Small cell carcinoma of the bladder: A population-based analysis of long-term outcomes after radical cystectomy and bladder conservation with chemoradiotherapy

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Cite as: Oh J, Eigl B, Black PC, et al. Small cell carcinoma of the bladder: A population-based analysis of long-term outcomes after radical cystectomy and bladder conservation with chemoradiotherapy. *Can Urol Assoc J* 2022;16(2):55-62. http://dx.doi.org/10.5489/cuaj.7411

Published online September 24, 2021

Abstract

Introduction: We aimed to describe the oncological outcomes after radical cystectomy and chemo-radiation for localized small cell bladder cancer (SCBC).

Methods: This population-based analysis of localized SCBC from 1985–2018 in British Columbia included an analysis (analysis 1) of cancer-specific survival (CSS) and overall survival (OS) of patients treated with curative-intent radical cystectomy (RC) and radiation (RT), and an analysis (analysis 2) of CSS and OS in patients treated with RC and chemoRT consistent with the SCBC Canadian consensus guideline.

Results: Seventy-seven patients who were treated with curative intent were identified: 33 patients had RC and 44 had RT. For analysis 1, five-year OS was 29% and 39% for RC and RT, respectively (p=0.51), and five-year CSS was 35% and 52% for RC and RT, respectively (p=0.29). On multivariable analysis, higher Charlson comorbidity index (CCI) and the lack of neoadjuvant chemotherapy (NAC) were associated with worse OS, while higher CCI and Eastern Cooperative Oncology Group (ECOG) were associated with worse CSS. For analysis 2, five-year OS was 56% and 58% for the RC and chemoRT groups, respectively (p=0.90), and five-year CSS was 56% for RC and 71% for chemoRT (p=0.71). Four of 42 (9.5%) chemoRT patients had RC at relapse.

Conclusions: SCBC is a rare entity with a poor prognosis. RC and chemoRT offer similar CSS and OS for localized SCBC, even when focusing the analysis on patients treated according to the modern consensus guidelines. NAC should be considered for eligible patients. Both chemoRT and RC treatment options should be discussed with patients with SCBC.

Introduction

Small cell cancer of the bladder (SCBC), a poorly differentiated neuroendocrine tumor, is an uncommon entity associated with a poor prognosis.[1-4] The incidence of SCBC is rising, but there is a paucity of literature regarding the optimal management of SCBC. Both the National Comprehensive Cancer Network (NCCN) and the Canadian bladder cancer guidelines have proposed treatment options for localized SCBC — defined as disease confined to the pelvis and associated lymph nodes — that include neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and definitive chemoradiation (chemoRT) with 4–6 cycles of platinum-based chemotherapy and 60 Gy equivalent dose 2 Gy (EQD2) of radiation (RT).[5-7]

Previously, our center published a case series of patients who were treated with chemoRT between 1985 and 1996, demonstrating a two-year and five-year OS of 70% and 44%, respectively.[8] Since then, there has been a limited number of retrospective studies comparing the outcomes between RC and chemoRT, but no prospective, randomized trials addressing the optimal local therapy.[2,9,10]

This study describes the cohort characteristics, treatment patterns, and oncological outcomes of localized SCBC patients after both RC and curative-intent RT in a population-based cohort. Two analysis were performed: one including all curative RC and RT patients (analysis 1), and one focusing on those patients who had RC or RT in accordance with the Canadian consensus guidelines (analysis 2).[6]

Methods

Study design and patient selection

A population-based review of patients who received RC or chemoRT from 1985–2018 for pure or mixed SCBC in the province of Britch Columbia was performed. BC Cancer consists of six regional centers and provides all RT in the province. All incident cancers are registered in a central cancer registry, which includes all pathology reports from both the transurethral resection of a bladder tumor (TURBT) and cystectomy specimens. All RT and chemotherapy details in the province have been prospectively collected since 1982 and 1998, respectively. All surgical records from 2012 have been captured electronically in the Canadian Institute for Health Information (CIHI) discharge summary data. Patients who had distant metastasis or palliative treatment upfront were excluded. This study received University of British Columbia (UBC) ethics approval (H18-02234).

Data abstraction and outcomes

All incident cases of neuroendocrine cancer of the bladder captured in the BC Cancer Registry were identified from 1985–2018. Any primary bladder histology with a small cell component was included in the study. The pathology reports were reviewed by a BC Cancer-sanctioned expert pathologist to ensure they meet the criteria for SCBC. All patients who received RT for SCBC in the province after diagnosis were identified using the BC Cancer Agency Information System (CAIS). The charts with either a cystectomy or TURBT specimen showing small cell histology were reviewed. For the years 2012–2018, the provincial hospital discharge summary data was used to help verify the surgical patients and to supplement CAIS data after 2012. The proportion of surgical cases that were missed using the cancer registry and CAIS for the years 2012–2018 were assessed to extrapolate the potential missing surgical cases prior to 2012. Data abstracted included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, T stage, N stage, year of diagnosis, type of surgery, radiation technique, dose, fractionation, and type of chemotherapy. Clinical staging was assigned in accordance with the American Joint Committee on Cancer (AJCC) eighth edition based on the TURBT, physical examination, and imaging findings at diagnosis. Charlson comorbidity index (CCI) score was calculated based on age and comorbidities at diagnosis.[11] Outcomes were determined using the reports from imaging studies and followup notes. Death date and the cause of death were available from the BC Cancer Registry.

Outcomes and data analysis

Two analyses were performed: analysis 1 compared RC and curative-intent RT cases and analysis 2 was restricted to cases in which small cell cancers patients were treated according to the consensus guidelines.[6] For analysis 2, inclusion implied that small cell histology was identified on TURBT, NAC was given prior to RC, and RT dose was within 15% of the 60 Gy EQD2 using A/B of 10, and at least 4–6 cycles of chemotherapy were delivered. The A/B ratio was determined based on the prior small cell lung cancer literature.[12,13]

For the RT group, NAC and adjuvant chemotherapy (ACT) were defined as any cycle of chemotherapy given prior to or after RT, respectively. Primary outcome for both analyses was overall survival (OS), as defined from the date of diagnosis to the date of death from any cause. Secondary outcomes included cancer-specific survival (CSS), rate of brain metastasis, and the rate of salvage therapy. For analysis 1, univariate Cox regression analysis (UVA) was performed to assess the association of demographic, clinical, and treatment variables with OS and CSS. Multivariate Cox regression analysis (MVA) was performed to compare the OS and CSS between the surgical and RT groups, and the patients who did or did not receive NAC or ACT. Clinical stage and treatment group were included in the MVA. All variables with $p<0.25$ in univariate analysis were entered in backward stepwise regression analysis for the MVA. When treatment group and stage were forced in the model, the entry criterion was $p<0.25$ and the removal criterion was $p\geq0.15$. For analysis 2, UVA and MVA Cox regression were not performed for OS and CSS, as the event counts were low and the proportional hazards (PH) assumptions were violated. Instead, the univariate OS and CSS results were reported as Kaplan-Meier estimates. Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.).

Results

Patient and disease characteristics

In total, 188 patients were identified (Fig. 1). Seventy-six patients received RT for localized SCBC: 32 were excluded due to palliative intent of RT (prospectively specified in the database) and dose of RT (defined as an EQD2 dose of <30 Gy). The CIHI system was able to identify one additional surgical patient who was registered under the CAIS system but not flagged as a surgical patient during the 2012–2018 era (6% of surgery cases during this era).

For analysis 1, 77 patients were identified: 44 (57%) patients had chemoRT and 33 (43%) had RC. Sixty-eight (88%) patients had SCBC histological diagnosis on TURBT, and nine (12%) had urothelial histological diagnosis from

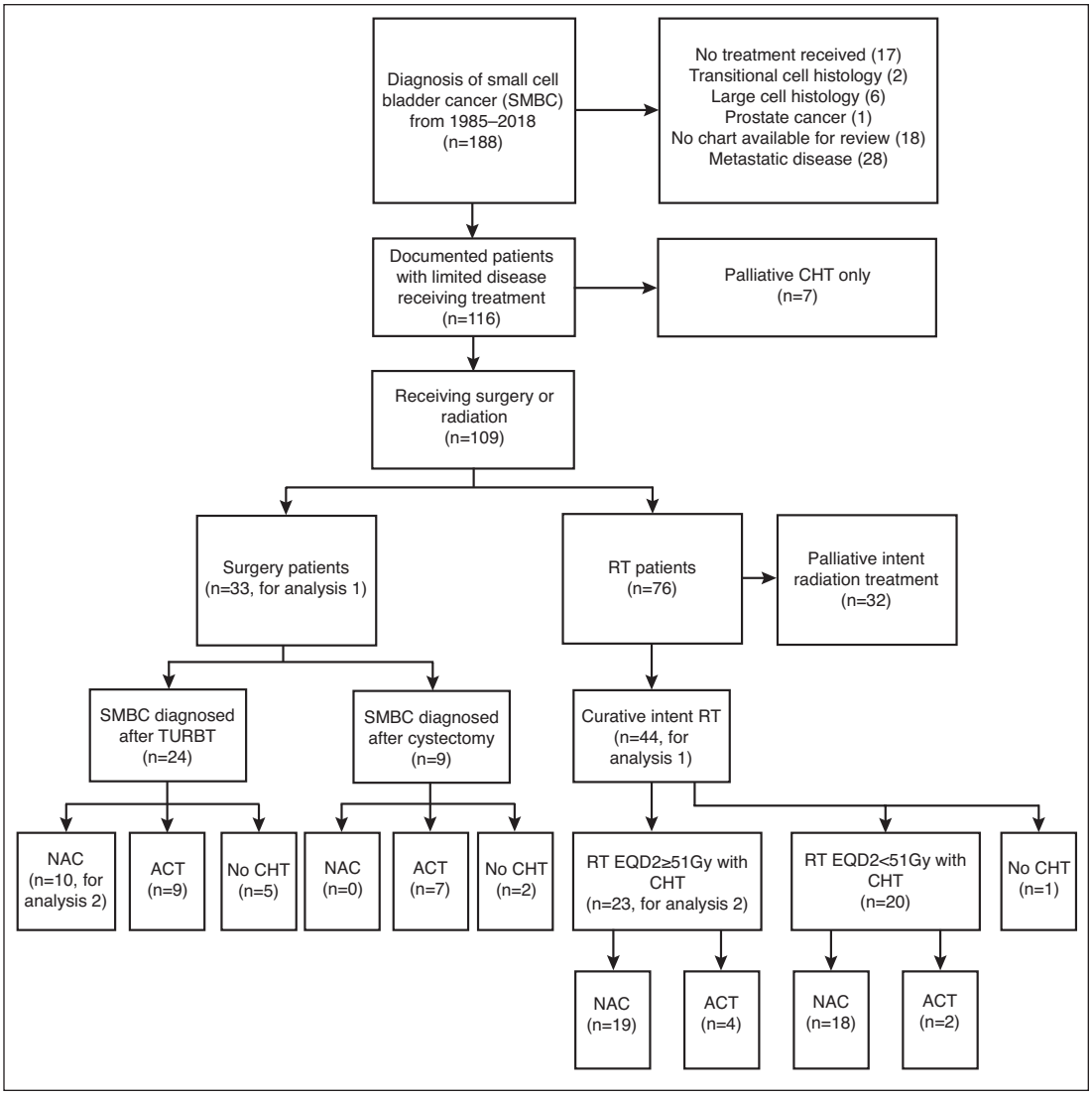


Fig. 1. Patient flowchart diagram. ACT: adjuvant chemotherapy; CHT: chemotherapy; EQD2: equivalent dose in 2 Gy fractions; NAC: neoadjuvant chemotherapy; RT: radiation therapy.

TURBT that was changed to SCBC after RC. Seventy-six of 77 (99%) patients had a staging workup with at least a computed tomography (CT) of the abdomen/pelvis, and either a CT chest or chest X-ray. Fifty-nine of 77 (77%) had a bone scan, 29 (38%) had a brain CT/magnetic resonace imaging (MRI), and seven (10%) had an fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan, which only became available for cancer patients in BC in 2001. All but one case had adequate information recorded in the chart to assign stage, and the one patient was treated as limited stage in the medical record and was included as localized stage.

For analysis 2, 33 patients had small cell diagnosed on TURBT, of whom 10 had NAC prior to RC and 23 had NAC/ACT in addition to RT.

Demographic data and disease characteristics for both analyses are presented in Table 1.

Treatment characteristics

In the RT group, one patient had received a curative dose of radiotherapy (66 Gy/33 fractions) alone. All chemoRT patients received some neoadjuvant (n=37, 84%) or adjuvant chemotherapy (n=6, 14%) in addition to the concurrent chemotherapy. Most RC cases received either neoadjuvant (n=10, 30%) or adjuvant (n=16, 49%) chemotherapy, 10 of whom were in analysis 2. Of the seven that did not receive chemotherapy in the RC group, there was a plan to use ACT in 57% (4/7), but postoperative complications and/or a functional decline prohibited its use. In the remaining cases, there was no record of a medical oncology consult in the charts. Of the 24 patients who had small cell histology identified on TURBT, five did not receive chemotherapy. Cisplatin-based chemotherapy was the most commonly used regimen in both groups. The majority of patients were treated with cisplatinum and etoposide (n=51, 66%), and the remaining cases were treated with carboplatin and etoposide (n=13, 16.9%), cyclophosphamide, doxorubicin, and vincristine (CAV)-based regimens (n=6, 7.8%), or no chemotherapy (n=7, 9.1%).

Median EQD2 for analysis 1 was 52 Gy (interquartile range [IQR] 46–58) and for analysis 2 was 58 Gy (IQR 54–60). Prophylactic cranial irradiation (PCI) was used in 7/42 (17%) of the chemoRT group and 1/35 (3%) of the RC group. Median dose for PCI was 25 Gy (IQR 25–25). EQD2 for PCI was 21 Gy using an A/B ratio of 10. Treatment characteristics are shown in Table 1.

Table 1. Demographic, disease, and treatment characteristics

		Analysis 1		Analysis 2	
		Chemo/RT (n=44)	Surgery (n=33)	NAC/ACT + RT (n=23)	NAC + surgery (n=10)
Age at diagnosis	Median (IQR)	72 (64 –76)	69 (59–74)	69 (59–74)	69 (62–79)
Sex, n (%)	F	14 (31.8)	5 (15.2)	9 (39.1)	2 (20.0)
	M	30 (68.2)	28 (84.8)	14 (60.9)	8 (80.0)
Stage groupings, n (%)	I/II	11 (25.0)	25 (75.8)	2 (8.7)	9 (90.0)
	III/IV	31 (70.5)	6 (18.2)	20 (87.0)	1 (10.0)
	X	2 (4.5)	2 (6.1)	1 (4.3)	0 (0.0)
TNM stage subgroups	T1N0	0 (0.0)	3 (9.1)	0 (0.0)	0 (0.0)
	T2N0	11 (25.0)	18 (54.5)	1 (4.3)	8 (80.0)
	T3N0	13 (29.5)	3 (9.1)	8 (34.8)	1 (10.0)
	T4N0	4 (9.1)	0 (0.0)	4 (17.4)	0 (0.0)
	Tx N0	0 (0.0)	1 (3.0)	0 (0.0)	1 (10.0)
	T1 N (+)	2 (4.5)	0 (0.0)	1 (4.3)	0 (0.0)
	T2 N (+)	1 (2.3)	2 (6.1)	1 (4.3)	0 (0.0)
	T3 N (+)	9 (20.5)	1 (3.0)	4 (17.4)	0 (0.0)
	T4 N (+)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Tx N (+)	1 (2.3)	0 (0.0)	1 (4.3)	0 (0.0)
	T1 Nx	1 (2.3)	0 (0.0)	1 (4.3)	0 (0.0)
	T2 Nx	1 (2.3)	3 (9.1)	1 (4.3)	0 (0.0)
	T3 Nx	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	T4 Nx	1 (2.3)	0 (0.0)	1 (4.3)	0 (0.0)
	Tx Nx	0 (0.0)	2 (6.1)	0 (0.0)	0 (0.0)
Dx small cell	On TURB	44 (100)	24 (73)	23 (100)	10 (100)
	Cystectomy only	0 (0)	9 (27)	0 (0)	0 (0)
ECOG, n (%)	0/1	22 (50.0)	24 (72.7)	13 (56.5)	9 (90.0)
	2/3	20 (45.5)	8 (24.2)	10 (43.5)	1 (10.0)
	Missing	2 (4.5)	1 (3.0)	0 (0.0)	0 (0.0)
Charlson comorbidity index, n (%)	0–4	13 (29.5)	15 (45.5)	9 (39.1)	5 (50.0)
	5–7	25 (56.8)	18 (54.5)	13 (56.5)	5 (50.0)
	8–10	6 (13.6)	0 (0.0)	1 (4.3)	0 (0.0)
Diagnosis year (%)	1988–2007	29 (65.9)	11 (33.3)	17 (73.9)	1 (10.0)
	2008–2018	15 (34.1)	22 (66.7)	6 (26.1)	9 (90.0)
Chemotherapy regimen, n (%)	Carboplatin-based	12 (27.3)	5 (15.2)	5 (21.7)	3 (30.0)
	Cisplatin-based	29 (65.9)	22 (66.7)	16 (69.6)	7 (70.0)
	Other	2 (4.5)	0 (0.0)	2 (8.7)	0 (0.0)
	None	1 (2.3)	6 (18.2)	0 (0.0)	0 (0.0)
Adjuvant/neoadjuvant chemo, n (%)	Concurrent only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Neoadjuvant ± concurrent	37 (84.1)	10 (30.3)	19 (82.6)	10 (100.0)
	Adjuvant ± concurrent	6 (13.6)	16 (48.5)	4 (17.4)	0 (0.0)
	None	1 (2.3)	7 (21.2)	0 (0.0)	0 (0.0)
Prophylactic cranial irradiation, n (%)	No	37 (84.1)	32 (97.0)	18 (78.3)	10 (100.0)
	Yes	7 (15.9)	1 (3.0)	5 (21.7)	0 (0.0)

ACT: adjuvant chemotherapy; ECOG: Eastern Cooperative Oncology Group; F: female; IQR: interquartile range; M: male; NAC: neoadjuvant chemotherapy; RT: radiation therapy; TURBT: transurethral resection of the bladder tumor.

Survival outcomes

Analysis 1: All cases treated with curative intent

For analysis 1, the five-year OS was 39% for the RT group and 29% for the RC group (non-significant) (Fig. 2). Median survivals were 2.8 years (95% confidence interval [CI] 1.9–6.6) for RT and 2.2 years (95% CI 1.4–3.4) for RC (p=0.51). There was no significant difference in OS between the chemoRT and RC groups in the UVA (Table 2). Higher CCI remained as a significant variable in the OS MVA (Table 3).

Table 2. Analysis 1: Univariate analysis for overall survival and cancer-specific survival

Variables	Overall survival			Cancer-specific survival		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Treatment group	Ipsum					
Chemo RT	1			1		
Primary surgery	1.19	0.71–2.00	0.51	1.39	0.79–2.59	0.29
Sex						
Female	1			1		
Male	1.44	0.78–2.67	0.25	2.02	0.85–4.82	0.11
Stage						
I & II	1			1		
III & IV	0.69	0.40–1.20	0.19	0.76	0.42–1.45	0.41
Unknown	1.78	0.62–5.11	0.28	1.17	0.27–5.03	0.83
ECOG						
0	1			1		
1	1.98	0.98–4.00	0.058	2.62	0.99–6.96	0.054
2	1.85	0.84–4.06	0.12	2.79	0.96–8.09	0.059
3	2.67	0.83–8.58	0.1	2.18	0.42–11.34	0.36
Charlson comorbidity index						
0–4	1			1		
5–7	1.69	0.95–3.03	0.075	1.88	0.92–3.80	0.08
8–10	5.04	1.91–13.30	0.001	3.21	0.86–11.92	0.08
Diagnosis year (median split)						
1988–2007	1			1		
2008–2016	0.9	0.52–1.56	0.72	1.18	0.63–2.21	0.6
Chemotherapy regimen						
Carboplatin-based	1			1		
Cisplatin-based	0.93	0.48–1.79	0.82	1.05	0.47–2.33	0.9
None	1.93	0.76–4.91	0.17	2.29	0.79–6.61	0.13
Other	1.12	0.25–5.05	0.89	1.03	0.13–8.27	0.98
Adjuvant/neoadjuvant						
Adjuvant	1			1		
Neoadjuvant	0.6	0.34–1.05	0.07	0.6	0.3 –1.05	0.11
None	1.63	0.71–3.75	0.25	1.76	0.70–4.43	0.23
Age at diagnosis	1.01	0.98–1.04	0.43	1	0.97–1.03	0.96

ECOG: Eastern Cooperative Oncology Group; CI: confidence interval; RT: radiation therapy.

NAC was associated with longer median OS compared to the ACT/no chemotherapy group (p=0.04).

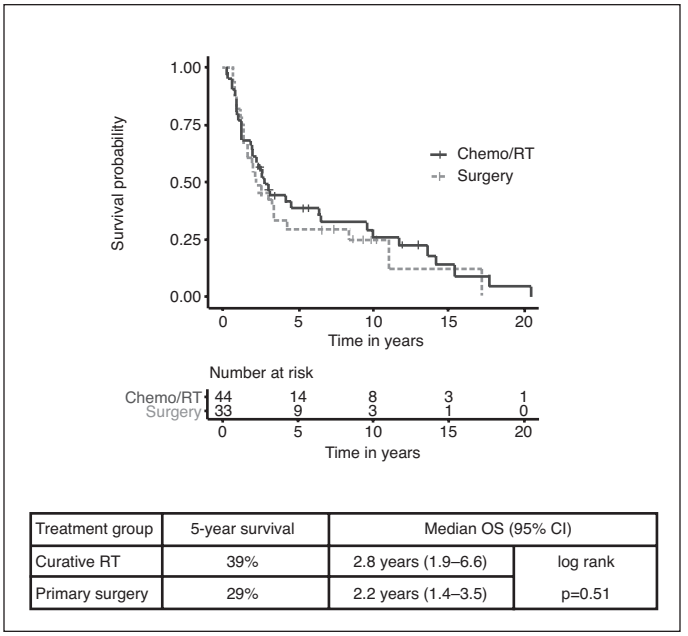
CSS was 52% and 35% at five years for the RT and RC groups, respectively (Fig. 3). Median CSS was 6.3 years for chemoRT (95% CI 2.2–not estimable) and 3.3 years (95% CI 1.6–8.4) for RC (p=0.29). There was no significant difference in CSS between the RT and RC groups on UVA. Higher CCI and ECOG at diagnosis were also associated with worse CSS in MVA (Table 4).

Four of 42 (9.5%) chemoRT patients eventually required salvage cystectomy. One patient developed urothelial carcinoma and the other three developed local recurrence of the SCBC. Of these four patients, one died of bladder cancer, two died of unrelated causes, and one is alive at last followup six years after the salvage cystectomy.

In total, 14/77 patients (18%) developed brain metastasis, with a median time from diagnosis of 17 months (range 9–38). Of these patients, seven did not have baseline brain imaging prior to initial treatment, one did not receive any systemic therapy due to postoperative complications, and four received PCI. In total, eight patients had PCI: one had unknown stage at presentation, one had stage II disease, and the rest had stage IIIA/B disease.

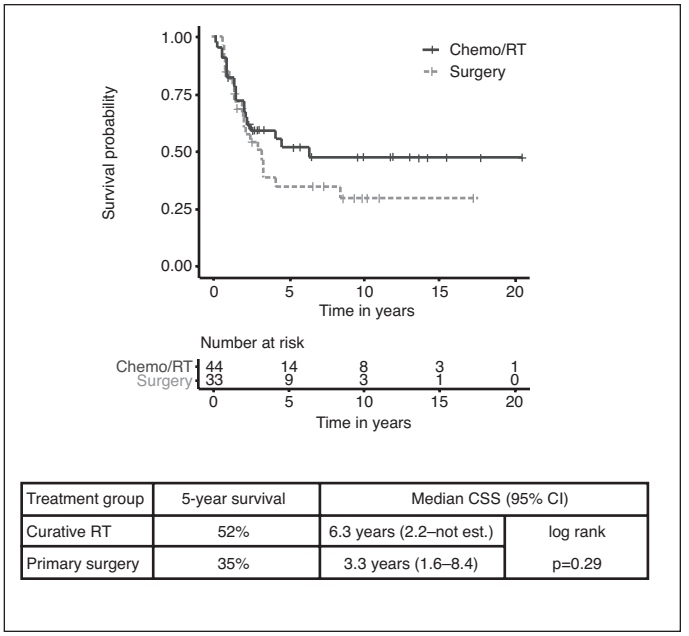
Analysis 2: All curative cases treated according to the modern Canadian consensus guideline

There were 10 RC patients who had NAC and 23 RT patients who received at least 60 Gy EQD2 RT with chemotherapy in accordance with the consensus guideline. OS at five years in these patients was 56% for RC and 58% for RT (p=0.9 on Kaplan-Meier). CSS at five years in these patients was 56% for RC and 71% for RT (p=0.71 on Kaplan-Meier) (Fig. 4).



Treatment group	5-year survival	Median OS (95% CI)	
Curative RT	39%	2.8 years (1.9–6.6)	log rank
Primary surgery	29%	2.2 years (1.4–3.5)	p=0.51

Fig. 2. Analysis 1: Kaplan-Meier curve for overall survival (OS) by initial treatment. CI: confidence interval; RT: radiation therapy.



Treatment group	5-year survival	Median CSS (95% CI)	
Curative RT	52%	6.3 years (2.2–not est.)	log rank
Primary surgery	35%	3.3 years (1.6–8.4)	p=0.29

Fig. 3. Analysis 1: Kaplan-Meier curve for cancer-specific survival (CSS) by initial treatment. CI: confidence interval; RT: radiation therapy.

Discussion

To our knowledge, this is the largest population-based, retrospective comparison of curative-intent RC and chemoRT for SCBC. Our study found that SCBC patients have a poor prognosis, and both curative-intent treatment groups had a similar five-year OS and CSS on UVA and MVA. Although the numbers of cases in both groups are small, MVA did not show a significant difference in OS and CSS between the groups. The observed five-year OS of 39% (n =44) in the current RT cohort is consistent with the previously published five-year OS of 44% (n=14) at our center.

There is no prospective trial comparing RT and RC for SCBC to date. However, the reported small number of retrospective reviews are consistent with the findings of this

Table 3. Analysis 1: Multivariate analysis for overall survival

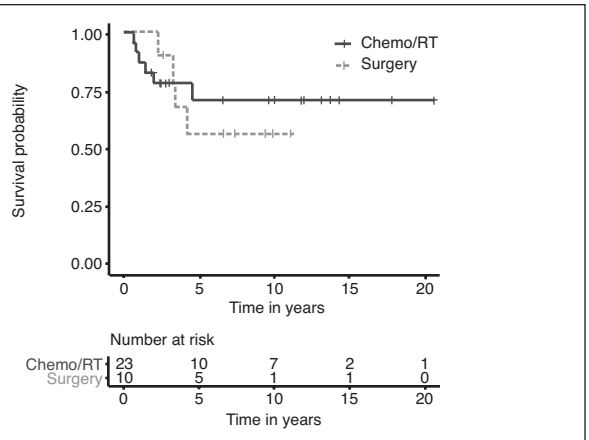
Variables	Hazard ratio	95% CI	p
Treatment group			
Chemo RT	1		
Primary surgery	1.09	0.52–2.27	0.82
Stage			
I & II	1		
III & IV	0.99	0.49–1.98	0.97
Unknown	2.02	0.68–6.02	0.21
Charlson comorbidity index			
0–4	1		
5–7	1.58	0.83–3.01	0.16
8–10	6.82	2.15–21.7	0.001
Adjuvant/neoadjuvant			
Adjuvant	1		
Neoadjuvant	0.50	0.26–0.97	**0.04**
None	1.39	0.58–3.37	0.46

CI: confidence interval; RT: radiation therapy.

Table 4. Analysis 1: Multivariate analysis for cancer-specific survival

Variables	Hazard ratio	95% CI	p
Treatment group			
Chemo RT	1		
Primary surgery	1.78	(0.66–4.79)	0.26
Stage			
I & II	1		
III & IV	1.07	(0.44–2.60)	0.88
Unknown	1.23	(0.27–5.60)	0.79
Charlson comorbidity index			
0–4	1		
5–7	2.06	(0.90–4.71)	0.09
8–10	5.75	(1.15–28.7)	**0.03**
ECOG			
0	1		
1	3.09	(1.06–8.98)	**0.04**
2	2.92	(0.89–9.59)	0.08
3	1.84	(0.29–11.6)	0.52
Adjuvant/neoadjuvant			
Adjuvant	1		
Neoadjuvant	0.51	0.21–1.21	0.12
None	0.87	0.30–2.53	0.79

ECOG: Eastern Cooperative Oncology Group; CI: confidence interval; RT: radiation therapy.



Treatment group	5-year survival	Median CSS (95% CI)	
Curative RT	71%	Not est. (4.5–not est.)	log rank
NAC surgery	56%	Not est. (2.2–not est.)	p=0.71

Fig. 4. Analysis 2: Kaplan-Meier curve for cancer-specific survival (CSS) by initial treatment. CI: confidence interval; NAC: neoadjuvant chemotherapy; RT: radiation therapy.

study. A recent retrospective study based on National Cancer Database (NCDB) identified 856 patients with SCBC and showed a similar finding with five-year OS for chemoRT (24%) and surgery (24%).[9] However, the authors were not able to identify or compare many baseline characteristics, clinical staging, and chemotherapy use from the NCDB. Recently, an abstract was presented for a large, retrospective study comparing chemoRT vs. surgery across 26 institutions in the U.K., which identified 409 patients with SCBC and found that median OS did not significantly differ between the chemoRT (30 months) and the RC (27 months) groups, although again, the ability to compare baseline prognostic and treatment parameters was limited.[14] Both of these larger, retrospective studies are consistent with our finding of similar survival outcomes between chemoRT and surgery for SCBC.

In contrast, a smaller, retrospective series (n=38) at Fox Chase Cancer Center suggested that patients who had RC had better OS and progression-free survival (PFS) on UVA compared to RT.[10] However, after accounting for age, histology, and stage, the MVA did not demonstrate significant difference between the two treatment modalities. Despite the MVA, the authors noted that all of the longest survivors (n=7, as defined by 1.5 times 75% interquartile range OS) had RC, and the institutional standard of therapy for localized SCBC remains NAC followed by RC.[10] The discrepancy may be due to selection bias or lack of baseline characteristic comparisons of the treatment groups. The study also did not consider censored patients who would have met the criteria for longest survivors if a longer followup were conducted. In the present analysis, there are equal numbers of long-term survivors after both RC and chemoRT.

Our analysis supports the use of the current Canadian consensus guideline for the limited SCBC. A separate analysis was performed to reflect the current guideline, limiting the analysis to the RC patients who were diagnosed on TURBT only and received NAC, and the RT patients that received near 60 Gy EQD2 dose and 4–6 cycles of cisplatin. In this analysis, five-year OS and CSS between the RC and RT groups were similar as well. Although direct comparison is limited by small numbers, five-year OS and CSS in both RC and RT groups were seemingly better in analysis 2 than in analysis 1. It is difficult to comment on whether the apparently better outcomes are due to treatment regimen or selection bias, but without a larger or prospective trial, limited SCBC management, as proposed by the consensus guideline, seems appropriate.

For the patients who are planned for RC, the Canadian consensus guideline suggests NAC. A retrospective study at MD Anderson demonstrated that preoperative chemotherapy (n=48) had improvement in OS and CSS compared to upfront RC (n=47).[15] The authors suggested that some of the improvements in outcomes may be due to effective downstaging and early control of micrometastatic disease.

In our RC cohort, 10/33 (30%) of all cases were treated with NAC. Of the patients with a pre-RC diagnosis of SCBC, 11/24 (46%) had NAC. All NAC patients went onto planned RC, while four patients could not receive planned ACT due to postoperative complications, suggesting that patients are better able to tolerate NAC or that fit patients were selected for the purpose of NAC. However, completion of RC or RT was an inclusion criterion in our analysis, and it is possible that some patients intended for a RC or RT after NAC are excluded in our analysis due to disease progression.

For primary RT treatment, the guideline suggests starting RT with cycle 1–2 of chemotherapy.[16-18] In our RT cohort, 37/44 (84%) had NAC and 6/44 (14%) ACT. Although the influence of the sequencing of chemotherapy on the outcomes for RC and RT separately was not assessed, five-year OS inclusive of both groups in the MVA was significantly longer for the neoadjuvant group compared to the adjuvant group (hazard ratio [HR] 0.5, 95% CI 0.26–0.95, p<0.04). Given that there was no association between NAC and CSS, this may suggest that more fit patients eligible for NAC have better OS, or that CSS analysis was not powered to detect such a difference. Thus, despite the limitation of the analysis, administration of NAC may be the best approach for both the RC and RT groups, as per the Canadian consensus guideline, based on the current study result and the biological rationale.

This study should be interpreted in the context of strengths and limitations. The retrospective nature of the study cannot adequately account for the confounding factors, as well as a

survivor bias, as the patients were retrospectively identified. The long timespan of the study may also add to the variability in the staging investigations, which may not reflect the distribution of the clinical stages in the current era. The comprehensiveness of the database in identifying the surgical cohort may be limited, as only the BC Cancer medical records could be accessed, although CIHI and CAIS registry were quite concordant for the years of overlap, with only one additional surgical patient identified by CIHI. Some of the TURBT or RC histology in the community would not have been reviewed centrally, and there may have been specimens that would have met the criteria for SCBC. Despite the limitations, the study has a relatively larger sample size in comparison to the previous single-institute studies, and a population-based design reduces treatment heterogeneity and referral bias and provides access to patient baseline characteristics and clinical staging, which allow a more balanced comparison of the treatment groups.

Conclusions

SCBC is a rare entity with a poor prognosis. This study is the largest, population-based, retrospective comparison of the patients treated with curative RC and RT for limited SCBC. There was no significant difference in the OS or CSS between the two treatment groups, even when the comparisons were limited to the population treated by the most recent consensus guideline. NAC showed better outcomes than ACT, consistent with the consensus guideline. Both RC and chemoRT should be considered treatment options for localized SCBC.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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