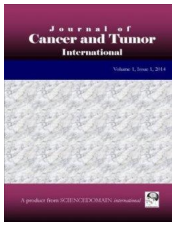

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Long Time Survival in Small Cell Carcinoma of the Bladder: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Small cell carcinoma of the bladder only accounts for 0,35 – 1% of all bladder cancers. It is a rare, but aggressive tumor. As for other types of bladder cancer, first symptoms are most often painless hematuria [1,2]. The clinical presentation does not differ from other bladder cancers and work-up to diagnosis is mostly identical. Literature regarding small cell bladder cancer is not extensive. Only a few non-randomized prospective trials are available [3-6]. Treatment options are multiple and mainly based on institutional retrospective data. As other anaplastic tumors, small cell bladder cancer has a poor prognosis given the high risk for metastatic disease. Different treatment options have been published over the past several years. With time, two commonly used treatment schedules remain for limited disease: neo-adjuvant chemotherapy in combination with cystectomy and chemo-radiation therapy after initial transurethral resection of the bladder wall. Even at an early stage, no invasion of the muscle tissue, a radical treatment is required because SCC of the bladder has a propensity for early metastasis. In general, SCC of the bladder has a poor prognosis and long-term survival percentages are very low. However, we report the case of a 76-years old woman who was treated nine years ago by neo-adjuvant chemotherapy followed by radiation therapy. A review of the literature on this topic is also presented.

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Keywords: Small cell carcinoma of the bladder; urinary bladder neoplasm; cystectomy; radiation therapy; chemotherapy.

ABBREVIATION

SCC : Small Cell Carcinoma

1. INTRODUCTION

The first report on small cell invasive bladder cancer was published in 1981 by Cramer et al. [7]. Small cell carcinoma of the bladder represents 0,35 – 1% of all malignant bladder cancers [8,9]. SCC of the bladder represents a specific histological entity with in general a poor prognosis and a rapid metastatic evolution. Literature regarding small cell bladder cancer is not extensive. Only a few non-randomized prospective trials are available [3-6]. Treatment options are multiple and mainly based on institutional retrospective data. We will report on a case of a patient with a small cell bladder carcinoma that answered excellent to our treatment. In this report, we will review the epidemiology, the clinical and histo-pathological presentation, the diagnosis, staging and treatment algorithms of this specific disease.

2. CASE PRESENTATION

In 2006, a 76-year old obese woman with asymptomatic gross hematuria was referred to our outpatient urology clinic. Her medical history was only significant for kidney stones and diabetes. In 1982 she underwent a right ureterotomy to free a ureteral stone. Three years later she developed an asymptomatic right uretero-hydronephrosis. Because there was no alteration of the kidney function or any related symptomatology, no intervention was planned. During follow up, an abdominal ultrasound showed right known uretero-hydronephrosis and a vesical polyp located on the right lateral bladder wall. The cystoscopy confirmed the presence of a papillary tumor and a transurethral resection was planned. Staging with a Contrast Enhanced Computed Tomography of the abdomen, Chest X-ray and Nuclear Bone Scan didn't reveal any lymph nodes or distant metastasis. Histological analysis of the transurethral resection of the bladder specimen showed a pure small cell carcinoma of the bladder. Tumor markers were positive for synaptophysine and negative for chromogranine CK 7, CK 5,6 and CK 20. Tumor stage was pT1 Nx M0. The patient refused a surgical intervention. So, a treatment proposition was made consisting of neo-adjuvant chemotherapy followed by external beam radiotherapy. The patient accepted this treatment modality. Three cycles of neo-adjuvant intravenous chemotherapy containing carboplatin AUC 5 (air under the curve) on day 1 and Etoposide 100mg /m² on day 1-3 were administrated every 20 days. The chemotherapy was administrated on time and without any dose-reduction. Complete radiologic remission was observed immediately after chemotherapy. Endoscopic transurethral control with a video endoscope showed no residual tumor. Thereafter external beam radiotherapy was given. The bladder and pelvic lymph nodes were irradiated up to a total dose of 46 Gy in 23 sessions of 2 Gy. Close transurethral video endoscopic follow-up didn't show any local recurrence. Recurrent cytology, obtained during cystoscopy controls, remained negative. Ten years after treatment, the patient is still alive showing no local or distant recurrence.

3. THE EPIDEMIOLOGY OF SMALL CELL BLADDER CANCER

Small cell carcinoma (SCC) of the urinary bladder is a rare tumor representing 0.35-1% of all bladder cancers [7]. Established risk factors are male sex, advanced age and smoking [8,9]. Other risk factors such as chronic inflammation due to stone disease or recurrent urinary infections have been suggested [8]. Men/Female ratio is 3 to 1 [8-10]. Median age at presentation is 73 years. 65% to 79% of the patients are smokers [10]. Caucasians are 10 times more at risk to develop SCC compared to other ethnicities [8].

4. CLINICAL AND HISTO-PATHOLOGIC PRESENTATION AND DIAGNOSIS

Clinical presentation does not differ from other bladder cancers. The most common presentation is asymptomatic gross hematuria [11,1]. Other symptoms like dysuria and irritative symptoms, pelvic pain, recurrent urinary infections, urinary obstruction or a combination of all are also reported. More general symptoms like weight loss or fatigue may occur. Exceptionally, paraneoplasic syndromes like Cushing syndrome, hypercalcemia, hypophosphatemia, hypernatremia or hypokalaemia have been

mentioned in some articles [11,1,2]. Small cell carcinoma of the bladder is known as an aggressive tumour. At time of diagnosis, the tumour load is often already high and in a large number of cases the disease has already spread loco-regionally or at distant. Most common tumour spread is to the lymph nodes of the large vessels, to the liver and/or bone metastasis. Pulmonary metastasis often occurs in a later phase [12]. A large retrospective study showed 11% of brain metastasis at diagnosis [13].

At cystoscopy a papillary like lesion is seen, often ulcerated with a diameter between 1,5 cm and 13 cm. Most frequently these tumours are located at the lateral wall of the bladder (in more than 50% of the cases). However they can also be found in the fundus, the trigonum, the anterior wall or the dome of the bladder [14,11,1,2].

Staging and classification of small cell carcinoma of the bladder follows either the classical TNM-classification or the World Health Organization (WHO) – classification for small cell carcinoma [11].

The cyto-histologic pattern is commonly composed of irregular nests or sheets of small or intermediate round cells separated by a delicate fibro-vascular stroma. Cells have a high mitotic karyorrhetic index. The cells have small round to oval overlapping nuclei. The chromatin is regularly distributed with discrete nucleoli, with a thinly scattered cytoplasm [14,11,1,2,15]. Small cell carcinoma of the bladder can present as a unique entity or might be in association with other histological types. In 38% to 70% small cell carcinoma presents together with urothelial carcinoma, adenocarcinoma or squamous cell carcinoma [14,11,1,2,15]. Most frequently, the tumour cells deeply invade the bladder wall and extend to or throughout the muscular bladder wall into the peri-vesical fibro-adipose tissue [15].

Definitive histological diagnosis is obtained after immunohistochemistry studies. Immuno-histochemical examination showing a positive immunostaining with synaptophysin, neuron-specific enolase and chromogranine can support the definitive histological diagnosis. Epithelial markers such as cytokeratine 7, epithelial membrane antigen and CAM 5.2 can also help to confirm the diagnosis or to exclude other tumor types [14]. Electron microscopy shows systematically membrane-limited dense core granules that are 150 to 250 nm in diameter [14,11,1,2,15].

These markers can also contribute to make a distinction between primary small cell carcinoma of the bladder and a secondary location in the bladder from another primary (for example lung) tumor, a high grade transitional cell carcinoma, a primary or secondary urinary bladder lymphoma and/or Merkel cell carcinoma [15].

5. STAGING

The staging of SCC is based upon the same principals we use for urothelial bladder cancer. As mentioned before, SCC of the bladder is a very aggressive tumor. In most of cases the tumor is muscle invasive, locally advanced (70%) or already metastatic at diagnosis (28 to 50%) [14,11,1,2]. Dissemination might occur rapidly so we must keep in mind that even at a local stage, undetectable (micro-) metastases could already occur. Treatment decision will not depend if the tumor is muscle invasive or not, like in the case of transitional cell carcinoma of the bladder. It is a fact that SCC of the bladder will metastasize quicker, regardless of the T-stage. In this context a lot of authors proposed to use another staging system and to distinguish limited (T1-4N0-1M0) and extended disease (TxN2-3M0 and TxNXM1) [2]. Limited disease also takes in account that the tumor should be resectable or that all disease is encompassable within the same radiation field [16].

Because surgery is one of the treatment options, staging must take into account the local extension of the tumor. Contrast Enhanced Computed Tomography of the thorax, abdomen and lower pelvis are the golden standard. MRI can be useful to evaluate the local extension since it is more sensitive than CT-scan in regard to the extra-vesical extension and eventual infiltration of the surrounding organs. Brain imaging (CT or MRI) is also indicated. A Nuclear Bone scan is recommended in symptomatic patients. However, considering bone metastasis is one of the most frequent locations of tumor spread, even asymptomatic patients could benefit from it. Although Pet-CT-scan is not yet recognized as a standard staging tool, it can be very useful [16].

6. REVIEW ON THE TREATMENT OPTIONS FOR PATIENTS WITH A LIMITED DISEASE (T1-4 N0-1 M0)

Clear indications or guidelines on the treatment of small cell bladder cancer are few. Only the

National Cancer Care Network and the CAGMO (Canadian Association of Genitourinary Medical Oncologists) have published guidelines [17,16,18]. A few prospective studies have been published, as well as a phase II non-randomized study and a single-center prospective study of 25 cases [19,3,4,5,6]. Furthermore, a limited number of case reports and retrospective studies with small cohorts are available in recent literature. Also different review articles have been published over the last years [20-22,17,16,18,23-27,13,28-34]. An additional cause of confusion might be that pure SCCB and mixed SCCB have been reported mingled in some of these studies.

6.1 Treatment Options Including Surgery (Radical Cystectomy)

Cheng et al. [11] showed no difference in survival between patients treated with radical cystectomy and the ones who were not. Both groups showed a very poor 5-year disease-specific survival (15% and 18% respectively). However, patients receiving a combination therapy (surgery + chemotherapy) had better disease specific survival than patients treated by surgery alone (66% versus 45%).

The Mayo Clinic experience, published by Choong [12], showed that radical cystectomy alone should perhaps be reserved for a small group of patients with a limited disease, maximum stage II.

In a small retrospective analysis of 25 patients, Quek et al. [22] showed an improved overall survival in patients having received neo-adjuvant or adjuvant chemotherapy in addition to surgery compared to patients treated by cystectomy only.

Lynch et al. [35] reported their results on 95 patients. 26 patients received only surgery, 48 patients neo-adjuvant chemotherapy and surgery and 21 patients adjuvant chemotherapy after surgery. A down staging and an increased median overall survival was observed in the neo-adjuvant group. In 36 out of the 48 patients, a clear down staging to ≤ pT2N0M0 was observed. In addition, a clear increase of the median overall survival was also noted (187 months). The addition of adjuvant chemotherapy did not show an increase in overall survival in comparison the surgery only group (around 18 months).

A publication by Siefker-Radtke [36] of a retrospective study at the MD Anderson Cancer Center also showed that chemotherapy administrated before surgery improved the median overall survival. 78% of the 21 patients receiving pre-operative chemotherapy survived at 5-years compared to the group of 25 patients who received only a cystectomy had only 36% of survival at 5-years. So, they also confirmed that neo-adjuvant chemotherapy has the capacity to induce a pathologic down staging of the tumor (observed in 57% of the cases). These initial observations were later confirmed in a small prospective study [6]. In this prospective analysis on 18 patients, a pathological down staging of the tumor was obtained in 14 out of the 18 cases (78%). They also showed a better survival outcome (58 months) compared with the patient receiving only chemotherapy (13.3 months).

Based on the above-mentioned studies, we can state that radical cystectomy, as sole treatment is probably not sufficient. The use of neo-adjuvant chemotherapy followed by surgery seems the best treatment option. Evidence is shown that neo-adjuvant chemotherapy induces in a vast majority of the cases a clear down staging of the initial tumor. In addition, the use of neo-adjuvant chemotherapy seems to offer better survival outcomes. On the contrary, there seems to be no indication to use chemotherapy in an adjuvant setting after surgery.

6.2 Treatment Options without Surgery (Bladder-sparing Approach)

Therapeutic approaches without surgery (cystectomy) have also been studied and some studies are reported in the literature. In the bladder conservation option, radiation therapy is the cornerstone of the treatment but is always associated to a chemotherapy regimen. The applied treatment schedules and the total delivered radiation dose appears to be highly variable in the different studies [17,16,18,23,24]. The used chemotherapy regimens also differ tremendously, as well as considering the administration schedules (neo-adjuvant or concomitant) as the used drugs. Common used drugs are carboplatin, etoposide, vindesine, ifosfamide, cisplatinum, cyclophosphamide and vinblastine in all possible combinations. Details on the administration- as well as the dose schedules, are rarely fully reported on [16]. As small cell cancer of the bladder is often associated with other histological types, the addition of other antimitotic drugs, such as for example taxanes, has been considered [2].

Bex et al. [19] reported on a retrospective study including 17 patients who had limited-disease.

After transurethral resection of the tumor (TURBT), neo-adjuvant chemotherapy (types: MVAC, etoposide-cisplatin or carboplatin and cyclophosphamide-doxorubicin-etoposide) followed by radiation therapy was administered. Four of the seventeen patients developed a local recurrence. A complete response was obtained in 88%. The overall survival at 1, 2 and 5 years was respectively 82%, 56% and 36%.

Karpaman et al. [23] published a review on 23 patients who received chemo-radiation. At 34 months follow-up, overall survival was 70%. In the majority of these patients, a complete local control of the disease was observed.

Lorish et al. [4] performed a small study on 10 patients with limited disease SCBC using chemo-radiation therapy (concomitant or sequentially). In 9 out of these 10 patients a complete response was observed. Results showed a median overall survival of 47 months. Seventy percent of the patients survived at 2 years and 44% at 5 years. A smaller study, published by Bastus [5], of only 5 patients treated with platinum-based chemotherapy and radiotherapy showed no evidence of recurrence for 80% of the patients either at 10 to 60 months follow up.

Asmis et al. [29] reported on 12 consecutive cases with SCBC treated by combination therapy. The median survival in the group of limited disease patients was 19.8 months.

Koay et al. [10] analyzed data from the SEER-Medicare database from 1991-2005. He compared a tri-modality approach (TURBT, chemotherapy and radiotherapy) with the combination of cystectomy and chemotherapy. Analysis of these data shows no difference in overall survival between both treatment options.

Eswara et al. [34] reported data of a single-institution study of small cell carcinoma of the bladder. It was demonstrated that patients with lower-stage disease (T1-T2 N0 M0) had an improved overall survival compared to those with advanced disease. In their small group of patients (28 evaluable patients), five patients survived a minimum of 4 years, 2 were T1N0M0 (survival of 8- and 12 years) and 3 were T2N0M0 (survival of 4-, 4- and 6 years).

With the limitation that only few studies are available and that the majority of data are obtained by retrospective analysis of small patients groups, conclusion can however be made that the combination of chemotherapy and radiation therapy appears to be a valuable option to treat limited disease of SCC of the bladder.

6.2.1 Follow-up

Given the aggressive pattern of this type of tumors, close follow-up is warranted [16,18]. In the case when a bladder sparing approach was used, a cystoscopy must be done on a regular basis (for example: every 3 months during the first 2 years, every 6 months during the following 3 years and than once a year) [22]. PET-CT evaluation might have (in analogy to other tumor sites of small cell cancer) an impact on early detection of metastases and might limit the number of follow-up examination.

6.2.2 For extended disease (TxN2-3M0 and TxNXM1)

Chemotherapy is the standard treatment. Platinum-based regimens are most frequently used [12,36] and are recommended in the CAGMO guidelines [16].

Because small cell lung cancer is more frequent and a lot more studies have been realized, chemotherapy regimens for extended small cell bladder cancer are based on the ones used for SCLC. Mackey et al. [26] stated however that only cisplatinum-based chemotherapy improved survival. Various treatment regimes using associations of chemotherapeutic agents (for example: etoposide-cisplatinum in alternation with ifosfamide-doxorubicin) or single agents (such as irinotecan or paclitaxel) have also been used [12,36,19,3,4,5,6,20,21,22,17,16,18,23-27].

Siefker-Radtke et al. [6] published a phase II trial on 12 patients with extended disease. Although high response rates were obtained, the (overall) survival remained low (13 months). Bex et al. [3] also showed a very poor survival outcome after cisplatinum and etoposide in their population of patients with extended disease. Their small prospective study showed an overall survival of only 5 months in this group of 8 patients.

We can conclude that despite a good chemo-sensitivity the survival rate remains very low.

7. GENERAL CONCLUSION

Small cell bladder cancer is a rare and aggressive tumor. Even at an early stage radical treatment is required because SCC of the bladder has a propensity for early metastasis.

The prognosis is in general very poor. However, as shown by Eswara et al. [34], better results and long-term more favorable outcome can be observed in patients who had a complete trans-urethral resection followed by multi-modality treatment for very early stage (T1-2N0M0) small cell carcinoma of the bladder. They observed a nearly three-fold greater overall and cancer specific survival in this group of patients compared to patients with a more advanced disease at presentation. This might explain the favorable evolution we also observed in our presented case. Prospective trails should be done to give us better information on how to treat our patients. But in limited disease the studies seem to show the importance of a multimodal treatment approach. Systemic treatment, neoadjuvant chemotherapy combined with a local treatment either surgery or radiation therapy. For extended disease chemotherapy is the standard care.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nicholas WW, Choong MD, Fernando Quevedo MD, et al. Small cell carcinoma of the urinary bladder, The Mayo Clinic Experience. American Cancer Society. 2005;103(6):1172-1178.
2. Chekrine T, De Bari B, Cassier P, et al. Carcinome neuroendocrine à petites cellules de la vessie: À propos d'une observation et revue de la literature. Cancer/Radiothérapie. 2011;15:250-253.
3. Bex A, de Vries R, Pos F, et al. Long term survival after sequential chemoradiation for limited disease small cell carcinoma of the bladder. World J Urol. 2009;27:101-6.
4. Lorisch C, Murray N, Pickels T, et al. Small cell carcinoma of the bladder: Long term outcome with integrated chemoradiation. Cancer. 1999;86:2346-52.
5. Bastùs R, Caballero JM, Gonzalez G, et al. Small cell carcinoma of the urinary bladder treated with chemoratherapy and radiotherapy: results in five cases. Eur Urol. 1999;35:323-6.
6. Siefke-Radtke AO, Kamat AM, Grossman HB, et al. Phase II clinical trial of neoadjuvant alternating doublet chemo-therapy with ifosfamide/doxorubicine and etoposide/cisplatin in small-cell urothelial cancer. J Clin Oncol. 2009;27:2592-7.
7. Cramer SF, Aikawa M, Cebelin M. Neurosecretory granules in small cell invasive carcinoma of the urinary bladder. Cancer. 1981;47:724–30.
8. Lohrisch C, Mursay N, Pickles T, Sullivan L. Small cell carcinoma of the bladder: Long-term outcome with integrated chemo-radiation. Cancer. 1999;86:2346–52.
9. Blomjous CEM, Vos W, De Voogt HJ, Van Der Valk P, Meijer CJLM. Small cell carcinoma of the urinary bladder: A clinicopathologic, morphometric immuno-histochemical and ultrastructural study of 18 cases. Cancer. 1989;64:1347–57.
10. Koay EJ, Teh BS, Paulino AC, et al. Treatment trends and outcomes of small-cell carcinoma of the bladder. Int J Radiat Oncol Biol Phys. 2011;83:64–70.
11. Liang Cheng, Chong-Xian Pan, Ximing J Yang, et al. Small cell carcinoma of the bladder a clinicopathologic analysis of 64 patients. American Cancer Society. 2004;101(5):957-962.
12. Choong NW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. Cancer. 2005;103:1172-8.
13. Bex A, Sonke GS, Pos FJ, et al. Symptomatic brain metastases from small-cell carcinoma of the urinary bladder: The Netherlands Cancer Institute experience and literature review. Ann Oncol. 2010;21:2240–5.
14. Thota S, Kistangari G, Daw H, et al. A clinical review of small-cell carcinoma of the urinary bladder. Clinical Genitourinary Cancer. 2013;11(2):73-7.
15. Seyd Z Ali, Victor E Reuter, Maureen F, et al. Small cell neuroendocrine carcinoma of the urinary bladder. A clinicopathologic study with emphasis on cytologic features. Cancer. 1997;79:356-61.
16. Moretto P, Wood L, Emmenegger U. Management of small cell carcinoma of the bladder: Consensus guidelines from the Canadian Association of Genitourinary

Medical Oncologists (CAGMO). Can Urol Assoc J. 2013;7(1-2):E44–E56.
17. National Cancer Care Network Guidelines. Available:http://www.nccn.org/professionals/physician_gls/PDF/bladder
18. Bladder Cancer - Alberta Health Services. Available:http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gu002-bladder
19. Axel Bex, Jakko A, Nieuwenhuijzen, et al. Small cell carcinoma of the bladder: A single-center prospective study of 25 cases treated in analogy to small cell lung cancer. Urology. 2005;65:295-299.
20. June RR, Dougherty DW, Reese CT, et al. Significant activity of single agent vinorelbine against small-cell cancer of the bladder as second line chemotherapy: A case series and review of the literature. Urol Oncol. 2012;30:192-32.
21. Swapna Thota, Gaurav Kistangari, Hamed Daw, Timothy Spiro. A clinical review of small-cell carcinoma of the urinary bladder. Clinical Genitourinary Cancer 2013;11(2): 73-7.
22. Quek ML, Nichols PW, Yamzon J, et al. Radical cystectomy for primary neuroendocrine tumors of the bladder: The University of Southern California experience. J Urol. 2005;174:93-96.
23. Karpman E, Goldberg Z, Saffarian, et al. Analysis of treatment for small cell cancer of the bladder and report of three cases. Urology. 2004;64:494–8.
24. Hiroko Akamatsu, Takuma Nomiya, Mayumi Harada. Bladder-sparing approach with radiotherapy in patients with small cell carcinoma of the bladder. Journal of Cancer Therapy. 2014;5:797-805.
25. Schreiber D, Rineer J, Weiss J, et al. Characterization and outcomes of small cell carcinoma of the bladder using the surveillance, epidemiology, and end results database. Am J Clin Oncol; 2012.
26. Mackey JR, Au HJ, Hugh J, et al. Genitourinary small cell carcinoma: Determination of clinical and therapeutic factors associated with survival. J Urol. 1998;159:1624–9.
27. Ismaili N, Heudel PE, Elkarak F, et al. Outcome of recurrent and metastatic small cell carcinoma of the bladder. BMC Urol. 2009;6:9-4.
28. Vijaya Raj Bhatt, Fausto R Loberiza, Pavankumar T, et al. Risk factors, therapy and survival outcomes of small cell and large cell neuro-endocrine carcinoma of the urinary bladder. Rare Tumors. 2014;6(1):5043.
29. Asmis TR, Reaume MN, Dahrouge S, et al. Genitourinary small cell carcinoma: A retrospective review of treatment and survival patterns at The Ottawa Hospital Regional Cancer Center. BJU Int. 2006;97(4):711–5.
30. Celik O, et al. Diagnosis and treatment in primary bladder small cell carcinoma: Literature review. Arch Ital Urol Androl. 2016;88(1):52-5.
31. Roy C, et al. Small cell carcinoma of the urinary bladder: A case report and review of the literature. J Indian Med Assoc. 2014;112(1):57-9. Review.
32. Gkirlemis K, et al. Small cell carcinoma of the bladder: A search of the current literature. J BUON. 2013;18(1):220-6. Review.
33. Fahed E, et al. Small cell bladder cancer: biology and management. Semin Oncol. 2012;39(5):615-8. Review.
34. Eswara JR, Heney N, Wu CL, et al. Long-term outcome of organ preservation in patients with small cell carcinoma of the bladder. Urol Int. 2015;94:401-405.
35. Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancers improves pathologic downstaging and long-term outcomes: Results from a retrospective study at the MD Anderson Cancer Center. Eur Urol. 2012;64:307-313.
36. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder a retrospective review of the M. D. Anderson cancer experience. J Urol. 2004;172(2):481-4.

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