REVIEWS

Systemic therapy for bladder cancer – a medical oncologist's perspective

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Received: March 7, 2014 **Accepted:** May 6, 2014 **Online Published:** May 16, 2014
DOI: 10.5430/jst.v4n2p25 **URL:** http://dx.doi.org/10.5430/jst.v4n2p25

Abstract

Advanced bladder cancer, both muscle-invasive localized disease and metastatic disease, is managed with systemic chemotherapy. Cisplatin-based multi-agent chemotherapy remains the cornerstone for systemic therapy. MVAC (methotrexate-vinblastine-doxorubicin-cisplatin) has been most rigorously studied, both neoadjuvantly and for palliation of metastatic disease. For metastatic disease, cisplatin-gemcitabine (GC) has compared favorably to MVAC due to improved tolerability with similar efficacy. GC has been adopted as standard therapy. Neoadjuvant chemotherapy for muscle-invasive bladder cancer improves survival among those patients eligible to receive cisplatin. Adjuvant chemotherapy is difficult to administer effectively given morbidity of radical cystectomy, and studies have shown mixed results about its benefit. Non-cisplatin regimens have been investigated but remain experimental and reserved for those not candidates for cisplatin in the metastatic setting. While multiple agents have been studied after metastatic disease progression after cisplatin-based therapy, there remain no FDA-approved therapies for the second line. Future trials with anti-VEGF therapy and immunotherapy are actively being investigated. This review examines the systemic therapy available to oncologists with current evidence and future directions.

Key words

Bladder Cancer, Chemotherapy, Cisplatin, Neoadjuvant, Metastatic

1 Introduction

Bladder cancer is the sixth most common malignancy diagnosed in the United States, disproportionally affecting men in older age who commonly have medical comorbidities, which complicate options for surgery and chemotherapy. The majority of bladder cancers are diagnosed at an early stage, i.e. confined to the urothelium and lamina propria. These patients are often managed successfully with local therapies. Intravesical therapy is used routinely after resection of these superficial tumors to reduce risk of recurrence of higher risk tumors. Intravesical BCG (bacillus calmette-guerin) is the most commonly used agent and is thought to act by generating immune response against the residual tumor [1]. Intravesical chemotherapy has also been used, including agents such as mitomycin, gemcitabine, thiotepa, and valrubicin [2].

While most patients with non-muscle-invasive disease generally have favorable outcomes, approximately one-third of patients will present with tumors that invade into the muscularis propria and/or beyond. Advances in surgery, local therapy, and systemic chemotherapy have led to modest improvements in outcome in recent years; yet muscle-invasive

urothelial cancer remains challenging to treat and often results in high morbidity and mortality. Given the need to improve patient outcomes, experimental approaches (including novel chemotherapeutic regimens, biologic agents, immunotherapy and vaccines) are being studied. This review will provide an overview of current and investigational systemic therapies for muscle-invasive and metastatic urothelial carcinoma.

2 Localized muscle-invasive disease

Although there is risk of recurrence for non-muscle-invasive disease—which often requires repeated local therapies—disease that invades into the muscularis propria has high risk of recurrence, local invasion, spread, and thereby mortality. The prognosis for these T2 and greater lesions are significantly poorer than with T1, Ta, or Tis disease. While initial local management involves maximal transurethral resection of the tumor, the high rates of both local and distant recurrence generally require more aggressive management strategies (Table 1). Although some reports suggest that certain patients can be managed with maximal TURBT alone, the standard approaches to muscle-invasive bladder cancer have involved either radical cystectomy or definitive radiation therapy with or without chemotherapy.

Historically, muscle-invasive disease was managed surgically with removal of the bladder, lymph nodes, and adjacent organs (prostate and seminal vesicles in men; uterus, cervix, fallopian tubes and ovaries in women). In one case series examining long-term outcomes after radical cystectomy, patients undergoing radical cystectomy with pelvic lymph node dissection had a 5-year recurrence-free survival rate of 68% [3]. The risk of recurrence was higher for patients with locally invasive primary tumors (beyond the bladder); the risk was particularly high for those with involvement of the pelvic lymph nodes. The surgery tended to yield local control. The most common sites of recurrence were at distant metastatic sites (75% in the Stein et al. series), and peri-operative chemotherapy was then explored to improve patients' clinical outcomes.

Patients with muscle-invasive bladder tumors are staged prior to their definitive therapy to rule out metastatic disease. The most sensitive modality is PET/CT, which has been studied prospectively in patients being considered for cystectomy. The addition of PET to CT increased sensitivity for pelvic lymph node involvement, while in total identifying new metastatic disease (local or distant) in 5.6% of the 233 patients in the study [4].

2.1 Neoadjuvant chemotherapy prior to radical cystectomy

Neoadjuvant chemotherapy is the most attractive peri-operative strategy for delivery of systemic therapy for bladder cancer patients. Radical cystectomies are large, involved procedures that require extended hospitalizations and recovery periods. They are also unfortunately associated with high rates of complications. In a recent study that reported rates of complication in the 90-day period following surgery, the overall rate of post-surgical complications was 64% [5]. The rate of serious complications (defined as illness requiring major intervention or debility requiring prolonged rehabilitation, for example) was 13%. The delivery of post-operative adjuvant chemotherapy may not be possible in some patients, may be interrupted or delayed due to post-operative recovery, and may potentially contribute to post-operative morbidity. Given the high rates of complication after surgery, delivering the chemotherapy neoadjuvantly—when the patients are most fit to receive therapy—has been explored and has met with success in trials to have a favorable impact in overall patient prognosis with this disease.

Trials have investigated the role for several regimens of neoadjuvant chemotherapy prior to radical cystectomy. The best evidence is for 3 cycles of MVAC (methotraxate, vinblastine, doxorubicin, and cyclophosphamide). As reported by Grossman et al., patients with muscle-invasive bladder cancer were randomized to either cystectomy alone or 3 cycles of neoadjuvant MVAC [6]. The primary outcome for the study was survival. Patients who received neoadjuvant MVAC survived a median of 31 months longer than those who received cystectomy alone (77 *vs* 46 months, $p = 0.06$). The trial met the secondary outcome of improved complete response rates at time of cystectomy (compared to maximal TURBT) (38% *vs* 16%). When stratified for T stage, patients with more advanced tumors (T3 or T4) appeared to have the greatest

 ISSN 1925-4067 E-ISSN 1925-4075

benefit. Median survival with neoadjuvant MVAC for these patients with T3 or T4 tumors was 65 months compared to 24 months for cystectomy alone ($p = 0.05$).

Other combination chemotherapy regimens have been investigated in the neoadjuvant setting. In a similar study design, patients were randomized to either 3 cycles of CMV (cisplatin, methotrexate, or vinblastine) or local therapy alone (cystectomy and/or radiation therapy) [7]. When this trial was initially reported (with a median follow-up of 4 years), median overall survival was 44 months in the neoadjuvant CMV cohort compared with 37.5 months in the local therapy alone ($p = 0.075$). With longer-term follow-up, statistical significance was reached when analyzing survival at 5 and 8 years [8].

Although not investigated in the phase III setting, gemcitabine-cisplatin (GC) doublet chemotherapy has been studied neoadjuvantly [9]. In this single-institution phase II study, 22 patients with muscle-invasive bladder cancer were enrolled to receive 3 cycles of GC with primary end-points of pathologic and radiologic response rates. The radiographic partial response rate was 70%, and the complete pathologic response rate was 26%. GC has compared favorably to MVAC in the metastatic setting (similar efficacy with improved tolerability), and GC is commonly used in lieu of either MVAC or CMV in modern practice. Similarly, while not studied specifically in the neoadjuvant setting, a dose dense regimen of MVAC, which has been studied in comparison to traditional MVAC in metastatic patients [10], could be employed. A dose dense strategy would potentially reduce time to the surgery, as a delay of that definitive therapy is a potential criticism of neoadjuvant chemotherapy.

Many patients are not candidates for cisplatin chemotherapy given the comorbidities that often affect bladder cancer patients. Thus, other non-cisplatin-based neoadjuvant chemotherapy has been investigated, but no high level evidence for its use has been published. In particular, studies using combinations of carboplatin in combination with taxanes and gemcitabine have demonstrated some efficacy but also high levels of toxicity [11-13]. In the study by Smith et al. employing neoadjuvant carboplatin-gemcitabine-paclitaxel in both resectable and borderline resectable patients, the pathologic complete response rates were 17.6% by intention to treat analysis with higher than expected toxicity. Grivas et al. studied neoadjuvant carboplatin-gemcitabine-(nab)paclitaxel and reported a higher pathologic T0 rate (27.6%); however the study did not meet the primary endpoint chosen for expanded investigation.

2.2 Adjuvant chemotherapy after cystectomy

Despite good evidence for neoadjuvant chemotherapy, its use is still limited for a variety of reasons, including patient and physician preference. For patients who do not receive neoadjuvant chemotherapy, adjuvant chemotherapy is another option to minimize cancer recurrence after radical cystectomy. As discussed above, adjuvant chemotherapy may be difficult to administer given extended post-operative recoveries and complications. However, adjuvant therapy may be safely administered with similar benefits as with neoadjuvant chemotherapy for the majority of patients who recover well after radical cystectomy.

The use of adjuvant chemotherapy has been studied, largely with mixed results. Cisplatin multidrug combinations (MVAC, CMV, GC) have produced both positive and negative studies for survival benefit. An early study of adjuvant MVAC or MVEC (substituting epirubicin for doxorubicin) in patients with high risk for recurrence (non-organ confined tumors at the time of cystectomy) demonstrated a statistically significant benefit regarding recurrence-free survival [14]. Long-term median overall survival data showed a non-statistically significant advantage for the adjuvant chemotherapy compared to the surgery alone group (35.1 months *vs* 20.4 months) [15]. More recently, Cognetti et al. reported a phase III trial using the contemporary regimen of GC [16]. Patients were randomized to either 4 cycles of adjuvant GC or GC at the time of disease relapse. Overall survival was not different between groups, including in subgroup analysis of non-organ confined and lymph node positive disease. The authors commented that adjuvant studies continue to face difficulty with accrual and remain difficult to conduct.

A Cochrane review with meta-analysis of available adjuvant chemotherapy trials found insufficient evidence to draw strong conclusions regarding the use of adjuvant chemotherapy [17]. Despite the conflicting data, there was a trend toward improved overall survival (9% improvement) in the adjuvant chemotherapy group compared to surgery alone. More studies are needed to precisely define the role of adjuvant chemotherapy. Based upon the currently available trials, adjuvant chemotherapy should remain a consideration only for those carefully selected and informed patients who did not receive neoadjuvant chemotherapy.

Despite the available evidence regarding perioperative chemotherapy, a recent analysis of patterns of chemotherapy administration in Ontario showed that adjuvant chemotherapy is employed more frequently than neoadjuvant chemotherapy [18]. Patients with T3 or T4 primary tumors or node-positive disease at the time of cystectomy were most likely to receive adjuvant chemotherapy. These patients appeared to have a survival benefit compared to the population not receiving perioperative chemotherapy.

2.3 Bladder preserving techniques

While the standard of care is often viewed as neoadjuvant chemotherapy followed by radical cystectomy, some patients may elect for therapy with the purpose of bladder preservation. This preference may be due to a desire to avoid a major surgery with its associated risks. In addition, some patients may be poor surgical candidates and require definitive local therapy without surgery. Radiation therapy with or without chemotherapy has been investigated as an option for bladder sparing definitive treatment for bladder cancer. Patient selection is critical for consideration of bladder conserving strategies. Tumor location and multifocality in particular may exclude a patient from consideration of a bladder preservation technique. In addition, patients must also be fully informed of the late toxicities of chemoradiation, with many not having satisfactory bladder function after treatment despite the bladder preservation. Despite interest in developing bladder preservation strategies, none have been compared to radical cystectomy to determine optimal management.

Initially, radiation therapy alone as a definitive local therapy was investigated as an alternative to radical cystectomy. When investigated as a monotherapy after TURBT in patients with invasive bladder cancer, radical radiation therapy resulted in approximately a 50% complete response rate based upon several historical series [19]. This level of response led many patients to go on to further definitive therapy (surgery) or palliative therapies for those that were not surgical candidates. Given the low rates of success with radiation therapy alone, oncologists investigated whether the addition or neoadjuvant chemotherapy and/or concurrent chemotherapy could improve these outcomes. Radiation alone has been compared to concurrent chemoradiation (mitomycin-5FU) by James et al [20]. In this randomized phase III study, concurrent chemotherapy did not significantly increase toxicity and resulted in both improved local control and survival (5 year survival in the chemoradiation group of 48% compared with 35% in radiation alone group).

The majority of studies into bladder-preservation have aimed to combine chemotherapy and radiation in an optimal fashion. Kaufman et al. investigated the feasibility of bladder preservation after neoadjuvant chemotherapy, and definitive chemoradiation produced good local control of tumor with patients retaining functional bladders [21]. Specifically, the study used CMV neoadjuvant chemotherapy followed by concurrent cisplatin-radiation therapy. Repeat staging was then performed to detect residual tumor. Those patients with residual tumor underwent salvage radical cystectomies. In those patients with complete responses, though, consolidative chemoradiation was administered, and bladders were preserved. Further trials studying radiation therapy with various radiosensitizing agents have been performed since. These studies have investigated single-agents (cisplatin [22], gemcitabine [23], vinblastine [24], amifostine [25], liposomal doxorubicin [26]) and combinations (cisplatin-paclitaxel [27], cisplatin-5FU [28], carbogen-nicotinamide [29]).

While this approach is attractive to avoid surgery and potentially preserve normal voiding function, studies examining quality of life comparing patients who underwent cystectomy with those who underwent chemoradiation do not show improvement for the bladder preservation cohort [30, 31]. In fact, patients may rate bladder function unsatisfactory following

treatment with concurrent chemoradiation due to late complications, including scarring with low bladder capacity or hemorrhagic cystitis [32].

3 Advanced disease

3.1 First line cisplatin-based therapy

The chemotherapy regimens used peri-operatively are also used in the metastatic setting. In fact, GC has been most rigorously studied in the advanced/metastatic setting, and those data are largely extrapolated for the use of GC in the neoadjuvant setting. Similar to the neoadjuvant setting, cisplatin-based combination therapy is viewed as the first line. Early studies demonstrated that cisplatin combination chemotherapy (specifically MVAC) was superior to cisplatin monotherapy as a first line therapy [33].

Traditional MVAC was also compared to dose-dense MVAC in the phase III setting. In this study, a 14-day cycle of MVAC with G-CSF was used. Sternberg et al. demonstrated that dd-MVAC led to significantly greater complete responses (21% *vs* 9%) with equivalent overall and progression free survival [10]. With longer-term follow-up, however, the survival curves separated, and 5-year overall survival was 21.8% in the dose-dense group compared with 13.5% in the traditional group [34]. With similar toxicity profiles, dd-MVAC appeared superior.

Many subsequent research efforts have sought to match the response rate of MVAC while finding regimens with more tolerability. MVAC was compared with GC in a phase III study in newly diagnosed metastatic bladder cancer patients by von der Maase et al [35]. Response rates (49% *vs* 46%) and median overall survival (14.8 *vs* 13.8 months) were comparable for both MVAC and GC, respectively. Events of severe neutropenia, neutropenic fever, sepsis, and severe mucositis were significantly reduced in the GC group, which led authors to suggest that GC should become the standard of care due to decreased toxicity. Later published long-term survival data by the same authors showed similar 5-year survival rates [36].

GC has similarly been studied in dose-dense fashion. In the study of Bamias et al., which compared dose dense (2 week cycles with G-CSF support) regimens of both MVAC and GC, similar findings were observed as with the regular intensity regimens [37]. Median overall survival for the dd-MVAC and dd-GC groups, respectively, was 19 months vs. 18 months. Again, similar to the normal intensity regimens, dd-GC was better tolerated and similarly efficacious to dd-MVAC.

Other chemotherapeutic agents are active in bladder cancer, and several have been studied in combination with GC in the metastatic setting. Paclitaxel-cisplatin [38] and docetaxel-cisplatin [39] are regimens with activity, but neither has been compared to either GC or MVAC. In a phase III study comparing the addition of paclitaxel to GC *vs* GC alone, a trend toward better overall response rates and improved median overall survival (benefit of 3.1 months) was seen in the paclitaxel-GC group [40]. However, that difference was not statistically significant, while febrile neutropenia was significantly increased. Other agents similarly added to GC include pemetrexed [41] and docetaxel [42], with various signals of activity. Further combinations of chemotherapeutics with cisplatin remain an active area of investigation.

3.2 First line non-cisplatin based approaches

Alternative platinum chemotherapy agents have been investigated regarding their activity in bladder cancer. Carboplatin and oxaliplatin have different toxicity profiles and are better tolerated than cisplatin in some patients. In addition, many patients with metastatic bladder cancer have contraindications to cisplatin, most commonly renal insufficiency.

Gemcitabine-carboplatin has been studied as first line therapy for patients felt not to be candidates for cisplatin chemotherapy. Linardou et al. enrolled “medically unfit” patients with metastatic bladder cancer – those with poor performance status and renal dysfunction – to receive gemcitabine-carboplatin [43]. An overall response rate of 36% and favorable tolerability was shown with this particular regimen. A single-arm study by Bamios et al. in medically fit patients

using carboplatin-gemcitabine showed a similar response rate of 38% [44]. Gemcitabine-oxaliplatin similarly was reported to have activity in medically unfit patients with response rates reported of 36%-48% [45, 46]; however, it was not clear that the doublet had improved activity over single agent gemcitabine [47]. Oxaliplatin is not routinely used.

GC has been compared in a randomized phase II trial with gemcitabine-carboplatin reported by Dogliotti et al [48]. The primary objective of this study was to demonstrate improved treatment toxicity with the gemcitabine-carboplatin compared to GC in patients with adequate renal function (GFR > 60). No statistically significant differences in toxicity were found, although the gemcitabine-carboplatin cohort experienced increased hematologic toxicity and decreased nephrotoxicity. Gemcitabine-carboplatin had a lower response rate than GC (56.4% *vs* 65.9%), decreased overall survival (9.8 *vs* 12.8 months), increased hematologic toxicity, and lower rates of nephrotoxicity. These differences were not significant.

Studies have investigated whether additional chemotherapeutics in addition to gemcitabine-carboplatin would maintain the regimen's tolerability yet improve the response rate and survival.

Paclitaxel-carboplatin-gemcitabine was active yet had significantly increased toxicity [49]. To improve tolerability, further investigations have examined sequential treatment with carboplatin-gemcitabine then paclitaxel [50]. A sequential approach was similarly studied with dose-dense doxorubicin-gemcitabine followed by carboplatin-paclitaxel [51]. A four drug regimen of MTEC (methotrexate, paclitaxel, epirubicin, carboplatin) has been tested with a response rate of 60% (included CR rate of 30%) as first-line therapy [52]. Follow-up studies with this regimen studied patients refractory to GC [53]. The role of these sequential or combination regimens remains unclear in the absence of randomized phase III data.

Several non-platinum containing first-line regimens have also been explored, including gemcitabine-docetaxel [54], gemcitabine-pemetrexed [55], gemcitabine-epirubicin [56], gemcitabine-vinorelbine [57]; none have been evaluated in phase III trials for high-level evidence for routine use. Selected trials are summarized in the Table 2.

Table 1. Key points for medical oncology management of bladder cancer

- Neoadjuvant cisplatin-based chemotherapy is indicated for muscle-invasive bladder cancer.
- Adjuvant chemotherapy after definitive therapy is controversial, but may have a role in selected patients with high risk features (such as node-positive disease at time of surgery).
- Second-line chemotherapy options are limited; only vinflunine has been proven to have survival benefit in a phase III trial. There are no FDA-approved second-line therapies.
- Targeted therapies are under active investigation; a trial of bevacizumab in combination with chemotherapy for metastatic disease is expected to be reported.

Table 2. Selected second line trials for metastatic bladder cancer

Trial	Treatment	Result
Bellmut et al. [60]	Vinflunine	2.3 month increased overall survival
Albers et al. [62]	Gemcitabine-Paclitaxel	Overall response rate ~40%
Akaza et al. [67]	Gemcitabine	Overall response rate 25%
Sweeney et al. [68]	Pemetrexed	Overall response rate 28%
Ko et al. [69]	Nab-Paclitaxel	Overall response rate 28%
Kouno et al. [70]	Carboplatin-Paclitaxel	Overall response rate 32%
Rozzi et al. [71]	Pegylated Liposomal Doxorubicin	Overall response rate 13% [as 3rd line therapy]

3.3 Surgery for metastatic disease

In general, patients whose disease responds to first line chemotherapy may be treated up to 6 cycles of chemotherapy, or 2 cycles beyond best response. After that time, they may be observed and again treated at time of relapse. Several studies have examined whether consolidative cystectomy and/or metastasectomy may lead to improved long-term outcomes. In an

analysis performed by Dodd et al. among patients who were treated with MVAC for metastatic bladder cancer, a consolidative surgery in partial responders was found to improve their survival to nearly mirror the survival for those patients who achieved a complete response after therapy [58]. Their analysis suggested that the best candidates for surgery after treatment for metastatic disease were those who had significantly responded to chemotherapy with sites of metastatic disease limited to pelvic lymph nodes.

In addition to this data regarding cystectomy following response to chemotherapy, there have been studies of visceral metastatectomy leading to long-term survival in selected patients. In a case series of 31 patients with recurrence of urothelial carcinoma, patients underwent surgery with the intention of resecting all known disease [59]. In this series, the location of the metastatectomy was lung in 77% of patients. A 5-year survival of 33% was achieved, significantly higher than historical medians in studies for chemotherapy alone.

These strategies have not been prospectively studied, but these case series of highly selected populations of patients appeared to suggest long-term benefit. Further study is needed.

3.4 Second line therapy

For patients who have progressed after first line therapy, options are limited and only vinflunine monotherapy has been proven to be superior to best supportive care alone. Bellmunt et al. compared vinflunine plus best supportive care to best supportive care alone in a randomized phase III trial for patients who had previously received a platinum-containing regimen [60]. The vinflunine arm had a significantly longer median overall survival of 6.9 months vs. 4.6 months for best supportive care alone, which reached statistical significance [61]. The study included quality of life measures, and the chemotherapy arm did not reduce quality of life in this palliative setting.

A second recently reported phase III study for second-line chemotherapy randomized patients to either a maximum of 6 cycles of gemcitabine-paclitaxel or to indefinite prolonged therapy [62]. There were no significant differences between groups. Without comparison to either vinflunine or best supportive care alone, the significance of this study is uncertain and a further phase III study would be needed.

Vinflunine has been approved for second line use in metastatic bladder cancer in Europe; yet, there remain no FDA-approved regimens for second-line use in the US. Many phase II studies have been conducted to seek activity of alternative agents, and further study is needed to identify options in the second line.

3.5 Targeted and experimental therapies

Targeted therapies, either individually or in conjunction with chemotherapy, have been investigated for use in patients with advanced and metastatic urothelial cancer. The most active area under investigation is targeting the VEGF pathway. Bevacizumab in combination with cisplatin-gemcitabine was tested as first-line therapy in the metastatic setting [63]. In the study by Hahn et al., the overall response rate was 73%, but the study did not meet the primary endpoint regarding improvement in progression-free survival. The treatment was toxic, however, with 3 treatment-related mortalities out of 43 patients on the trial. A phase III trial using bevacizumab in the first-line metastatic setting is pending and yet to be reported.

Trastuzumab was investigated in combination with carboplatin-gemcitabine-paclitaxel in HER2/neu-expressing advanced bladder cancer for first line metastatic therapy [64]. Approximately 50% of tumors screened in this series expressed HER2/neu, and those patients had a 70% response rate to therapy. Other experimental approaches included MTOR inhibition, EGFR blockade, immune checkpoint inhibition, and vaccines [65]. At this time, no phase III trials with these experimental approaches have been reported, and further investigation is needed.

In addition to novel therapies, adjunctive medications to either sensitize the tumor to chemotherapy or ameliorate toxicities are under pre-clinical investigation. In particular, a strategy for modulating the tumor microenvironment or inflammatory milieu may yield future targets for therapy [66].

4 Conclusions

Bladder cancer remains a common and challenging malignancy to manage, especially in advanced settings. For localized muscle-invasive disease, certain patients can undergo bladder-sparing chemoradiation, while the standard remains cisplatin-based combination neoadjuvant chemotherapy followed by radical cystectomy. Metastatic disease is similarly treated with cisplatin-based combination chemotherapy, and many agents and combinations remain under investigation for those who progress after cisplatin therapy or are not eligible for cisplatin. Recent investigation has looked for alternative dosing strategies, and attempted to find non-cisplatin based regimens to improve on efficacy and tolerability. Molecularly targeted approaches and immunotherapy remain under active investigation but further work is needed before they may be routinely used against advanced bladder cancer.

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