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SHORT COMMUNICATION

Impact of systemic therapy on clinical T1 small-cell neuroendocrine carcinoma of the bladder

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Background: The purpose of this study was to analyze survival outcomes and pathologic response of patients with cT1N0 small-cell neuroendocrine carcinoma (SCNEC) of the bladder treated with neoadjuvant chemotherapy (neoCTX).

Materials and methods: All cases of bladder SCNEC treated at our institution from January 1996 to July 2023 were identified. cT1N0 was defined as transurethral resection pathology showing lamina propria invasion with present and uninvolved muscularis propria. Pathologic downstaging and recurrences were evaluated. Disease-free survival (DFS) and overall survival (OS) were analyzed using the Cox regression and Kaplan–Meier method.

Results: A total of 30 patients with cT1N0 bladder SCNEC were included. Median follow-up was 88 months [95% confidence interval (CI) 44-131 months]. NeoCTX was given to 21 (70%) patients with a median of 4 cycles (range 1-6 cycles). A total of 27 (90%) patients received definitive local therapy. In cT1 bladder SCNEC, neoCTX was associated with decreased odds of pathologic upstaging [odds ratio = 0.07 (95% CI 0.01-0.45), $P = 0.004$], decreased odds of relapse [odds ratio = 0.12 (95% CI 0.02-0.65), $P = 0.01$], improved DFS [hazard ratio (HR) 0.30, 95% CI 0.09-0.96, $P = 0.04$], and improved OS (HR 0.32, 95% CI 0.10-1.02, $P = 0.05$). Compared with cT2N0 treated with neoCTX, cT1N0 treated with neoCTX had improved median DFS (HR 0.44, 95% CI 0.19-1.03, $P = 0.05$) and improved median OS (HR 0.52, 95% CI 0.22-1.24, $P = 0.14$).

Conclusions: NeoCTX had suggestive benefit in patients with cT1 bladder SCNEC with decreased odds of pathologic upstaging, metastatic relapse, and improved survival.

Key words: neoadjuvant chemotherapy, small cell carcinoma of the bladder, bladder cancer

INTRODUCTION

Small-cell neuroendocrine carcinoma (SCNEC) of the bladder carries a poor prognosis due to its high metastatic potential and limited therapeutic options.[1] These factors frequently result in a diagnosis of bladder SCNEC at a locally advanced or metastatic stage. Studies of bladder SCNEC have primarily focused on treating advanced disease, often excluding or not separately analyzing clinical T1N0M0 (cT1) cases.[2-4] Consequently, the prognosis for patients with early-stage cT1 bladder SCNEC is unknown.

No standard treatment is established for cT1 bladder SCNEC, which presents a management challenge. An approach to manage cT1 bladder SCNEC often involves neoadjuvant chemotherapy (neoCTX), driven by the risk of understaging and occult metastases, and by drawing from the treatment paradigm of the histologically similar small-cell lung cancer (SCLC).[5,6] This approach contrasts with cT1 urothelial carcinoma of the bladder, where neoCTX is seldom employed, even when extirpative surgery is indicated.[6,7]

Given this backdrop, there is a notable absence of literature regarding the outcomes and efficacy of neoCTX for cT1 bladder SCNEC. Thus, we investigated the treatment outcomes of neoCTX in cT1 bladder SCNEC. Additionally, we benchmark the outcomes of cT1 bladder SCNEC against cT2N0M0 bladder SCNEC as a comparator.

MATERIALS AND METHODS

Study cohort

This study was conducted with approval from the University of Texas MD Anderson Cancer Center institutional review board (PA16-0736). We built our institutional clinical and

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pathological database by querying the pathological reports for: 'small cell,' 'poorly differentiated neuroendocrine,' or 'high-grade neuroendocrine' between January 1996 and July 2023. All pathologic specimens were reviewed by a specialized genitourinary pathologist at our institution.

We included patients with cT1N0M0 bladder SCNEC and examined patients with cT2N0M0 bladder SCNEC as a comparator. cT1N0 bladder SCNEC was defined as transurethral resection (TUR) pathology showing lamina propria invasion with uninvolved muscularis propria. Patients with no muscle in the TUR specimen and those with muscle invasion on restaging TUR were excluded. We also excluded patients solely evaluated for a pathologic second opinion who did not get therapy at MD Anderson because they did not have enough data regarding the exposure and outcome.

Exposure and outcomes

The exposure of interest was the receipt of neoCTX. At our institution, neoCTX regimens for bladder SCNEC generally comprised etoposide plus cisplatin (EP) before 2009. After 2009, neoCTX regimens for bladder SCNEC generally comprised EP alone or alternating doublet chemotherapy with ifosfamide plus doxorubicin (IA) and EP based on the observed success of this regimen in a phase II trial at our institution.[5] The IA/EP regimen per the previously published protocol is preferentially used for patients with higher performance status.[8]

The outcome of interest was disease-free survival (DFS) and pathologic stage. Pathologic downstaging was defined as pT0 or pTis, and no lymph node involvement at cystectomy and lymph node dissection, respectively. Pathologic upstaging defined as pT2-4 or pN+. Finally, to describe the prognosis of cT1 bladder SCNEC, DFS and overall survival (OS) were evaluated for cT1 patients using cT2 as a comparator.

Statistical analysis

Continuous variables are described with medians [interquartile range (IQR)] and categorical variables with frequencies (percentages). Baseline characteristics were compared using the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. DFS was defined as the time from diagnosis of bladder SCNEC to progression or death from any cause. OS was defined as the time from diagnosis of bladder SCNEC until death from any cause. Patients without an event were censored at the time of the last follow-up at which the patient was known to be event-free. Median follow-up was calculated using the reverse Kaplan–Meier method. The Kaplan–Meier method was used to visualize and estimate survival curves for time-to-event outcomes, and the log-rank test was used to compare survival between groups. Firth's bias-reduced logistic regression was used to assess the association between variables and survival outcomes due to separable data. All statistical analyses were conducted in R version 4.2.1.

RESULTS

A total of 30 patients with cT1N0M0 bladder SCNEC were included. Of these, 21 (70%) patients received neoCTX and 9 (30%) did not. Table 1 summarizes the baseline clinicopathologic characteristics. Indication for neoCTX was primarily the presence of SCNEC histology, with increased uptake noted with time. The proportion of patients receiving neoCTX significantly increased after 2013 ($P = 0.04$).[4] The definitive local therapy rate was similar between the two groups ($P = 0.51$). Definitive local therapy was carried out in 27 (90%) patients with 24 (80%) cystectomy, 2 radiotherapy, and 1 partial cystectomy. Three patients declined local therapy, including one patient who received NeoCTX and two patients who did not. Median follow-up among all was 88 months [95% confidence interval (CI) 44-131 months]. Median follow-up among survivors was 10.6 years (IQR 6.4-12.9 years) for patients without neoCTX and 5.7 years (IQR 3.4-8.7 years) for patients with neoCTX.

NeoCTX regimens used for cT1N0M0 bladder SCNEC were IA/EP in 14 patients and EP in 7 patients with a median of 4 cycles (range 1-6 cycles) given. Adjuvant therapy was received by one patient in the no NeoCTX group and none in the NeoCTX group.

Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103964 summarizes the outcomes of cT1N0M0 bladder SCNEC in patients treated with and without neoCTX. Of the 21 patients treated with neoCTX, 3 patients (14%) developed metastatic disease, and none developed brain metastasis. Of the nine patients who did not receive neoCTX, five (56%) developed metastatic disease, and one patient developed brain metastasis. The median time to relapse with neoCTX and without neoCTX was 18 months (IQR 14-20 months) and 8.0 months (IQR 4.6-10 months), respectively. Patients with cT1N0M0 bladder SCNEC who received neoCTX had increased odds of pathologic complete response [odds ratio (OR) 19; 95% CI 1.8-254; $P = 0.01$] and decreased odds of metastatic relapse (OR 0.12; 95% CI 0.02-0.65; $P = 0.014$) than patients who did not receive neoCTX (Table 2).

As shown in Figure 1A and B, patients with cT1N0 bladder SCNEC who received neoCTX had longer median DFS compared with those who did not receive neoCTX [median DFS 216 months versus 22 months, hazard ratio (HR) 0.30 (95% CI 0.09-0.96), $P = 0.032$] and median OS [median OS 216 months versus 15.9 months, HR 0.32 (95% CI 0.10-1.02), $P = 0.044$].

Patients with cT2N0 bladder SCNEC ($n = 164$) were used as a comparator to examine survival outcomes. Clinicopathologic characteristics of the cT2N0 cohort are provided in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103964. The cT1N0 and cT2N0 cohorts were balanced with similar percentage of patients having definitive local therapy with radical cystectomy (89% versus 87%), partial cystectomy (7.4% versus 8.1%), and radiation (3.7% versus 4.7%), respectively ($P > 0.9$). As shown in Figure 2A and B, compared with cT2N0, cT1N0 patients had longer DFS (median 163 versus 30 months; HR

Table 1. Clinicopathologic characteristics

	cT1 without NeoCTX ($N = 9$)	cT1 with NeoCTX ($N = 21$)	*P* value
Age, median (IQR), years	71 (66-75)	66 (58-73)	0.6
Sex, male, *n* (%)	6 (67)	19 (90)	0.14
Diagnosis year, *n* (%)			
1996-2005	3 (33)	1 (4.8)	0.04
2006-2012	5 (56)	9 (43)	
2013-2023	1 (11)	11 (52)	
Amount small cell, *n* (%)			
Minority (<50%)	4 (44)	6 (29)	0.4
Predominant (>50%)	5 (56)	15 (71)	
Carcinoma *in situ*, *n* (%)	8 (89)	16 (76)	0.6
Restaging TUR, *n* (%)	4 (44)	17 (81)	0.07
Definitive local therapy, *n* (%)			
Cystectomy	7 (78)	17 (81)	>0.9
Partial cystectomy	0	1 (4.8)	
Radiation	0	2 (10)	
None	2 (22)	1 (4.8)	

IQR, interquartile range; NeoCTX, neoadjuvant chemotherapy; TUR, transurethral resection.

0.47; 95% CI 0.25-0.87; $P = 0.02$) and OS (median 163 versus 48 months; HR 0.53; 95% CI 0.28-1.0; $P = 0.05$). As shown in Figure 2C and D, compared with cT2N0 treated with neoCTX, cT1N0 treated with neoCTX had longer DFS [median 219 versus 69 months, HR 0.44 (95% CI 0.19-1.03) $P = 0.055$] and OS [median 219 versus 90 months HR 0.52 (95% 0.22-1.24) $P = 0.14$]. Univariate cox regression analysis for DFS among patients with cT1 and CT2 bladder SCNEC is outlined in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103964.

DISCUSSION

In this retrospective study of 30 patients with cT1N0M0 bladder SCNEC, we observed improved outcomes with neoCTX. Notably, neoCTX was associated with a statistically significant increase in pathologic complete response, decrease in pathologic upstaging, and decreased odds of disease relapse. Specifically, only 14% of patients receiving neoCTX experienced a relapse, and none developed brain metastasis. In contrast, 56% of those not treated with neoCTX had disease recurrence, including one case of brain metastasis. This contrast suggests a benefit of neoCTX to reduce relapse rates in our case series.

Table 2. Odds ratio for patients with cT1N0M0 bladder SCNEC who received neoadjuvant chemotherapy compared with those who did not receive neoadjuvant chemotherapy

Outcome	Odds ratio (95% CI)	*P* value
Pathologic complete response (pT0N0)	19 (1.8-254)	0.01
Pathologic downstaging (pT0N0, pCISN0 or pTaN0)	66 (5.9-752)	<0.001
Pathologic upstaging (pT2-4N0 or pAnyN1-3)	0.07 (0.01-0.45)	0.004
Metastatic relapse	0.12 (0.02-0.65)	0.014

CI, confidence interval; SCNEC, small-cell neuroendocrine carcinoma.

Previous studies have linked neoCTX in bladder SCNEC to pathologic downstaging and survival benefits. Two studies, however, did not include cT1,[8,9] one did not report clinical stage,[10] and one study included only one cT1 tumor treated with neoCTX.[4] Our study adds to these previous findings by uniquely focusing on cT1 bladder SCNEC and reporting treatment outcomes with neoCTX for these early-stage tumors.

For cT1N0 urothelial carcinoma, treatment typically includes bladder-sparing local therapy or radical cystectomy without neoCTX.[11] However, the bladder SCNEC treatment approach mirrors that of the histologically similar SCLC, where chemotherapy is the mainstay treatment for localized disease.[4] The divergence in treatment approaches reflects the distinct biological behavior of small-cell carcinoma and its pronounced responsiveness to chemotherapy. Our institutional data have corroborated this notion, finding that neuroendocrine chemotherapy regimens (IA/EP or EP) lead to improved survival over urothelial-specific regimens (MVAC/GC) in cT2+ bladder SCNEC.[8]

Bladder SCNEC frequently coexists with urothelial carcinoma and other histologic subtypes whereas SCLC is mostly pure.[10] Thus, unlike SCLC, after chemotherapy, extirpative surgery is recommended for localized bladder SCNEC. Patel et al.[12] reported that neoCTX followed by cystectomy had the most favorable survival outcomes on review of administrative data. In our cohort, after neoCTX, 17/21 (81%) patients underwent cystectomy. Previously, chemotherapy and radiation therapy for limited disease were reported with a 22% rate of local recurrence and 35% rate of distant metastasis. Thus, cystectomy is our preferred management strategy.[13] Finally, neoCTX did not prohibit cystectomy in our cohort.

Our study also underscores the prognostic importance of tumor staging. Patients with cT1 bladder SCNEC demonstrated a significantly improved median OS of 163 months, compared with 48 months for those with cT2 disease. This highlights the distinct prognoses between these stages in patients predominantly treated with neoCTX. While patients with bladder SCNEC have varying amounts of small-cell histology at diagnosis, prior work suggests that the small-cell component drives the prognosis with a significant difference in outcomes based on the amount of small cell in the tumor.[8,14] In line with these findings, we observed a decreased risk of relapse among patients with <50% small-cell component at diagnosis (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103964). Nonetheless, the baseline clinical characteristics were not significantly different between cT1 and cT2 (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103964) indicating the prognosis difference may be primarily driven by the invasion of muscularis propria.

Additionally, the high rate of pathologic upstaging among patients with cT1 bladder SCNEC treated without neoCTX highlights the limitations of clinical staging with imaging and initial transurethral resection of bladder tumor, as well as the rapid growth patterns of small-cell carcinoma, further

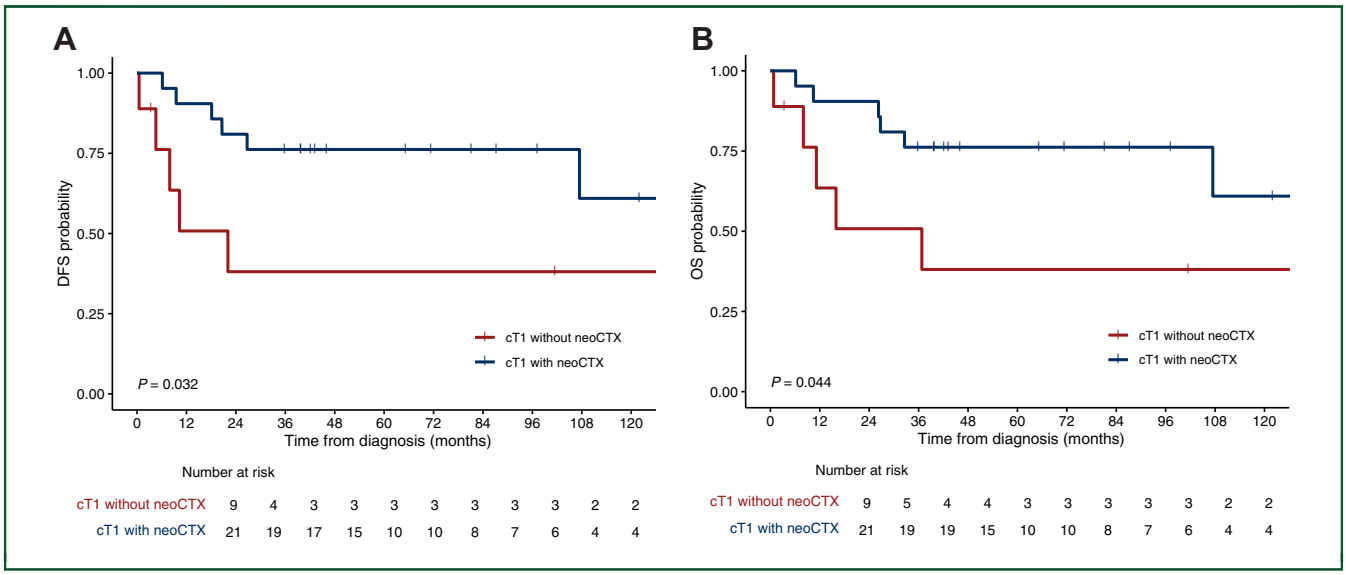

Figure 1. Survival curves for cT1N0 bladder SCNEC with and without neoCTX. (A) Disease-free survival (DFS). (B) Overall survival (OS).
NeoCTX, neoadjuvant chemotherapy; SCNEC, small-cell neuroendocrine carcinoma.

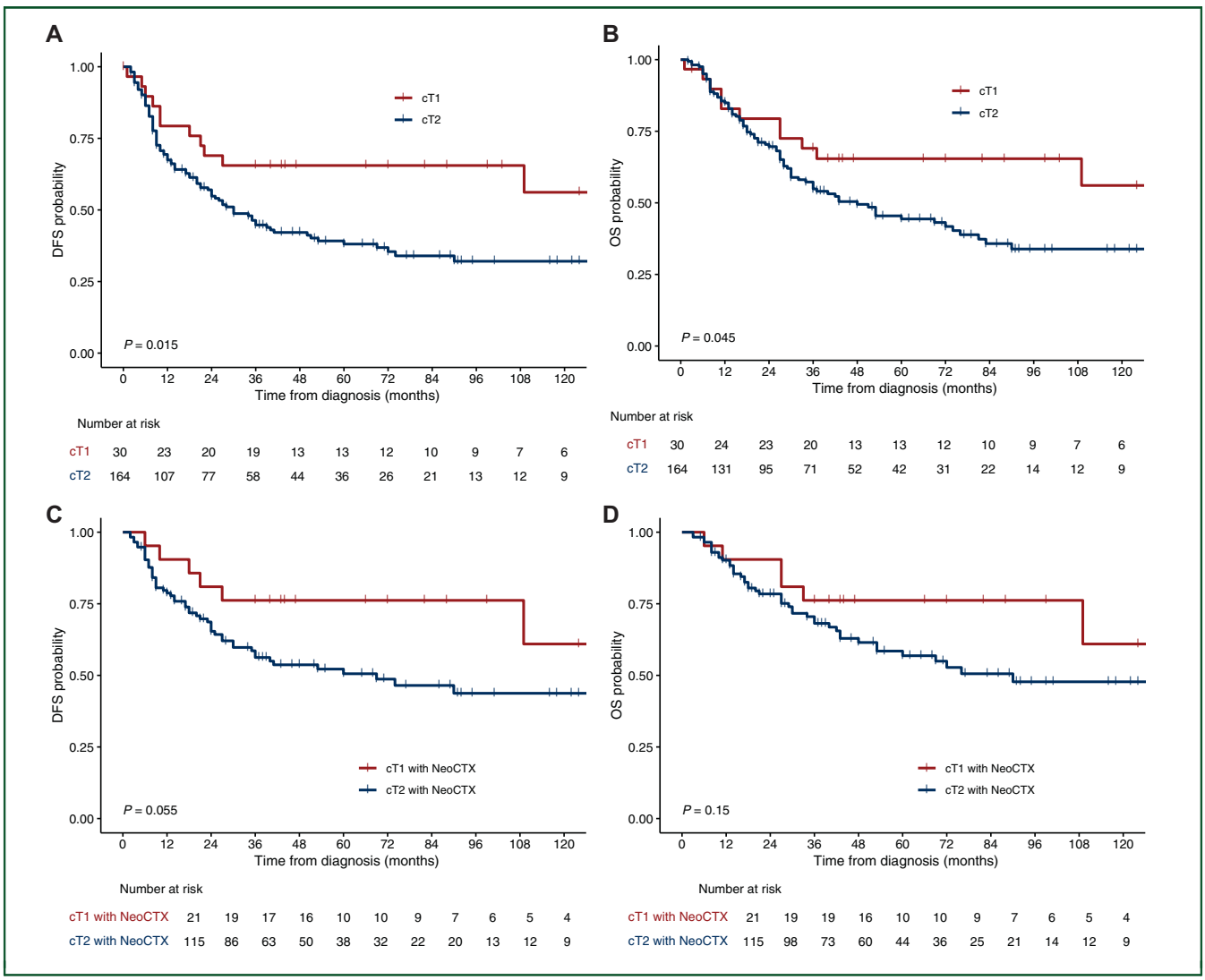

Figure 2. Survival curves for cT1N0 versus cT2N0 bladder SCNEC. (A) Disease-free survival (DFS). (B) Overall survival (OS). Survival curves for cT1N0 versus cT2N0 bladder SCNEC treated with neoadjuvant chemotherapy. (C) Disease-free survival (DFS). (D) Overall survival (OS).
NeoCTX, neoadjuvant chemotherapy.

emphasizing the importance of considering neoCTX. The evolving role of molecular diagnostics such as circulating tumor DNA may offer a more sensitive method to detect growth patterns of bladder SCNEC, but this remains to be explored.

Our study is limited by its retrospective design and relatively small sample size, which constrains our ability to adjust for potential confounders, such as performance status and patient preferences, which may impact the decision to use neoCTX and local therapy. Thus, our findings should be interpreted with caution and validated through future studies if feasible. Although, for rare diseases like bladder SCNEC, examining a large cohort of patients or performing a prospective investigation is challenging. Thus, our findings offer evidence to support neoCTX in treating cT1 bladder SCNEC in a cohort of patients with pathologic review and long-term follow-up.

Patients with cT1 bladder SCNEC treated with neoCTX had decreased odds of pathologic upstaging and metastatic relapse. To our knowledge, this is the first study to demonstrate that neoCTX is associated with improved outcomes for patients with cT1 bladder SCNEC and offers a more informed treatment strategy.

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DISCLOSURE

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