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Induction Chemotherapy for Locoregionally Advanced Sinonasal Squamous Cell Carcinoma

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Abstract

Background There is emerging evidence to suggest the role of induction chemotherapy (IC) in definitive management of locoregionally advanced sinonasal squamous cell carcinoma (SNSCC). We evaluated the influence of IC on survival and predictors of its use in SNSCC patients.

Methods The 2004 to 2017 National Cancer Database was queried for patients with locoregionally advanced SNSCC (T4/M0). Treatments were stratified into seven groups: definitive chemoradiation (CRT), IC with definitive CRT (IC + CRT), IC + CRT with salvage surgery (IC + CRT + Sx), definitive surgery (Sx), IC with definitive surgery (IC + Sx), definitive surgery with adjuvant radiation or CRT (Sx + ATx), or IC + Sx + ATx. Cox proportional-hazards regression assessed overall survival (OS) and logistic regression identified predictors of IC.

Results Of 3,162 patients, 1,088 (34.4%) were female with a mean age of 63.4 ± 13.4 years. The 2- and 5-year OS rates were 58.6 and 42.0%, respectively. Compared with CRT, Sx + ATx (hazard ratio [HR]: 0.663; $p < 0.001$), IC + Sx (HR: 0.606; $p = 0.005$), or IC + Sx + ATx (HR: 0.468; $p = 0.001$) exhibited reduced mortality. Among patients who were treated with definitive surgery, those receiving IC had additional OS benefit (all $ps < 0.05$). Older age (odds ratio [OR]: 0.607; $p < 0.001$), female sex (OR: 0.759; $p = 0.028$), Black race (OR: 1.650; $p < 0.001$, T4b stage (OR: 1.674; $p < 0.001$), and higher N stage (OR: 1.395; $p < 0.001$) were predictors of IC.

Conclusion IC prior to definitive surgery with or without adjuvant therapy exhibited the highest OS for locoregionally advanced SNSCC. Age, sex, race, and T/N staging were predictors of IC. Multimodal treatment regimens involving surgery as the primary modality may, therefore, provide the greatest therapeutic response.

Keywords
- sinonasal carcinoma
- neoadjuvant chemotherapy
- induction chemotherapy
- survival
- outcomes research

Introduction

Squamous cell carcinoma of the nasal cavity and paranasal sinuses (sinonasal squamous cell carcinoma [SNSCC]) is one of the most common histological subtypes of sinonasal malignancies, representing nearly 50% of all cases.[1,2] Despite recent decreases in SNSCC incidence, reports on patient outcomes have shown limited improvements in 5-year

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overall survival (OS) rates. This has been frequently attributed to delayed diagnoses due to SNSCC's tendency to manifest relatively nonspecific symptoms, such as nasal obstruction, facial pain, and rhinorrhea, at advanced stages of disease.[3,4] Furthermore, its propensity to locally recur has significantly hindered long-term patient survival following definitive treatment.

SNSCC is traditionally treated surgically, with recent protocols encouraging adjuvant radiotherapy with possible chemotherapy to mitigate risks of local recurrence.[4] However, surgical management of locoregionally advanced SNSCC continues to be a major challenge due to the tumor's close proximity to critical structures, such as the skull base and orbit. Recently, endoscopic surgery has become increasingly favored for SNSCC management, particularly in well-selected patients where R0 resection can be achieved, as it is less invasive and associated with lower morbidity and fewer surgical complications.[5,6] With advancements in endoscopic approaches and multimodal treatment strategies, there has been a growing interest in investigating and applying more organ-preserving treatment protocols for locally advanced SNSCC.[7]

Recent studies on induction chemotherapy (IC) use prior to definitive SNSCC management have shown promising results, with reports suggesting that IC may be able to improve morbidity and survival outcomes in select patients with locally advanced disease.[7,8] However, owing to the relatively low incidence of SNSCC, most investigations on IC efficacy for this sinonasal malignancy have been limited to single-institution studies. Therefore, in this study, we aimed to utilize the National Cancer Database (NCDB) to evaluate the influence of IC on survival and determine the predictors of its use in a large population-based cohort of patients with locally advanced SNSCC.

Materials and Methods

Study Population

Data were queried from the 2004 to 2017 NCDB, a deidentified and publicly available hospital-based registry that reports on approximately 70% of new cancer cases from Commission on Cancer-accredited facilities in the United States annually.[9] Due to the anonymized nature of the NCDB, this study was exempt from University of California, Irvine Institutional Review Board approval. We queried the database for patients with SNSCC using the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) topography code for the sinonasal tract (C30.0, C31.0-C31.9) and histology/behavior codes for locally advanced (T4, any N, M0) SNSCC (8052/3, 8070-8078/3, 8083-8084/3).

The cohort was restricted to patients receiving one of seven treatment regimens: chemoradiation (CRT) only, IC with definitive CRT (IC + CRT), IC + CRT with salvage surgery (IC + CRT + Sx), definitive surgery only (Sx), IC with definitive surgery (IC + Sx), definitive surgery with adjuvant radiation and/or chemotherapy (Sx + ATx), or IC with definitive surgery and adjuvant therapy (IC + Sx + ATx). Induction chemotherapy was defined as starting between 6 months to 2 weeks before definitive surgery and/or radiotherapy.[10,11] Definitive CRT was defined as chemotherapy starting within 14 days of administering radiotherapy.[11] Salvage surgery was defined as a surgical date $\geq$ 60 days after CRT initiation. Neoadjuvant and adjuvant therapies were also identified using NCDB data on treatment sequences. Cases with unknown or missing treatment information were excluded. In cases involving surgery, patients were excluded if surgical margins were reported as macroscopic positive or unknown. Finally, patients who received palliative care or had unknown survival status were excluded.

Study Variables

Independent covariates used for analysis included age, sex, race, Charlson/Deyo (CD) comorbidity index, insurance type, year of diagnosis, T/N staging, surgical margins, and treatment regimen. CD indices were binarized as 0 and $\geq$1 to indicate the absence or presence of comorbidities, respectively. To account for changes in medical diagnostics and therapies, the year of diagnosis was included as a covariate and stratified into three groups ($<$ 2008, 2008–2011, and $\geq$ 2012). The primary measured outcomes were all-cause mortality and OS starting at the time of diagnosis. The use of IC served as a secondary outcome for identifying predictors of IC.

Statistical Analysis

Statistical analyses were performed using R (version 3.6.1; The R Foundation for Statistical Computing) in RStudio (version 1.2.1335). A p-value of $<$0.05 was considered statistically significant. Multivariable Cox proportional-hazards (CPH) analyses were performed to evaluate the relationship between patient variables and all-cause mortality. Variables with p-values of $<$0.1 on univariate CPH analysis were included as covariates in multivariable models. Regression models were assessed for multicollinearity by ensuring that all covariates possessed variance inflation factors less than 10.[12] Covariate-adjusted Kaplan–Meier analyses were generated to evaluate the relationship between treatment regimen and OS. Univariate and multivariable logistic regressions were performed to identify factors predictive of IC.

Results

A total of 3,162 patients met the study's inclusion criteria, which consisted of 1,088 (34.4%) females and an average age of 63.4 $\pm$ 13.4 years. The most common treatment regimens were Sx + ATx (55.3%), CRT (15.1%), and Sx (13.9%). About 13.0% of patients received IC. Overall, the cohort's 2- and 5-year OS rates were 58.6 and 42.0%, respectively. Patients' baseline demographic and clinical characteristics are listed in ►**Table 1**.

Survival Analysis

Associations between sociodemographic or clinical factors and all-cause mortality were evaluated using univariate CPH analysis, as listed in ►**Table 1**. On multivariable CPH

Table 1 Demographic and clinical factors of patients ($N = 3,162$) with locoregionally advanced sinonasal squamous cell carcinoma. Univariate Cox proportional-hazards regression demonstrated factors associated with mortality

Characteristics	*N* (%)	Hazard ratio (95% CI)	*p*-Value
Age (y)[b]			
< 55	832 (26.3)	1 (reference)	<0.001[a]
≥ 55	2,330 (73.7)	1.616 (1.446–1.806)	
Sex			
Male	2,074 (65.6)	1 (reference)	0.505
Female	1,088 (34.4)	0.968 (0.880–1.065)	
Race[b]			
White	2,541 (81.1)	1 (reference)	
Black	454 (14.5)	1.125 (0.991–1.277)	0.069
Asian	95 (3.0)	1.002 (0.762–1.317)	0.991
Other	44 (1.4)	0.559 (0.342–0.916)	0.021[a]
Insurance[b]			
Private	1,050 (36.0)	1 (reference)	<0.001[a]
Government	1,863 (64.0)	1.552 (1.402–1.719)	
Charlson/Deyo Score[b]			
0	2,452 (77.5)	1 (reference)	<0.001[a]
≥1	710 (22.5)	1.285 (1.157–1.426)	
Year of diagnosis[b]			
2004–2007	735 (23.2)	1 (reference)	
2008–2011	980 (31.0)	0.970 (0.864–1.088)	0.599
2012–2016	1,447 (45.8)	0.829 (0.738–0.932)	0.002[a]
T stage[b]			
4A	2,145 (67.8)	1 (reference)	<0.001[a]
4B	1,017 (32.2)	1.345 (1.224–1.478)	
N stage[b]			
0	2,424 (76.7)	1 (reference)	
1	253 (8.0)	1.317 (1.115–1.555)	0.001
2	468 (14.8)	1.617 (1.432–1.826)	<0.001[a]
3	17 (0.5)	1.927 (1.116–3.328)	0.019[a]
Surgical margins[b]			
Negative	1,028 (58.2)	1 (reference)	<0.001[a]
Positive	739 (41.8)	1.421 (1.248–1.618)	
Treatment[b]			
CRT	398 (15.1)	1 (reference)	
IC + CRT	254 (9.7)	0.875 (0.719–1.065)	0.183
IC + CRT + salvage Sx	26 (1.0)	0.778 (0.477–1.271)	0.316
Sx	365 (13.9)	0.946 (0.794–1.127)	0.534
IC + Sx	74 (2.8)	0.549 (0.392–0.768)	<0.001[a]
Sx + ATx	1,455 (55.3)	0.573 (0.498–0.659)	<0.001[a]
IC + Sx + ATx	58 (2.2)	0.412 (0.271–0.625)	<0.001[a]
1-y OS rate (95% CI)	74.8 (73.3–76.3)	–	–

(*Continued*)

Table 1 (*Continued*)

Characteristics	*N* (%)	Hazard ratio (95% CI)	*p*-Value
2-y OS rate (95% CI)	58.6 (56.9–60.4)	–	–
5-y OS rate (95% CI)	42.0 (40.2–43.9)	–	–

Abbreviations: ATx, adjuvant therapy; CI, confidence interval; CRT, chemoradiation; IC, induction chemotherapy; OS, overall survival; Sx, surgery.
[a]Statistically significant, $p < 0.05$.
[b]Variable included as a covariate in multivariable analysis.

regression, Sx + ATx (hazard ratio [HR]: 0.663; 95% confidence interval [CI]: 0568–0.775; $p < 0.001$), IC + Sx (HR: 0.606; 95% CI: 0.426–0.862; $p = 0.005$), or IC + Sx + ATx (HR: 0.468; 95% CI: 0.295–0.741; $p = 0.001$) were associated with reduced mortality compared with CRT.

Covariate-adjusted Kaplan–Meier survival curves were generated to evaluate the association between treatment regimen and patient OS (►**Fig. 1**). Among patients with definitive CRT, there was no significant difference in OS between those who received CRT, IC + CRT, and IC + CRT + Sx ($p > 0.05$). In contrast, among patients who received definitive surgery, IC + Sx ($p = 0.002$), IC + Sx + ATx ($p < 0.001$), and Sx + ATx ($p < 0.001$) exhibited higher OS than Sx alone. Moreover, IC + Sx + ATx exhibited higher OS than Sx + ATx ($p = 0.041$). Covariate-adjusted 1-, 2-, and 5-year OS rates for each treatment-stratified cohort are listed in ►**Table 2**.

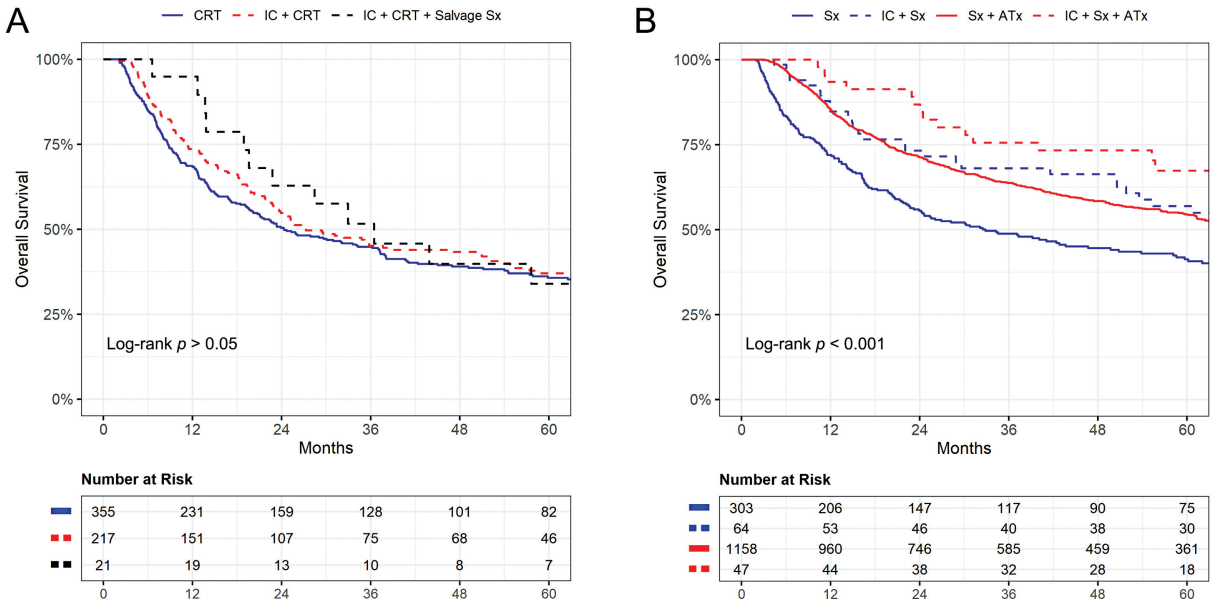

Fig. 1 Covariate-adjusted Kaplan–Meier survival curves of patients with locoregionally advanced sinonasal squamous cell carcinoma who underwent definitive (**A**) nonsurgical or (**B**) surgical treatment. ATx, adjuvant therapy; CRT, chemoradiation; IC, induction chemotherapy; Sx, surgery.

Table 2 Overall survival rates for sinonasal squamous cell carcinoma patients, stratified by treatment

Treatment	1-y OS rate (95% CI)	2-y OS rate (95% CI)	5-y OS rate (95% CI)
CRT	68.4 (63.6–73.4)	50.4 (45.3–56.1)	35.7 (30.6–41.6)
IC + CRT	73.1 (67.4–79.3)	54.8 (48.4–62.0)	37.0 (30.6–44.8)
IC + CRT + Salvage Sx	89.5 (76.8–100.0)	62.8 (44.3–89.1)	34.0 (17.6–65.6)
Sx	71.9 (67.1–77.1)	55.6 (50.1–61.6)	40.7 (34.9–47.4)
IC + Sx	84.8 (77.4–94.0)	71.5 (61.1–83.8)	54.9 (43.3–69.7)
Sx + ATx	85.3 (83.3–87.4)	71.3 (68.7–74.0)	54.4 (51.4–57.7)
IC + Sx + ATx	93.5 (86.6–100.0)	84.6 (75.1–95.8)	67.3 (54.4–83.3)
Log-rank *p*-value	<0.001	<0.001	<0.001

Abbreviations: ATx; adjuvant therapy; CI, confidence interval; CRT, chemoradiation; IC, induction chemotherapy; OS, overall survival; Sx, surgery.

Predictors of Induction Chemotherapy

Patient characteristics stratified according to treatment modality are listed in ►**Supplementary Table S1** (available in online version). Associations between patient factors and IC use were evaluated using logistic regression, as listed in ►**Table 3**. On multivariable logistic regression, female patients (odds ratio [OR]: 0.759; 95% CI: 0.591–0.968; $p = 0.028$) and those aged $\geq$ 55 years (OR: 0.607; 95% CI: 0.479–0.772; $p < 0.001$) were less likely to receive IC. In contrast, Black race (OR: 1.650; 95% CI: 1.226–2.202; $p < 0.001$), T4b stage (OR: 1.674; 95% CI: 1.325–2.111; $p < 0.001$), and higher N stage (OR: 1.395; 95% CI: 1.220–1.590; $p < 0.001$) were positively associated with IC use.

Discussion

In this retrospective cohort study of 3,162 cases of SNSCC from the NCDB, we compared the survival outcomes for cohorts treated definitively with surgical resection or chemoradiotherapy, with or without adjuvant therapy, and with or without IC. Overall, our patients were predominantly male, older, and White. Our 2- and 5-year OS rates of 58.6 and 42.0% were consistent with other studies of survival outcomes in SNSCC.[13–15] We found that treatment with IC followed by surgery was associated with a survival benefit compared with T4-stage patients treated with surgery without IC. The survival benefit of IC was present when

Table 3 Logistic regression of sinonasal squamous cell carcinoma patients, demonstrating demographic and clinical factors associated with induction chemotherapy use

Characteristics	Univariate		Multivariable	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age, y				
<55	1 (reference)		1 (reference)	<0.001[a]
≥ 55	0.552 (0.439–0.697)	<0.001[a]	0.607 (0.479–0.772)	
Sex				
Male	1 (reference)		1 (reference)	0.028[a]
Female	0.767 (0.600–0.973)	0.031[a]	0.759 (0.591–0.968)	
Race				
White	1 (reference)		1 (reference)	
Black	1.867 (1.400–2.467)	<0.001[a]	1.650 (1.226–2.202)	<0.001[a]
Asian	1.255 (0.638–2.271)	0.480	1.251 (0.631–2.286)	0.491
Other	1.338 (0.499–3.028)	0.519	1.424 (0.526–3.261)	0.439
Insurance				
Private	1 (reference)		1 (reference)	
Government	0.818 (0.645–1.040)	0.099	–	–
Charlson/Deyo Score				
0	1 (reference)		1 (reference)	
≥ 1	0.938 (0.713–1.220)	0.638	–	–
Year of diagnosis				
2004–2007	1 (reference)		1 (reference)	
2008–2011	1.160 (0.853–1.586)	0.346	–	–
2012–2016	1.066 (0.800–1.431)	0.668	–	–
T stage				
4a	1 (reference)		1 (reference)	<0.001[a]
4b	1.797 (1.431–2.253)	<0.001[a]	1.674 (1.325–2.111)	
N stage				
0	1 (reference)		1 (reference)	
1	1.665 (1.117–2.424)	0.010[a]	1.722 (1.142–2.534)	<0.001[a]
2	2.075 (1.571–2.723)	<0.001[a]	1.915 (1.440–2.527)	<0.001[a]
3	2.150 (0.480–7.085)	0.247	2.270 (0.502–7.585)	0.219

Abbreviation: CI, confidence interval.
[a]Statistically significant, $p < 0.05$.

comparing surgical cohorts treated both with and without adjuvant therapy. However, IC was not associated with a survival benefit when followed by definitive CRT.

Sinonasal malignances such as SNSCC are rare, accounting for <5% of head and neck neoplasms and are often excluded from clinical trials, limiting the ability to investigate new treatment regimens.[16] Despite advances in endoscopic surgery, the incidence and survival of SNSCC has remained relatively unchanged.[13,17] The mainstay of SNSCC treatment remains surgical resection with negative margins followed by radiotherapy. In a NCDB study of SNSCC, Jafari et al highlighted the importance of achieving negative margins, observing positive margins in 22% of cases and a median survival of 90.5, 56.7, and 38.4 months for negative margins, micropositive margins, and macropositive margins, respectively.[18] Further, while negative and micropositive margins were both associated with a survival benefit, macropositive margins were not associated with a survival benefit when compared with nonsurgical patients. In separate NCDB studies, negative margins were achieved in >90% T1/T2 tumors, but T3/T4 tumors were associated with higher rates of positive margins, with only 56% of T4b tumors achieving negative margins.[11,19]

IC has been proposed as a method of increasing the chances of achieving negative surgical margins in advanced T stage tumors or to downstage an otherwise unresectable tumor. While IC has been explored more extensively in other head and neck malignancies, there has been a growing body of literature exploring the efficacy of IC in sinonasal neoplasms. In one of the more recent, large-scale prospective studies, Amit et al demonstrated the potential use of IC to predict treatment response and guide treatment selection for sinonasal undifferentiated carcinoma (SNUC).[20] In contrast, in our previous retrospective study of 440 SNUC patients, we did not observe an OS benefit with IC administration, suggesting that further trials may be necessary to clarify the benefits of IC in SNUC.[10] This study serves as a continuation of our previous investigations with the goal of elucidating how IC may influence survival outcomes in different sinonasal malignancies.

Several case series have investigated IC only in advanced SNSCC, finding an OS benefit when surgery was included as a potential definitive treatment.[21] Within these studies, response to IC was strongly predictive of survival outcomes. Four series found that long-term survival for patients who responded to IC ranged from 68 to 93%, which dropped to 25 to 54% among patients who responded poorly.[22–25] In a single study of inoperable SNSCC, which included only radiation as the definitive therapy, there was no survival benefit to IC.[26] Our findings were consistent with these previous studies, demonstrating that IC may provide a survival benefit to patients with advanced tumors, but only if IC was followed by surgical resection with negative margins. In our study, 2-year OS for patients treated with IC followed by surgical resection and adjuvant therapy was 84.6%, compared with 71.3% when treated without IC. This difference persisted when treated without adjuvant therapy; patients treated with IC and surgery demonstrated survival rates of 71.5% compared with 55.6% for surgical patients who did not receive IC.

Given the evidence supporting surgical resection, poor OS among patients receiving CRT may reflect a baseline poor prognosis. Although some patients may have elected to pursue CRT despite being candidates for surgery, a significant portion of the CRT cohort likely included patients in whom negative margins were unlikely to be achieved. In our study, patients treated with definitive CRT alone had the worst survival of all cohorts, with 2- and 5-year OS rates of 50.4 and 35.7%. This was notably lower than patients treated with surgery followed by adjuvant therapy, which demonstrated 2- and 5-year OS rates of 71.3 and 54.4%. We found that the addition of IC to CRT was associated with little survival benefit, with 2- and 5-year OS rates of 54.8 and 37.0%, similar to patients treated with definitive CRT alone. As discussed previously, response to IC was strongly predictive of survival, and the lack of survival benefit when treated with definitive CRT may reflect selection for poor responders to IC. Further investigation may be warranted to compare survival outcomes of surgical resection versus definitive CRT among positive responders to IC. Salvage surgery had minimal impact on the OS of patients treated with IC and CRT, although the sample size for this group was likely too low to be able to detect any differences.

Two similar studies of sinonasal malignancies using the NCDB differ in their conclusions regarding IC.[11,19] Whereas Robin et al found a survival benefit with neoadjuvant therapy, Farrell et al found no survival benefit. Robin et al included all T stages and defined neoadjuvant therapy to include chemotherapy alone, radiotherapy alone, and chemoradiotherapy, whereas Farrell et al only included neoadjuvant chemotherapy and performed analyses with both all T stages and a subgroup of T3 and T4 tumors. In comparison, our study analyzed neoadjuvant chemotherapy in T4 tumors only, with a sizeable number of "unresectable" (T4b) cases. Additionally, whereas we separated our surgical cohorts based on whether they received adjuvant therapy, Farrell et al did not. Given the importance of adjuvant therapy in this population, we believe that our more granular analysis provides additional insights into the impact of IC in advanced tumors.

However, in both these studies and in Jafari et al, IC was not associated with an increased rate of negative margins. As Farrell et al highlighted, this may be biased as the decision to treat with IC likely depends on the surgeon's expectations of achieving negative margins. Specifically, a surgeon may be more likely to use IC to treat tumors with a lower likelihood of achieving negative margins. Of note, Robin et al found that neoadjuvant CRT was associated with an increased rate of negative margins.

One additional benefit of IC is the potential for orbit preservation. Motivated by trials for head and neck malignancies of other sites, such as for larynx preservation, small series have demonstrated the potential for IC to increase rates of orbit preservation.[27] Among these, Hanna et al first studied 46 patients with T3 or T4 tumors and noted at least a partial response to IC in 67% of patients. Despite orbital

invasion in 67% of patients, the orbit was preserved in 87% of patients.[22] A follow-up study by the same group affirmed these findings.[24] In a smaller study, Ock et al observed orbital preservation in 82% of the 17 patients with T4 disease.[23] In these studies, definitive treatments included both surgery and CRT. Larger sample sizes and additional cohorts are needed to directly compare the effect of IC on orbit preservation rates, and this information cannot be assessed through the NCDB data.

Predictors of treatment with IC included patients with T4b or higher N stage cancers. This is consistent with the use of IC among patients with advanced tumors, which may otherwise be unresectable, or for which negative margins were unlikely to be achieved. Interestingly, female sex and Black race were both identified as significant predictors of IC treatment despite controlling for tumor stage. Further study of patient and provider preferences regarding IC are needed to understand these predictors.

This study is limited primarily by its retrospective analysis of a coded database. As noted previously, IC was likely used in patients with more advanced or unresectable tumors, which was supported by our analysis of predictors of receiving IC. Similarly, patients receiving definitive CRT may have had poorer prognoses at baseline, although we were unable to assess if patients received CRT due to preference or poor surgical candidacy. Separately, although we excluded cases receiving palliative care, some patients may have received CRT without intent to cure, which also may have contributed to the worse OS rates observed with CRT. Additionally, we were unable to assess the treatment response to IC, which may have led to patients with favorable responses to IC being disproportionately treated with surgical resection. Lastly, the NCDB lacks information regarding key outcomes such as disease-free and recurrence-free survival.

Conclusion

In this retrospective, population-based study of locally advanced SNSCC, we demonstrated that IC followed by surgery was associated with an OS benefit at both 2 and 5 years, independent of the use of adjuvant therapy. This benefit was not seen when IC was followed by definitive chemoradiotherapy, which may reflect a selection for poor responders with worse baseline prognoses. We identified several predictors of receiving IC, including patients with T4b or higher N stage cancers. Further prospective trials are warranted to clarify the benefits and role of IC in SNSCC.

Previous Presentation
Portions of this work were presented as a talk at the 2023 Triological Society Combined Sections Meeting, Coronado, CA.

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Conflict of Interest
None declared.

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