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Neoadjuvant Chemotherapy in Small Cell Urothelial Cancer Improves Pathologic Downstaging and Long-term Outcomes: Results from a Retrospective Study at the MD Anderson Cancer Center

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Abstract

Background—Small cell urothelial carcinoma (SCUC) is a rare, aggressive malignancy with a propensity for early microscopic metastases. Data suggest that neoadjuvant chemotherapy may lead to improved survival compared with initial surgery.

Objective—To determine the influence of neoadjuvant chemotherapy on survival of SCUC patients in a large single-institution cohort.

Design, setting, and participants—Between 1985 and 2010, 172 patients were treated for SCUC at MD Anderson Cancer Center (MDACC). Clinical, pathologic, and surgical data were collected and analyzed.

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Outcome measurements and statistical analysis—Overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier method. Multivariable Cox proportional hazards models were used to evaluate the effects of neoadjuvant chemotherapy on survival.

Results and limitations—Of 125 patients with resectable disease (cT4aN0M0), 95 were surgical candidates. Forty-eight received neoadjuvant chemotherapy, and 47 underwent initial surgery. Neoadjuvant treatment was associated with improved OS and DSS compared with initial cystectomy (median OS: 159.5 mo vs 18.3 mo, $p < 0.001$; 5-yr DSS: 79% vs 20%, $p < 0.001$). Neoadjuvant chemotherapy resulted in pathologic downstaging to pT1N0 in 62% of tumors compared with only 9% treated with initial surgery (odds ratio: 44.55; 95% confidence interval, 10.39–191). Eight patients with clinically node-positive disease had surgical consolidation with cystectomy and extended lymph node dissection after clinical complete response to chemotherapy. Median OS and DSS in this group of patients were 23.3 mo and 21.8 mo, respectively, with 5-yr OS and DSS of 38%.

Conclusions—Neoadjuvant chemotherapy is associated with a high rate of pathologic downstaging and correlates with significantly higher survival compared with historical expectations. Although limited by a small sample size and retrospective analysis, in the context of a rare disease, this experience suggests neoadjuvant chemotherapy as a standard approach in treating SCUC.

Keywords

Small cell urothelial cancer; Bladder cancer; Neoadjuvant; Surgery; Chemotherapy

1. Introduction

Small cell urothelial carcinoma (SCUC) is an aggressive malignancy characterized by rapid progression and early microscopic metastases, even in surgically resectable disease. The current approach in most centers, initial cystectomy, has resulted in poor outcomes, with many patients pathologically upstaged, resulting in relapse and death within 2 yr of cystectomy [1–5]. Recent small case series [2,6] as well as the first prospective clinical trial in SCUC [7] suggest a potential benefit using neoadjuvant chemotherapy. Given the paucity of data, it is imperative that centers with significant experience treating SCUC share their approaches and outcomes.

2. Materials and methods

2.1. Data collection

We identified 172 patients with SCUC treated at MDACC between 1985 and 2010. The MDACC institutional review board reviewed and approved this retrospective review. Patients must have had a definitive small cell component based on review of the pathology. Patients with an equivocal diagnosis, with small cell differentiation in a small cluster of cells, or with small cell of nonurothelial origin were excluded. Records were reviewed for demographic, clinical, pathologic, treatment, and outcome information. Clinical staging was reported for presurgical staging, with pathologic staging reported at cystectomy.

2.2. Statistical analysis

Summary statistics including mean, median, standard deviation, and range were provided for continuous data; frequencies and percentages were reported for categorical variables. Patient characteristics were compared by chi-square test or Fisher exact test for categorical variables and by two-sample Wilcoxon rank-sum test for continuous variables. A binary variable was

defined to describe downstaging (pathologic stage below initial clinical stage and pT1N0M0). A logistic regression model was used to associate baseline risk factors and treatment with downstaging at surgery. Overall survival (OS), defined as the time from diagnosis to death, and disease-specific survival (DSS), defined as the time to SCUC-specific death, were estimated using the Kaplan-Meier method. Groups were compared with the log-rank statistic. Subgroup analysis was done by disease stage and treatment modality. Multivariable Cox proportional hazards models were used to evaluate the effects of neoadjuvant chemotherapy, adjuvant chemotherapy, or surgery alone on survival after adjusting for other risk factors (age, stage, extent of SCUC, carcinoma in situ [CIS], and gender). The final multivariable model (both Cox proportional hazards model and logistic regression model) was obtained using a backward selection approach, removing the least significant covariate from the full model, one at a time. All tests were two-sided. P values <0.05 were considered statistically significant. Analyses were conducted using R v.64 (R Project for Statistical Computing, Vienna, Austria) and S+ v.8.0 (TIBCO Software Inc., Somerville, MA, USA) statistical software.

3. Results

3.1. Patient and tumor characteristics

Most patients were older white men with a median age of 69.3 yr (Table 1a). Small cell was the predominant histology in 82%; 38% were characterized as having pure small cell histology. The majority of patients (125; 73%) presented with surgically resectable disease (cT4aN0M0).

3.2. Surgically resectable disease

Of the 172 cases reviewed, 125 patients had surgically resectable disease (clinical staging cT4aN0M0). Patients with clinically enlarged lymph node metastases historically have survival similar to other metastatic patients [1,2] and were classified as a separate cohort. Thirteen were not surgical candidates due to comorbid medical conditions, 12 patients declined surgery, 1 patient had a transurethral resection of bladder tumor (TURBT) only for a T1 lesion, and 4 had no further follow-up (Table 2). Of the 95 patients planning for cystectomy, 48 had neoadjuvant chemotherapy and 47 had initial surgery (Table 1b).

Neoadjuvant chemotherapy contributed to improved pathologic stage with 62% pT1N0 at cystectomy (pT0/TisN0: 58%). Median OS from neoadjuvant chemotherapy was 159.5 mo (95% confidence interval [CI], 74.8 to) compared with 18.3 mo (95% CI, 14.8-25.5) when treated with initial cystectomy (log-rank $p < 0.001$; Fig. 1A). Five-year DSS was 79% for patients treated with neoadjuvant chemotherapy compared with 20% for patients treated with initial surgery (log-rank $p < 0.001$; Fig. 1B). The majority (94%) were treated with cisplatin-based chemotherapy, 73% with a small-cell-directed regimen (Table 3). For those treated with initial cystectomy, adjuvant chemotherapy had no impact on OS (median OS with adjuvant chemotherapy: 18.1 mo [95% CI, 14.7–37.7]; median OS without adjuvant chemotherapy: 18.3 mo [95% CI, 14.4–27.3]; log-rank $p = 0.686$).

Those who were not candidates or who refused cystectomy were typically offered radiation ($n = 6$) or chemoradiation ($n = 6$). For 12 patients treated with radiation therapy, their outcomes were not significantly different from those treated with initial surgery, with a median OS of 29.2 mo (95% CI, 25.5 to) for radiation and 18.3 mo (95% CI, 14.8-25.5) for initial surgery (5-yr DSS: 29.2% for radiation, 20% for initial surgery).

3.3. Chemotherapy and pathologic downstaging

Patients were staged clinically using computed tomography (CT) to evaluate for metastases and a complete TURBT followed by exam under anesthesia to assess for extra-organ extension (cT3b) and fixation to the pelvic sidewall (cT4b). Patients who had an initial cystectomy had a much higher likelihood of finding metastatic disease at surgery compared with those receiving neoadjuvant chemotherapy (Table 4a and 4b), even when staged as cT1N0. Four patients had their cystectomy aborted on intraoperative detection of unresectable or metastatic disease. Conversely, only one patient in the neoadjuvant group did not have surgery after diagnosis of brain metastases.

By defining a binary variable as *downstaged* if pathologic stage was lower than clinical stage and pT1N0, 33 patients were downstaged. Among patients receiving neoadjuvant therapy, 62% were downstaged, whereas only 9% in the initial surgery group were downstaged (Table 4a and 4b). In the multivariate logistic model, independent predictors for downstaging were initial clinical stage and neoadjuvant chemotherapy. Patients with clinical stages lower than stage III were more likely to be downstaged with neoadjuvant chemotherapy (odds ratio [OR]: 7.79; 95% CI, 2.10–28.86). The OR for having downstaged pathology with neoadjuvant chemotherapy compared with initial surgery was 44.55 (95% CI, 10.39–191). Other baseline variables were not statistically significantly associated with downstaging.

3.4. Pathologic stage and survival

Downstaging to pT2N0M0 from neoadjuvant chemotherapy significantly affected long-term survival. For 36 patients with pT2N0M0 at surgery, the median OS was 187 mo (95% CI, 160 to ; Fig. 2A) and the 5-yr DSS was 94.4% (median DSS not met; Fig. 2B). No survival differences were seen among those downstaged to pT0N0M0, pT1N0M0, and pT2N0M0, although the small numbers seen in some of these subsets may limit our ability to detect a true difference. In contrast, those with persistent pT3, N+, or M+ disease at surgery had an OS of 10.8 mo (95% CI, 10.8 to) and a 5-yr DSS of 20.5% (log-rank $p < 0.001$ for both OS and DSS). For patients having initial cystectomy, pathologic stage had no impact on long-term outcomes.

In univariate and multivariate analyses, clinical stage was not significantly associated with OS (log-rank $p = 0.18$). In contrast, pathologic stage was significantly associated with OS ($p < 0.001$). This association was significant only for patients receiving neoadjuvant chemotherapy ($p < 0.001$) and not among those having initial cystectomy ($p = 0.09$). Pathologic stage strongly correlated with neoadjuvant therapy ($p < 0.001$ by Fisher exact test). After categorizing pathologic stages into two groups (pT2 vs >pT2), more advanced pathologic stage (>pT2) (hazard ratio [HR]: 4.756; $p < 0.001$) and initial surgery (HR: 1.996; $p = 0.039$) had a significantly shorter OS. Male patients had marginally shorter OS (HR: 1.781; $p = 0.073$) in the multivariable model. Pathologic stage <pT3N0, neoadjuvant chemotherapy, and female gender were all independent predictors of improved DSS on multivariate analysis (Table 5a and 5b).

3.5. Surgical consolidation of involved lymph nodes

Patients with metastases continue to have a poor prognosis, with a median OS of 11.8 mo (95% CI, 9.2–15.8; Fig. 3A). A few long-term survivors were observed among patients with clinically enlarged lymph nodes at diagnosis who had a clinical complete response with systemic chemotherapy followed by surgical consolidation with a cystectomy and extended lymph node dissection ($n = 8$; median OS was 23.3 mo [95% CI, 20.9 to] and median DSS was 21.8 mo [95% CI, 19.42 to] with 5-yr survival of 38% [Fig. 3A and 3B]). In one patient, the initial cystectomy was aborted due to persistent disease, but after responding

to chemotherapy, he successfully underwent surgical consolidation and is alive and disease-free >10 yr later.

4. Discussion

Neoadjuvant chemotherapy for SCUC was associated with a higher rate of pathologic downstaging at surgery, improving long-term survival. With initial surgery, there is an increased risk of pathologic upstaging, at times leading to an aborted cystectomy and resulting in poor outcomes. Other centers also suggest very poor survival with initial surgery, with few patients alive beyond 2 yr [1,3,8,9]. A small subset of patients with node-only metastases who achieve near-complete response following chemotherapy may experience long-term control of their tumor following surgical consolidation.

Most reports suggest a high likelihood of pathologic upstaging and poor survival with initial cystectomy [1–3,9]. One notable exception suggests 5-yr OS of 63% for patients with stage II SCUC [8], whereas patients with stage III or greater disease continue to have poor outcomes. It is not clear if these findings are based on clinical stage, which is highly inaccurate for SCUC, or on pathologic stage at the time of cystectomy. The risk in recommending initial cystectomy is a higher pathologic stage at surgery, resulting in poor survival.

While adjuvant chemotherapy is frequently considered, our data suggest little impact on OS. Neoadjuvant chemotherapy may provide more benefit by treating when the burden of microscopic metastases is low. Delaying chemotherapy to the adjuvant setting may allow microscopic metastases more time to develop. With the heterogeneity in adjuvant regimens and the low sample size, it is possible that the benefits of adjuvant chemotherapy are underestimated. Therefore, we still offer adjuvant chemotherapy for SCUC diagnosed at cystectomy but would recommend neoadjuvant chemotherapy when the diagnosis is known before cystectomy.

The optimal number of cycles of neoadjuvant chemotherapy is currently unknown. In a clinical trial of neoadjuvant chemotherapy for SCUC [7], 18 patients received four cycles of alternating chemotherapy. While patients with cT2N0 disease had a high likelihood of cure with this approach, those with stage III disease did not fare as well, with SCUC remaining at cystectomy. This may reflect either poor biology or the need for additional chemotherapy in the setting of bulkier tumor. The argument for further chemotherapy is supported by the long-term survival seen in some patients with clinically enlarged lymph nodes, where treatment aims for two cycles beyond maximal response (average of approximately six cycles), with cystectomy and extended node dissection performed in the setting of a complete response by CT imaging and repeat cystoscopy.

Given the similarities between SCUC and its counterpart in the lungs, where chemoradiation remains a standard in limited-stage disease, others have advocated for chemoradiation [10,11]. There is no consensus regarding whether radiation or surgery is the optimal method of local consolidation. As in our cohort, reported radiation data may include patients who are not surgical candidates and are likely to have worse outcomes related to their comorbid medical conditions. In one series of sequential chemoradiation, only 36% of patients remained alive at 5 yr [12]; the majority of deaths were cancer related. Another radiation study showed similar long-term outcomes with a recurrence rate of 60% at 3 yr [10]. While chemoradiation may provide short-term control and be an option for patients who are not surgical candidates, the benefits may be suboptimal in patients with greater life expectancy.

One potential reason for this high recurrence rate is the association with CIS observed with SCUC. In this series, CIS was observed in 54% of specimens, with another series reporting

CIS in upward of 76% of cases [1]. In our experience, CIS is often found only at the time of cystectomy. Evidence suggests that irradiating a bladder with CIS may increase the risk of local recurrence [13]. Therefore, we advocate for surgery as the optimal method of local consolidation, reserving radiation for patients who are not surgical candidates.

Brain metastases are infrequently reported in patients with SCUC [14]. One clinical trial reported brain metastases in 50% of patients with stage III or greater SCUC [7]. Our current report likely underestimates the true incidence of brain metastases because routine screening was not performed. Based on information from the prospective clinical trial [7], we now discuss prophylactic cranial radiation with stage III and IV patients who achieve good disease control.

Retrospective studies in SCUC have limitations; small sample sizes and nonuniform follow-up allow for selection biases that may affect the observed results. While an intent-to-treat analysis is difficult to perform retrospectively, we included patients in the neoadjuvant arm if they received any preoperative chemotherapy, regardless of whether or not they were candidates for an aggressive cisplatin-based regimen. We also included patients in the initial surgery arm if they were taken for cystectomy, even if the cystectomy was aborted due to the discovery of unresectable cancer. Despite these limitations, the survival differences between the neoadjuvant chemotherapy and initial surgery arms are quite large, suggesting that a paradigm shift to neoadjuvant chemotherapy may be appropriate. Prospective studies for rare tumors are difficult to complete, resulting in our reliance on retrospective data when treating patients.

5. Conclusions

Our findings support neoadjuvant chemotherapy for the treatment of SCUC and suggest pathologic downstaging to pT1N0 as an appropriate surrogate marker for eventual cure. Surgical consolidation with cystectomy and extended lymph node dissection should be considered for patients with lymph node metastases who have an excellent response to chemotherapy. Due to the high frequency of CIS and associated risk of future tumors, we advocate for surgery as the optimal local control modality.

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Fig. 1.

(A) Overall survival (OS) and (B) disease-specific survival (DSS) from diagnosis of small cell urothelial cancer in patients undergoing cystectomy. Patients treated with neoadjuvant chemotherapy had improved OS and 5-yr DSS (median OS: 159.5 mo; 95% confidence interval [CI], 74.8 to 244.2 mo; 5-yr DSS: 79%) compared with those treated with initial surgery (median OS: 18.3 mo; 95% CI, 14.8–25.5 mo; 5-yr DSS: 20%; log-rank $p < 0.001$).

Fig. 2.

(A) Overall survival (OS) and (B) disease-specific survival (DSS) from diagnosis of small cell urothelial cancer in patients treated with neoadjuvant chemotherapy. Patients who were downstaged to pT2N0M0 had an improved median OS and 5-yr DSS (median OS: 187 mo; 95% confidence interval [CI], 160 to ; 5-yr DSS: 94.4%) compared with those with pT3, N+, or M+ disease at surgery (median OS: 10.8 mo; 95% CI, 10.8 to ; 5-yr DSS: 20.5%; log-rank $p < 0.001$).

Fig. 3. (A) Overall survival (OS) and (B) disease-specific survival (DSS) from diagnosis of patients with T4b or N+ or M+ disease, stratified by surgical consolidation or no surgery. Eight patients with node-positive disease had a clinical complete response to chemotherapy and had surgical consolidation with cystectomy and extended lymph node dissection. The median OS for those who did not have surgery was 11.8 mo (95% confidence interval [CI], 9.2–15.8). For the eight patients having surgical consolidation of clinically evident lymph node metastases, median OS and DSS were 23.3 mo (95% CI, 20.9 to -) and 21.8 mo (95% CI, 19.42 to -), respectively, with a 5-yr OS of 38%.

Table 1
Characteristics of (a) all patients and (b) patients staged as cT4aN0M0 treated with initial surgery or neoadjuvant chemotherapy

(a)				
	No. of patients (%)			
Total	172 (100)			
Age at diagnosis				
Median	69.3			
Range	30.5–89.7			
Gender				
Male	145 (84)			
Female	27 (16)			
Race/ethnicity				
White	155 (90)			
Black	3 (2)			
Hispanic	12 (7)			
Asian	2 (1)			
Primary site				
Bladder	170 (99)			
Renal pelvis and/or ureter	2 (1)			
Clinical stage				
cT1N0	8 (5)			
cT2N0	80 (47)			
cT3–4aN0	37 (21)			
cT4B or N+	16 (9)			
Any M+	31 (18)			
Histology at presentation				
Small cell only	65 (38)			
Small cell predominant	75 (44)			
<50% small cell	32 (18)			
Presence of carcinoma in situ	95 (54)			
Presence of brain metastases	15 (8.7)			

(b)				
	Initial surgery	Neoadjuvant chemotherapy	Total (%)	p value
Total	47	48	95 (100)	
Age at diagnosis				0.320
Median	65	66.6	–	
Range	32.1–82.9	35.8–84.4	–	
Gender				0.560
Male	37	41	78 (82)	
Female	10	7	17 (18)	

(b)				
	Initial surgery	Neoadjuvant chemotherapy	Total (%)	p value
Race/ethnicity				0.564
White	44	43	87 (92)	
Black	0	0	0	
Hispanic	3	4	7 (7)	
Asian	0	1	1 (1)	
Primary site				
Bladder	47	48	95 (100)	NA
Renal pelvis and/or ureter	0	0	0	
Clinical stage				0.138
cT1N0	5	1	6 (6)	
cT2N0 (2)	31	30	61 (64)	
cT3-4aN0 (3)	11	17	78 (30)	
Histology at presentation				0.469
Small cell only	16	22	38 (40)	
Small cell predominant	20	18	38 (40)	
<50% small cell	11	8	19 (20)	
Presence of carcinoma in situ	32	28	60 (63)	0.440
Weeks from diagnosis to surgery or chemotherapy				
Median	4.1 *	4.3	–	0.576
Range	0–32.7	0.1–17.8		

NA = not available.

* This number excludes patients who were diagnosed with small cell at cystectomy. Including these patients, the median time from diagnosis to surgery was 2.0 wk (range: 0–32.7).

Table 2
Resection status and surgical setting

	No. of patients (%)
Patients planned for cystectomy	95
Neoadjuvant chemotherapy	48 (51) *
Initial surgery	47 (49) **
Adjuvant chemotherapy	21 (22)
No chemotherapy	26 (27)
Attempted surgical consolidation of metastatic disease (T4b/N+)	8 **
Patients not undergoing resection	69
Metastatic disease	39 (56)
Comorbid conditions	13 (19)
Patient choice	12 (17)
Lost to follow-up	4 (6)
T1 lesion (TURBT only)	1 (1)

TURBT = transurethral resection of bladder tumor.

* One of the 48 patients treated with neoadjuvant chemotherapy developed metastatic disease prior to surgery and never underwent cystectomy.

** Four patients treated with initial surgery and one patient taken for surgical consolidation of node-positive disease had their cystectomy aborted due to the presence of metastatic disease discovered intraoperatively.

Table 3
Chemotherapy regimens in the neoadjuvant and adjuvant setting

	Neoadjuvant (<i>n</i> = 48)	Adjuvant (<i>n</i> = 21)
No. of cycles, median	4	4
Range	1–5	1–6
IA/EP, no. (%)	26 (54)	4 (19)
EP, no. (%)	7 (15)	4 (19)
MVAC, no. (%)	5 (10)	4 (19)
TMP, no. (%)	3 (6)	0
CGI, no. (%)	2 (4)	0
EAP, no. (%)	2 (4)	1 (5%)
IA, no. (%)	1 (2)	0
GCtx, no. (%)	1 (2)	0
GTA, no. (%)	1 (2)	0
ECarbo, no. (%)	0	5 (24)
VACtx, no. (%)	0	2 (9)
5-FUCarbo, no. (%)	0	1 (5)

IA = ifosfamide, doxorubicin; EP = etoposide, cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; TMP = paclitaxel, methotrexate, cisplatin; CGI = cisplatin, gemcitabine, ifosfamide; EAP = etoposide, doxorubicin, cisplatin; GCtx = gemcitabine, cyclophosphamide; GTA = gemcitabine, doxorubicin, paclitaxel; ECarbo = etoposide, carboplatin; VACtx = vincristine, doxorubicin, cyclophosphamide; 5-FUCarbo = 5-fluorouracil, carboplatin.

Table 4

(a) Pathologic upstaging in patients treated with initial cystectomy (*n* = 45; pathologic stage unknown in two patients) and (b) pathologic downstaging in patients treated with neoadjuvant chemotherapy (*n* = 47; pathologic stage unknown for one patient)

(a)					
	pT1 (and pTa)	pT2	pT3–4a	N+ or M+	
cT1	2	–	2	1	
cT2	2	9	7	11	
cT3–4a	–	–	6	5	
(b)					
	pT0 or pCIS	pT1	pT2	pT3–4a	pN+ or M+
cT1	1 (in divertic)	–	–	–	–
cT2	22 (10 CIS)	1	2	–	4
cT3–4a	5	1	4	4	3

Table 5
Multicovariate Cox proportional hazard model by prognostic factors (*n* = 95) for (a) overall survival and (b) disease-specific survival

(a)					
Covariate	Group	<i>p</i> value	HR	95% HR confidence limits	
Gender	Male vs female	0.073	1.781	0.948	3.348
Pathologic stage	pT3 or pT4 vs <pT3	<0.001	4.756	2.383	9.491
Neoadjuvant	Yes vs no	0.039	1.996	1.034	3.853
(b)					
Covariate	Group	<i>p</i> value	HR	95% HR confidence limits	
Gender	Male vs female	0.016	2.608	1.193	5.698
Pathologic stage	pT3 or pT4 vs <pT3	<0.001	4.857	2.252	10.48
Neoadjuvant	Yes vs no	0.011	2.707	1.260	5.813

HR = hazard ratio.