Bladder Cancer: Highlights from 2006

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Superficial
Survivin

Abstract

Objectives: This paper provides an overview of the most relevant findings on bladder cancer (BCa) presented at the 2006 annual meetings of the European Association of Urology, American Urological Association, and the American Society of Clinical Oncology.

Methods: Experts in the field of BCa selected and discussed relevant new findings in BCa during a closed meeting in Marbella, Spain. Furthermore, the participants’ opinions on representative clinical cases were assessed via interactive voting. Voting results were commented on by an expert panel.

Results: Many studies examined the diagnostic and prognostic value of the biomarkers survivin and nuclear matrix protein-22, but results were not consistent. With respect to superficial BCa, a major revelation was the introduction of the European Organisation for Research and Treatment of Cancer tables to calculate the risk for recurrence and progression of superficial BCa patients. In addition, one study showed that Bacillus Calmette-Guerin + interferon-alpha might be a good alternative treatment for patients with recurrent superficial BCa. For patients with minimally invasive BCa who had undergone radical transurethral resection, a bladder-sparing treatment was cautiously suggested. For those with recurrent urothelial cancer, one study presented a new salvage chemotherapy consisting of paclitaxel, ifosfamide, and nedaplatin. Finally, two studies demonstrated that there was no difference in oncologic outcome between patients who underwent open or laparoscopic radical cystectomy or nephroureterectomy.

Conclusions: Many interesting new findings in the field of BCa have been presented at 2006 urologic/oncologic meetings, which aim to improve the diagnosis and treatment of patients with BCa.

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1. Introduction

Bladder cancer (BCa) is a common malignancy, being the fourth most frequent cancer in men and the ninth most frequent cancer in women in the United States [1]. In Europe, approximately 36,500 males and 13,000 females die from BCa each year [2]. The incidence of BCa varies considerably across
Europe. The highest mortality rates are observed in Southern and Western European men. The majority of newly diagnosed BCas, 70–80%, are classified as superficial disease. The remaining tumours initially present as either invasive or metastatic disease. About 70% of individuals with superficial BCa have a low-grade papillary tumour that involves only the urothelium. Although these patients will have numerous interventions after diagnosis, their overall prognosis is good and most of them will die from other causes. The other 30% of superficial BCas have a higher histologic grade, involve the lamina propria, and are often accompanied by a flat carcinoma in situ (CIS). Therefore, this population is at high risk for both progression and death from BCa. Since BCa has the highest recurrence rate of all cancers, not only patients with a high-grade tumour but also those with a low-grade tumour need very thorough surveillance [3].

This paper provides a selection of data on BCa presented in 2006 at annual meetings from the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society of Clinical Oncology (ASCO). A selection of abstracts on BCa presented at these congresses was discussed during the “New Horizons in Urology” meeting in Marbella, Spain. In addition, participants in this meeting were engaged in an interactive voting procedure to assess their opinions on representative clinical case studies illustrative of the chosen abstracts. Voting results were commented on by experts in the field of BCa.

2. Biomarkers for the detection and surveillance of BCa

Because of the high recurrence rate of BCa, a rigorous patient follow-up is necessary to monitor the disease by allowing appropriate detection and treatment in both low- and high-grade tumour patients to maximise their cure rate. The most important evaluation methods used so far include cystoscopy, voided urine cytology (VUC), and urinary tract imaging. However, because of the rather low sensitivity of VUC in detecting transitional cell carcinoma (TCC) of the urinary tract, particularly in low-grade disease, the invasive character of cystoscopy, and the significant costs associated with the elaborate surveillance protocol, additional follow-up strategies were investigated. Therefore, various biomarkers were introduced to detect disease in the urinary tract by analysing voided urine samples. Current biomarkers investigate biologic characteristics associated with different levels of the cancer cell evolution and can be grouped into several categories such as tumour-associated antigens, blood group antigens, growth factors, apoptosis/cell-cycle and extracellular matrix proteins, and DNA alterations [4].

Although these biomarkers have promising diagnostic and prognostic value, they are scarcely used in practise because of their rather insufficient sensitivity and/or specificity. A stumbling block in the generalised use of these biomarkers may be the lack of straightforward studies supporting their use for decision making, treatment, and prognosis of BCa. However, it has also been put forward that cost, difficult interpretation of results, or the unsuitability for use in the office contribute to their minimal use.

At the EAU 2006 congress, several new data on the biomarkers survivin and nuclear matrix protein-22 (NMP-22) was presented.

2.1. Survivin

Survivin, a 16.5-kDa protein, belongs to the type of proteins that serve to inhibit apoptosis. In contrast to normal cells, survivin is highly expressed in a large number of malignant neoplasms and is generally associated with adverse prognosis. In the case of BCa, survivin is differentially expressed in the neoplastic epithelium, but not in the normal epithelium or in the uninvolved mucosa. Therefore, several research groups have already explored the possibility of using urinary survivin as a molecular biomarker for the early detection of BCa, and the prognostic and diagnostic potentials of survivin remain under investigation by several groups [5–10].

Several teams found a correlation between high survivin levels and urothelial invasion, size, pathologic stage and grade, progression and/or mortality in primary or recurrent TCC [5,6,8]. However, in one study [7], the level of survivin messenger RNA (mRNA) measured by real-time polymerase chain reaction was not correlated to stage and grade. This discrepancy may be due to different methods that were used to analyse the survivin levels in the urine samples. Nevertheless, this latter study showed that urinary survivin mRNA is a highly specific (100%) and sensitive (75%) marker for the detection of TCC [7].

Although these data support the use of survivin as a diagnostic and prognostic tool for superficial BCa, one study did not support these findings. Using an enzyme-linked immunosorbent assay to detect survivin in serum or voided urine samples, the authors were unable to identify those patients with BCa [9].
2.2. Nuclear matrix protein-22

NMP-22 is a 238-kDa nuclear mitotic apparatus protein found in the nuclear matrix of all cell types, albeit with low expression levels in nondividing cells. Although healthy individuals have low levels of urinary NMP-22, BCa patients may have levels that are up to 25-fold higher [11]. Tests are currently available to measure NMP-22 in voided urine samples; nevertheless, controversy remains concerning their diagnostic value mainly because of inconsistent results regarding specificity [4]. This discrepancy was also seen at the EAU congress where contradictory data were presented concerning the specificity and sensitivity of NMP-22 versus VUC [12,13].

An updated analysis from a large-scale multicentre study that enrolled 1331 consecutive patients at risk for BCa demonstrated that the combination of cystoscopy with the noninvasive NMP-22 point-of-care test is superior to VUC combined with cystoscopy for the detection of BCa [12]. In contrast, a smaller study comprising 148 patients found that VUC has a better diagnostic accuracy compared with the NMP-22 point-of-care test [13].

In light of the inconsistencies in study results reported on the use of survivin or NMP-22 for the detection of BCa, it was put forward that more research is needed before either of these biomarkers is able to function as a reliable diagnostic tool for BCa. Conversely, the suggestion was made that future diagnostic developments should focus on the use of a set of markers for a combined detection of different tumour-specific molecules for reaching a reliable diagnostic and prognostic sensitivity and specificity.

3. Treatment of superficial bladder tumours

The current EAU guidelines for treatment of TaT1 tumours state that every patient needs some adjuvant intravesical therapy after transurethral resection (TUR). Deciding on the number and the type of therapy largely depends on the patient’s risk for recurrence and progression [14]. Recently, the European Organisation for Research and Treatment of Cancer (EORTC) developed easy-to-use tables for calculating the probability of recurrence and progression after TUR, which should aid in choosing the appropriate treatment [15]. According to the EAU guidelines, the standard treatment for low-risk superficial BCa patients is a single instillation of chemotherapy, whereas intravesical Bacillus Calmette-Guérin (BCG) therapy is recommended for patients with high-grade tumours. Patients with poor or no response to chemotherapy or BCG therapy, however, are usually offered radical cystectomy. Nevertheless, more conservative second-line treatments are under investigation, including chemotherapy, device-assisted instillations, or immunotherapy such as BCG combined with interferon-alpha (IFN-α) [16].

3.1. BCG combined with IFN-α

In a large phase 2 multicentre trial presented at the AUA meeting, the response of patients who recurred after or were intolerant to BCG therapy (BCG-F) and the response of BCG-naïve patients (BCG-N) to BCG + IFN-α treatment were evaluated [17]. BCG-N patients (N = 536) and BCG-F patients (N = 467) all received IFN-α (50 million units) in combination with BCG: BCG-N patients received a full dose BCG (81 mg), patients who failed prior BCG treatment received one third of the standard dose, and BCG-intolerant patients received one tenth of the usual dose. It was shown that BCG-N patients had the highest cancer-free survival rate. However, patients with recurrent superficial BCa after > 12 mo of remission had a similar cancer-free survival rate compared with BCG-N patients (Fig. 1). Therefore, BCG + IFN-α might be a good alternative treatment for those patients with recurrent superficial BCa.

Prior to discussing these new data on second-line treatment after BCG failure, the opinion of urologists present at the closed meeting in Marbella was assessed by interactive voting and discussion of a representative clinical case study. The case of a 70-year-old man with gross haematuria and normal
renal function was presented. Although he represented some surgical risk because of a myocardial infarction 3 yr previously, he had a good performance status. Upon examination with ultrasonography and cystoscopy, multiple lesions were observed in the bladder. The histopathologic findings after TUR were a T1 G3 tumour with no muscle invasion. Randomised biopsies taken upon TUR, however, showed two positive locations for CIS. The first-line treatment was a 6-fold instillation of BCG (81 mg). Nevertheless, a new course of randomised biopsies taken 3 mo later showed that two biopsies were positive for CIS. With this in mind, the attendees from the closed meeting were asked to choose a new treatment strategy through interactive voting. The majority of the participants voted for a new round of six BCG instillations (27 mg) or radical cystectomy, whereas only a small percentage opted for BCG + IFN-α therapy or an optimised mitomycin regimen (Fig. 2).

Although the patient received a new course of six BCG instillations (27 mg) after BCG failure, the experts would rather have chosen the combination of BCG + IFN-α, which is in line with the new data discussed above. Three months after the second round of BCG, new biopsies still revealed three sites positive for CIS. After radical cystectomy, multiple CIS sites were found in the bladder; however, all were pT0. Although this scenario could be seen as overtreatment, the expert was comfortable with his decision, knowing that around 60% of CIS-positive bladders would progress to muscle-invasive tumours during the next 3 yr.

3.2. EORTC prognostic tables

Grouping schemes such as the TNM staging system have been used to estimate outcomes and guide treatment of patients with BCa. More recently nomograms have been developed to provide a more accurate assessment of outcomes. For patients with invasive BCa the International Bladder Cancer Nomogram Consortium developed a prognostic outcomes nomogram to predict 5-yr disease recurrence risk after radical cystectomy [18]. For patients with superficial disease, the EORTC tables were presented at the EAU meeting as a tool for urologists to easily calculate the short- and long-term risks for recurrence and progression after (TUR) (electronical calculator available at http://www.eortc.be/tools/bladdercalculator/) [15]. A simple scoring system was based on the merged data from 2596 individual patients diagnosed with superficial BCa derived from seven randomised phase 3 EORTC clinical trials. Analysis of all the available data indicated that the most important prognostic factors for recurrence are the number of tumours, their size, and the prior recurrence rate, whereas the key prognostic factors for progression are the T category, grade, and presence of CIS. To each of these variables a coefficient was attributed, from which an individual patient score could be calculated. On the basis of these scores ranging from 0 (best prognosis) to 17 or 23 for recurrence and progression, respectively (worst prognosis) (Table 1), the probability of recurrence and progression can be ascribed, and they may vary from 15–61% and 0.2–17%, respectively, at 1 yr to 31–78% and 0.8–45%, respectively, at 5 yr (Table 2) [15]. By means of these probabilities, the urologist can discuss the options with the patient to determine the most suitable treatment.

To test the use of the EORTC tables in practise, participants from the closed meeting in Marbella were presented with the following patient characteristics: a 68-year-old man with macroscopic haematuria exhibited one exophytic tumour of 3 cm and two small satellites upon cystoscopy. He underwent a TUR and the histopathologic findings of the lesion were pT1 G2 with negative random biopsies. On the basis of the EORTC tables, the patient had 38% chance of recurrence and only 5% chance of progression after 1 yr. With this in mind, participants were asked to choose among four options for treatment after TUR. As seen in Fig. 3, there was no consensus between the participants. Those choosing the single dose of chemotherapy followed by BCG or chemotherapy were in line with the EAU 2006 treatment recommendations for
superficial BCa patients with low to moderate risk of progression, regardless of their risk for recurrence. According to these recommendations, one immediate instillation of chemotherapy is for patients with low to moderate risk of recurrence and very low risk of progression, whereas intravesical BCG for ≥1 yr and radical cystectomy are for those patients with high risk of progression [14].

4. Treatment of muscle-invasive and metastatic bladder tumours

According to the EAU guidelines, the gold standard for treatment of T2-T4a, N0-NX, M0 tumours is

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<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tumours</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Single</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 to 7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumour size</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1 rec/yr</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 rec/yr</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>T category</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ta</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CIS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Total score</td>
<td>0–17</td>
<td>0–23</td>
</tr>
</tbody>
</table>

EORTC = European Organisation for Research and Treatment of Cancer; rec = recurrence; CIS = carcinoma in situ. Reprinted from reference 15 with the permission of the European Association of Urology.

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Table 2 – EORTC table representing the probability of recurrence and progression according to total recurrence or progression score [15]

<table>
<thead>
<tr>
<th>Recurrence score</th>
<th>Prob recurrence 1 yr (95%CI)</th>
<th>Prob recurrence 5 yr (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15% (10%, 19%)</td>
<td>31% (24%, 37%)</td>
</tr>
<tr>
<td>1–4</td>
<td>24% (21%, 26%)</td>
<td>46% (42%, 49%)</td>
</tr>
<tr>
<td>5–9</td>
<td>38% (35%, 41%)</td>
<td>62% (58%, 65%)</td>
</tr>
<tr>
<td>10–17</td>
<td>61% (55%, 67%)</td>
<td>78% (73%, 84%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression score</th>
<th>Prob progression 1 yr (95%CI)</th>
<th>Prob progression 5 yr (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2% (0%, 0.7%)</td>
<td>0.8% (0%, 1.7%)</td>
</tr>
<tr>
<td>2–6</td>
<td>0.8% (0.4%, 1.6%)</td>
<td>6% (5%, 8%)</td>
</tr>
<tr>
<td>7–13</td>
<td>5% (4%, 7%)</td>
<td>17% (14%, 20%)</td>
</tr>
<tr>
<td>14–23</td>
<td>17% (10%, 24%)</td>
<td>45% (35%, 55%)</td>
</tr>
</tbody>
</table>

Prob = probability; 95%CI = 95% confidence interval. Reprinted from reference 15, with the permission of the European Association of Urology.
radical cystectomy without preoperative chemo- or radiotherapy, and with limited lymph node dissection and preservation of the urethra if margins are negative. However, because of the renewed interest in quality of life problems associated with radical cystectomy, the rising trend is to try to preserve the bladder when possible. A possible alternative to radical cystectomy may be bladder-sparing surgery together with neoadjuvant or adjuvant chemotherapy and/or radiation [19].

A more conservative management of minimally invasive BCa patients is also suggested as a result of the fact that approximately 10% of the cystectomy specimens are without tumour (stage pT0) [19]. Although these patients in general have a good prognosis, it has been suggested that stage pT0 cystectomy specimens do not confer a survival advantage [20]. These findings were confirmed in a study presented at the AUA, showing that, of 857 patients who underwent radical cystoscopy, 95 (11%) were found to have pT0N0M0 in the surgical specimen, albeit their clinical stages ranged from cT1 to cT4 (Table 3) [21]. Although most of these patients (73%) received neoadjuvant chemotherapy, 8 patients still developed recurrences (Table 3), with a median time to recurrence of 7.7 mo (range: 3–64). It was shown that a contributing factor to an elevated risk for recurrence and the associated shorter overall survival time was the presence of lymphovascular invasion on the TUR specimen. Therefore, patients with a pT0N0M0 upon cystectomy, especially those with lymphovascular invasion, cannot be considered cured and still need lifelong surveillance [21].

More than 50% of the patients diagnosed with muscle-invasive BCA may relapse following cystectomy because of hidden metastases in the region surrounding the bladder. Since response rates of 40–70% have been seen with cisplatin-based combination chemotherapy in these patients, the use of this type of chemotherapy has become an important treatment option for patients with locally invasive BCA [19]. However, a number of patients still progress or relapse after chemotherapy. At the ASCO meeting, a promising new salvage therapy was presented for patients with recurrent urothelial cancer. Thirty-two patients previously treated with cisplatin-based chemotherapy were enrolled in a phase 2 study for the evaluation of the efficacy of combination chemotherapy consisting of paclitaxel, ifosfamide, and nedaplatin (PIN) [22]. Among these 32 patients, complete and partial responses were attained in 5 patients and 19 patients, respectively, with an overall response rate of 75%. The median time to progression was 8 mo, whereas the median overall survival time was 22 mo. Although several grade three and four side-effects were observed, such as granulocytopenia, thrombocytopenia, anaemia, and neuropathy in 100%, 25%, 19%, and 3% of the patients, respectively, PIN therapy was considered to be tolerable, but—most importantly—highly active as a second-line treatment in patients with recurrent urothelial cancer [22].

5. Open versus laparoscopic surgery

The advances in laparoscopic surgical techniques have brought about a progressive shift from traditional open surgery towards the minimal-invasive access to treat genitourinary oncologic conditions. Both for radical cystectomy and nephroureterectomy, there is emerging evidence that laparoscopy is a promising technique as a replacement for invasive open surgery [23,24]. At the 2006 EAU meeting, two studies that examined the outcomes of laparoscopic surgery were presented. In the first study, a retrospective analysis was performed on a total of 100 patients who had undergone laparoscopic radical cystectomy (86 for oncologic reasons) between October 1999 and July 2005 to assess feasibility, postoperative complications, and, especially, oncologic outcome for this minimal-invasive technique during a mean follow-up period of 25 mo (range: 1–73) [25]. With a mean operative time of 100 min (range: 60–140 min) for performing laparoscopic radical cystectomy, the procedure was believed to be feasible. Although 28% and 26% of the patients had early (within 3 mo after surgery) and late (3 mo after surgery) complications, respectively, it was stated that laparoscopic surgery was a safe procedure. Notwithstanding that for 72 of 86 of the oncology patients, pathology results showed G3 lesions (8 pT1, 23 pT2, 29 pT3, and 12 pT4), only 2 patients recurred and 8 of 86 patients died from their oncologic disease during the follow-up period. Hence, these data indicate that laparoscopic radical cystectomy appears to have analogous results compared with its open surgical counterpart in terms of cancer control.

Table 3 – Clinical stages and number of recurrences in muscle-invasive bladder cancer patients with pT0 after radical cystectomy [21]

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>N</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>cT2</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>cT3b</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>cT4</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
A second study compared the long-term oncologic outcome of laparoscopic nephroureterectomy (LNU) and open nephroureterectomy (ONU) performed in patients with upper urinary tract TCC between January 2000 and December 2004 [26]. Of the 220 patients without concomitant or prior BCa who were reviewed in this study, 53 underwent LNU with a mean follow-up of 13.1 mo (range: 1–45), whereas 167 had an ONU with a mean follow-up of 24.1 mo (range: 1–64). The results indicated that the frequency of bladder recurrence, local recurrence, and distant metastases did not differ significantly between LNU and ONU, respectively (Fig. 4). Furthermore, the actual disease-free 2-yr survival rates were similar for both surgical strategies (80% for LNU and 85% for ONU; Fig. 4). Combined, these results indicate that the long-term oncologic control of upper tract TCC is not affected by the laparoscopic surgical approach.

Although both studies represent promising data, longer follow-up is needed to confirm these findings. It was put forward that more reliable data might be obtained when performing a randomised prospective study comprising a large group of patients with a follow-up period of several years.

6. Conclusions

At the key urologic and oncologic congresses in 2006, many interesting new data were presented on the surveillance and treatment of patients with BCa. A lot of research focussed on the diagnostic and prognostic value of biomarkers such as survivin and NMP-22. In light of the inconsistencies in research results regarding the specificity and sensitivity of these markers for the detection of BCa, it was put forward that more research is needed before either of these markers can replace cystoscopy and VUC in daily practise. The use of a set of biomarkers for the combined detection of different tumour-specific molecules, however, was suggested to have potential as a new diagnostic tool for BCa in the future.

The most important topic of the 2006 meetings was unmistakably the launch of the EORTC tables, which allow urologists to easily calculate the probability for progression and recurrence in patients with superficial BCa. It is believed that the use of these tables will greatly facilitate tailoring of the treatment and the frequency of follow-up to the patient’s prognosis and wishes.

Although the standard treatment of patients with recurrent superficial BCa after BCG failure is radical cystectomy, more conservative second-line treatments are under investigation. In this respect, BCG + IFN-α appears to be a promising new therapy in those patients with refractory superficial BCa. Moreover, for patients with minimally invasive BCa who underwent radical TUR, a more conservative management has been proposed instead of radical cystectomy, which is the gold standard treatment for invasive BCa. However, it was shown that even patients with a pT0 upon histopathologic analysis after radical cystectomy, are still at risk for progression and recurrence, especially in case of lympho-vascular invasion. Therefore, before a conservative treatment for minimally invasive BCa is considered, a thorough evaluation and selection of possible candidates is crucial.

Furthermore, one study presented a new promising salvage chemotherapy consisting of paclitaxel, ifosfamide, and nedaplatin for patients with recurrent urothelial cancer. Finally, there were two studies that presented the outcomes of laparoscopic surgery (radical cystectomy and nephroureterectomy) as an alternative to open surgery. Although the results from these studies showed that laparoscopic surgery is seemingly analogous to open surgery, more long-term data are needed to really support this statement.

Conflicts of interest

The author has nothing to disclose.

References


