollenbeck BK, et al. Hospital lymph node counts and survival after radical cystectomy. Cancer 2008;112(4):806-12.
[55] Siemens DMW, Peng P, Berman D, Rhee J, Li G, Booth C. Process of Care Variables Explaining the Influence of Surgical Volumes in Bladder Cancer Outcomes: A Population-Based Study in American Urological Association Annual Meeting 2013;e21-e22.
[56] Galsky MD, et al. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer 2015;121(15):2586-93.
[57] Logothetis CJ, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8(6):1050-5.
[58] von der Maase H, 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(21): 4602-8.
[59] Linardou H, et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: Phase II study of the Hellenic Co-operative Oncology Group. Urology 2004;64(3):479-84.
[60] Zaghloul MS, et al. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. Int J Clin Oncol 2010;15(4):382-9.
[61] Robinson AG, WX, Mackillop WJ, Booth CM. Utilization of palliative chemotherapy for advanced bladder cancer: Patterns of care in routine clinical practice. J Clin Oncol 2015;33(suppl; abstr 6525).