ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2018) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Intravesical recurrence after bladder sparing treatment of small cell carcinoma of the bladder: Characteristics, treatment, and outcome

Maaike van de Kamp, M.D., M.Sc.[a,*], Richard Meijer, M.D., Ph.D.[a], Floris Pos, M.D., Ph.D.[b], Martijn Kerst, M.D.[c], Eric van Werkhoven[d], Bas van Rhijn, M.D., Ph.D.[a], Simon Horenblas, M.D., Ph.D.[a], Axel Bex, M.D., Ph.D.[a]

[a] *Department of urology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*
[b] *Department of radiotherapy, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*
[c] *Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*
[d] *Department of Epidemiology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Received 30 November 2017; received in revised form 7 February 2018; accepted 26 February 2018

Abstract

Introduction: Small cell carcinoma of the bladder (SCCB) is a rare and lethal disease. Previously, we and others have reported a bladder sparing strategy with platinum-etoposide-based chemotherapy followed by radiotherapy of the bladder. Little is known on frequency and treatment of intravesical recurrence following this approach. The objective of this study is to describe the incidence of intravesical recurrences and their management.

Materials and methods: Retrospective study including all patients with SCCB treated at a single institution from 1993 until 2016. All patients with limited disease (LD) SCCB who had a bladder sparing approach with sequential chemotherapy and radiotherapy were identified. Intravesical and overall recurrence rate, overall and disease specific survival, salvage treatment options and their results were retrieved.

Results: Of the 110 patients with SCCB (82% male) with a mean age of 65 years and a median follow up of 48 months, 89 patients (81%) had LD-SCCB. Of these, 65 were treated with chemotherapy and radiotherapy, with a median overall recurrence free survival of 22 months (CI: 14–30). Of 65 patients, 23 (35%) progressed to distant metastasis without intravesical recurrence after a median of 9 months (CI: 8–11), whereas 14 patients (22%) developed isolated intravesical recurrence at a median of 24 months (CI: 14–34). Local recurrence contained SCCB, urothelial carcinoma, and carcinoma in situ and was treated with various local salvage treatments including TURB, cystectomy, neoadjuvant chemotherapy, and BCG. Following salvage treatment a complete response was seen in 64%. Median overall survival for intravesical vs. systemic recurrence was different, with 28 (CI: 9–47) and 8 (CI: 5–11) months, respectively ($P < 0.001$).

Conclusion: SCCB is a serious potentially lethal disease. Even in patients with LD-SCCB a high percentage rapidly develops systemic disease. This suggests that systemic therapy is more important than the type of local treatment to control the disease but small sample sizes limit the ability to distinguish between different treatment options in this study. A bladder sparing approach can be a reasonable alternative to major surgery. However, in those surviving long enough isolated intravesical recurrence occurs even after many years. Our results indicate that long term follow up is required because salvage therapy can be successful in the majority of patients.

Keywords: Bladder cancer; Chemoradiation; Small cell bladder carcinoma; Intravesical recurrence

1. Introduction

Small cell carcinoma of the bladder (SCCB) is a rare and aggressive disease with a poor prognosis. Although uncertain, the incidence of SCCB is currently estimated at about 0.7% of all bladder tumors. Until today the optimal treatment strategy remains unknown. Most patients die within 1 year of diagnosis. The median overall survival (OS) for advanced SCCB is 8.6 months with 13 months for lymph node metastases and only 5.3 months for distant metastatic disease [1,2]. SCCB has a high metastatic potential, even in the setting of clinically localized disease, and therefore staging according to the more common small cell carcinoma

* Corresponding author. Tel.: +31(0)648318234.
E-mail address: maaikevdkamp@hotmail.com (M. van de Kamp).

https://doi.org/10.1016/j.urolonc.2018.02.015
1078-1439/

of the lung (SCLC) has been proposed [3,4]. In SCLC limited (LD) and extensive disease (ED) have replaced the AJCC/UICC staging taking early metastasis into account. This is also reflected in management strategies, which include a multimodality approach [3,5].

LD SCCB (tumors confined to the bladder and a single regional lymph node) is now mostly treated with neoadjuvant chemotherapy followed by radiation or radical cystectomy [6]. Neoadjuvant chemotherapy followed by radical cystectomy is associated with a high rate of pathologic down staging (62%) and correlates with a significantly higher survival rate compared with upfront cystectomy [7]. Sequential chemotherapy and radiotherapy as a bladder sparing treatment has been reported as an alternative to cystectomy [8–11]. Chemotherapy and radiotherapy for LD SCCB is well tolerated, with encouraging local control and median OS of up to 32.5 months [9]. A high bladder preservation rate (85%) is seen in this patient population [12].

A Canadian guideline recommends that this aggressive disease is best treated with neoadjuvant chemotherapy, followed by either cystectomy or radiation [13]. Lynch et al. [14] described that a combination of neoadjuvant chemotherapy followed by cystectomy shows a median OS of 83 months, as compared to the group treated with initial surgery.

Given the paucity of SCCB and only few studies reporting a bladder sparing approach with chemotherapy and radiotherapy little is known about the incidence and treatment of intravesical recurrence. The objective of this retrospective study is to determine the intravesical recurrence rate from a single institutional database of patients who underwent chemotherapy and radiotherapy for LD SCCB and to describe their management and outcome.

2. Patient and methods

2.1. Study population

The study was based on an institutional prospectively-maintained database of 110 patients with primary SCCB treated at de Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NCI-AVL) and its affiliated center University Medical Center Utrecht between 1993 and 2016. Histological diagnosis of SCCB was according to the WHO classification system [15]. Medical charts were retrospectively reviewed and clinical parameters were collected.

We evaluated all patients with LD SCCB who underwent bladder sparing treatment (chemotherapy followed by radiotherapy) in order to describe the recurrence-free survival (RFS) and OS, the recurrence rate and salvage treatment in case of recurrence, including histopathology of recurrences and the follow-up results.

Briefly, LD SCCB was defined as tumors confined to the bladder with or without a suspicion of a single regional lymph node (cT1–4N0–1M0) on conventional imaging and ED SCCB as all others (TxN2–3M0 or TxN0–3M1) [4]. Patients with LD-SCCB were offered a bladder sparing approach with systemic chemotherapy followed by external beam radiotherapy (EBRT) as previously reported [9]. The percentage of SCCB in the TUR-B specimen was retrieved and if ≥30% SCCB, patients were treated accordingly.

All patients were routinely followed every 3 months with CT of the pelvis, abdomen and chest, and cystoscopy in the first 2 years. Every 6 months from year 2 until year 5 and then annually. In addition, urine cytology was obtained. In case of suspicious lesion(s) at cystoscopy or cytology, a TUR-B for histological sampling was performed.

2.2. Chemotherapy and radiotherapy

Briefly, patients received 4 courses of chemotherapy (mostly etoposide/cisplatin or carboplatin based) followed by 60 Gy EBRT to the bladder as previously reported [9,12]. Neoadjuvant chemotherapy was analogous to accepted regimens for SCLC. Over the past years, the cisplatin-based SCLC regimens have changed. Four courses of ifosfamide 1.2 g/m^2, VP-16 (etoposide) 75 mg/m^2, and cisplatin 20 mg/m^2 (VIP) on days 1 to 4, repeated after 21 days, were later replaced by 4 courses of cisplatin 75 mg/m^2 day 1 with etoposide 100 mg/m^2 on days 1 to 3, repeated after 21 days. Patients with contraindications for cisplatin, but a performance score WHO ≤2, received 5 courses of cyclophosphamide 1.0 g/m^2 (day 1), doxorubicine 45 mg/m^2 (day 1), and etoposide 100 mg/m^2 (days 1–3) repeated after 21 days. Later, that regimen was changed to carboplatin (day 1) with etoposide 100 mg/m^2 (days 1–3), repeated after 21 days. In NCI-AvL, patients were always treated with sequential chemotherapy and radiotherapy, in our affiliated center some patients were treated with concurrent chemoradiation.

2.3. Statistical analysis

We defined OS as time from diagnosis of SCCB to death of any cause. Cancer-specific survival (CSS) was defined as time from diagnosis to death of disease. RFS was defined as time from first diagnosis until first documentation of recurrence or death of any cause. Recurrence free interval was defined as time from diagnosis until date of recurrence. Follow-up data were calculated with an inverted OS curve. Data analysis was carried out with IBM SPSS Statistics, version 22 for Windows. CI for values and proportions are given as 95% CI. Significance was set at $P < 0.05$.

3. Results

We identified 110 patients treated for primary SCCB with a mean age of 65 years (range: 39–89 y). Of these, 82% were males ($n = 90$) and the median follow up was