


Efficacy of endoscopic sinus surgery for chronic rhinosinusitis following primary radiotherapy and concurrent chemotherapy for nasopharyngeal carcinoma

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Background: Chronic rhinosinusitis (CRS) is a downstream complication following radiotherapy or chemoradiation for nasopharyngeal carcinoma (NPC). Endoscopic sinus surgery (ESS) is an accepted therapy for medically refractory CRS, but its efficacy in addressing CRS symptoms in patients with previously irradiated NPC is unclear.

Methods: All patients at the Stanford Sinus Center with a history of radiation therapy or chemoradiation for NPC between 2006 and 2015 were reviewed. Patients without antecedent CRS prior to NPC treatment ($n = 26$) were retrospectively divided into 2 cohorts based on whether they developed postirradiation CRS and underwent ESS (surgical group, $n = 13$) or did not develop CRS (control, $n = 13$). Demographic and clinical characteristics were collected, and temporal changes in 22-item Sino-Nasal Outcome Test (SNOT-22) score were compared.

Results: The median time following primary irradiation to initial presentation was 6.8 and 6.5 years in the surgical and control groups, respectively. The surgical cohort had statistically greater baseline SNOT-22 scores than the control group (45 vs 14, $p = 0.0198$). At 6 to 12 months postoperatively, the surgical group demonstrated statistically significant and clinically meaningful improvements in SNOT-22 scores when compared to controls (15-point

decrease vs 0, $p = 0.0040$), ultimately resulting in similar SNOT-22 scores for both groups (28 vs 18, $p = 0.3687$). The rhinologic, extranasal, and ear/face subdomain scores of the surgical group were significantly greater than those of the control group preoperatively (rhinologic: $p = 0.0010$; extranasal: $p = 0.0179$; ear/face: $p = 0.0068$), but these disparities resolved postoperatively (rhinologic: $p = 0.1461$; extranasal: $p = 0.3131$; ear/face: $p = 0.3401$).

Conclusion: ESS appears to effectively manage recalcitrant CRS symptoms in patients previously treated with radiation therapy and concurrent chemotherapy for NPC.

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Key Words:

endoscopic sinus surgery; FESS; chronic rhinosinusitis; nasopharyngeal carcinoma; SNOT-22; quality of life; chronic disease

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Nasopharyngeal carcinoma (NPC) is one of the most common head and neck malignancies, with an

estimated 80,000 new patients diagnosed each year and 50,000 deaths yearly worldwide.¹ Chemoradiation is a mainstay of primary treatment, but irradiation of the nasopharynx and sinonasal cavity can lead to late sequelae, including sinusitis, oral mucositis, otitis media, epiphora, trismus, and osteoradionecrosis, that collectively have a detrimental impact on posttreatment quality of life.^{2,3} The advancements in NPC treatment and the prolongation of the 5-year life expectancy of these patients through updated chemoradiation protocols have made it increasingly necessary to maximize quality of life by minimizing treatment-related symptom burden.^{2,4}

Patients may suffer from acute sinusitis following exposure to lower doses of nasopharyngeal radiation

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(eg, 40 Gy) due to mucosal edema, damaged cilia, and thickened secretions.⁴ Higher doses (eg, 60 to 70 Gy) may cause more permanent changes to the nasal airway epithelium, including ischemic necrosis and sinonasal outflow tract scarring, which can ultimately result in chronic rhinosinusitis (CRS).⁴ Concurrent chemotherapy can heighten the risk for mucositis as well.⁵ As CRS is known to have a significant impact on the quality of life of patients in the general population, adequate control of sinonasal disease is necessary to optimize subjective patient outcomes in patients with a history of radiation therapy for NPC.⁶

Sinusitis in these patients may present with nasal obstruction, congestion, rhinorrhea, postnasal drip crusting, halitosis, or headaches.⁴ Affected patients typically initially undergo rounds of medical treatment with saline irrigations, oral antibiotics, and topical or oral steroids.⁷ Those who suffer from medically refractory CRS may elect to undergo sinus surgery to relieve obstruction and promote sinus drainage. While many studies have verified the various benefits on endoscopic sinus surgery (ESS) in the general population, the actual benefit of sinus surgery in a population of patients who have undergone chemoradiation remains unclear.^{8,9} There is concern that the tissue changes resulting from radiotherapy may impair postoperative healing and prevent appropriate mucosal and ciliary regeneration, reducing the potential benefits of ESS.⁹

We present our experience in treating CRS following radiotherapy or concurrent chemoradiation to provide insight into the efficacy of ESS in this patient population as reflected in the 22-item Sino-Nasal Outcome Test (SNOT-22), a validated, disease-specific questionnaire for CRS.

Materials and methods

Approval for data collection was obtained from the Stanford University Review Board. The Stanford Translational Research Integrated Database Environment (STRIDE) was utilized to obtain an initial cohort of potentially eligible patients by searching medical records for the International Classification of Disease ICD, 9th edition (ICD-9) code for malignant neoplasm of nasopharynx (147.0).¹⁰ In order to omit patients in whom development of CRS was clearly unrelated to NPC therapy (ie, CRS diagnosed prior to NPC), all patients with an ICD-9 code for chronic rhinosinusitis (473.x) recorded prior to diagnosis of malignant neoplasm of the nasopharynx (147.0) were excluded from the search results. Using this initial list of patients, STRIDE was then used to obtain the surgical cohort by searching for patients with an ICD-9 code for chronic rhinosinusitis (473.x) and Current Procedural Terminology (CPT) codes for maxillary antrostomy (31256 or 31267), ethmoidectomy (31254 or 31255), sphenoid sinusotomy (31287 or 31288), or frontal sinusotomy (31276). To attain an appropriate control group, the same ICD-9 code for malignant neoplasm of the nasopharynx was used, excluding any patients with a diagnosis of CRS (473.x) made after the diagnosis of NPC.

Patients were eligible for the study if they were referred to the Stanford Sinus Center between January 1, 2006, and October 1, 2015, were 18 years or older at time of initial clinic visit, had radiographic and pathologic confirmation of NPC, and had available baseline and 6 to 12-month follow-up SNOT-22 data. All patients with CRS met the Consensus Criteria for the diagnosis of CRS proposed by the American Academy of Otolaryngology–Head and Neck Surgery 2015 Clinical Practice Guidelines. Patients who underwent ESS for CRS in the years following radiation for NPC were included in the surgical group. Those who completed prior radiation treatment for NPC but had no subsequent diagnosis of CRS based on review of medical records, and thus never received ESS, were included in the nonsurgical group (an unmatched cohort). Patients were ineligible for the study if they had a history of CRS prior to radiotherapy or if they lacked baseline or follow-up SNOT-22 data.

NPC patients who have completed radiotherapy are followed in our clinic for tumor surveillance, usually on a rotating basis with other oncology providers, or for management of posttreatment complications, such as CRS or rhinitis. Patients without CRS are also referred for evaluation of non-CRS related effects of treatment, such as osteoradionecrosis requiring endoscopic endonasal debridement. Postirradiation patients without CRS are typically treated with nasal saline rinses for symptomatic relief of mucosal irritation and crusting. Patients diagnosed with CRS are initially managed medically with an escalating regimen consisting of saline rinses, oral antibiotics, and oral and/or topical steroids. Those who do not sufficiently improve with medical therapy alone are considered potential surgical candidates.

Data extraction

Patient demographics were extracted from electronic medical records. Data relevant to NPC diagnosis and management was collected, including T stage, number of years from radiation treatment, total radiation dose applied, and use of concurrent chemotherapy. Additional data relating to past medical history was gathered, including a history of asthma, allergies (verified by skin prick or radioallergen sorbent test), obstructive sleep apnea, depression, and smoking. For those patients undergoing surgery, preoperative computed tomography scans were collected and analyzed using the Lund-Mackay (LM) scoring system.¹¹ Intraoperative findings were gathered from the official operative reports and intraoperative culture results.

The SNOT-22 is a validated, disease-specific questionnaire that assesses sinonasal symptoms.¹² This questionnaire evaluates for the presence and severity of 22 signs and symptoms associated with sinusitis, with a total score ranging from 0 for completely asymptomatic to 110 for the most severe disease state. The mean score in patients without sinonasal disease is 9.3 (95% confidence interval [CI], 7.5 to 11.1), and an 8.9-point change in the total score

following intervention is deemed clinically meaningful (minimal clinically important difference [MCID]). The questionnaire can be divided into 5 subdomains that have been shown to predict treatment modality: rhinologic, extranasal, ear/face, psychological, and sleep.¹³ SNOT-22 scores were obtained preoperatively and 6 to 12 months postoperatively in the postradiotherapy, ESS surgical group. In order to provide parallel time points for SNOT-22 score comparison, scores in the nonsurgical group were collected at the initial clinic visit and 6 to 12 months afterward during routine follow-up for tumor surveillance. The absolute and change in total and individual subdomain SNOT-22 scores at the above time points were calculated.

Statistical analysis

Statistical analysis was performed using Prism, version 7.0 (GraphPad Software, La Jolla, CA). The baseline characteristics, comorbidities, complications of radiation, NPC characteristics, and symptom scores were compared across treatment groups using categorical and quantitative statistical tests, when appropriate. Given the sample sizes, Fisher's exact test was used rather than chi square testing for the categorical variables. All data was treated as nonparametric. A standard alpha level 0.05 was used to determine significance for all calculations.

Results

Baseline characteristics

Twenty-six patients met inclusion criteria (Table 1). Of these, 13 (50%) underwent ESS for CRS and were included in the surgical group, while the remaining 13 did not and comprised the nonsurgical group. In total, 11 (42.3%) patients were female with a mean overall age of 55.6 years. The average time from radiation to initial SNOT-22 collected was 6.8 and 6.5 years in the surgical and nonsurgical groups, respectively.

The surgical and nonsurgical groups had similar distributions of age (43.8 vs 46.3, $p = 0.3622$) and gender (30.8% vs 53.9% female, $p = 0.4283$), respectively. Both groups had comparable prevalences of comorbidities and possible complications of treatment, including asthma ($p = 0.4800$), allergies ($p = 1.000$), depression ($p = 0.3217$), otitis media ($p = 0.6951$), osteoradionecrosis ($p = 1.000$), and history of smoking ($p = 0.0730$). T stage could not clearly be determined in 4 of the 26 patients from examination of medical records. Of the patients who did have T stage data available, there was no significant difference in the incidence of low (1 and 2) T stage ($p = 0.0968$) or high (3 and 4) T stage ($p = 0.1152$) between the 2 groups. Similar to the findings of other studies, there was a trend toward significance for the incidence of CRS with higher T stage ($p = 0.0805$).⁴ The surgical group was treated with a median radiation dose of 70 Gy (range, 66 to 72 Gy), compared to a median of 66 Gy (range, 60 to 70 Gy) in the control

group ($p = 0.6699$). An equal number of patients (12/13) in each group underwent concurrent chemotherapy treatment ($p = 1.000$). Median preoperative Lund-Mackay score in the surgical group was 11 (range, 2 to 17).

All surgeries were performed on an outpatient basis and were tailored to the extent of radiologic disease (Table 2). The most common intraoperative findings were scarring ($n = 6$), crusting ($n = 8$), polypoid change ($n = 5$), and purulence ($n = 10$). *Staphylococcus aureus* was the most commonly cultured bacterial species (7/8 cultures sent), and 2 of 4 patients tested had positive intraoperative fungal cultures. No intraoperative or immediate postoperative surgical complications related to the ESS procedures occurred, and no patients underwent additional radiation therapy or revision ESS during the follow-up period.

Baseline CRS symptom severity

At baseline, the surgical cohort had statistically higher total SNOT-22 scores than the nonsurgical group (45 vs 14, $p = 0.0198$, Fig. 1, Table 3). Comparison of baseline subdomain scores showed that the surgical group had greater rhinologic ($p = 0.0010$), extranasal ($p = 0.0179$), and ear/face ($p = 0.0068$) scores than the nonsurgical group. Psychological ($p = 0.2126$) and sleep ($p = 0.2126$) scores did not significantly differ between the 2 groups.

Effect of sinus surgery on CRS symptoms

The surgical group achieved a statistically ($p = 0.0171$) significant improvement in SNOT-22 scores after surgery, with a decrease in the median score from a baseline of 45 to 28 in the 6-month to 12-month follow-up period after surgery, which also exceeds the MCID for the SNOT-22 (Table 4). During the same time interval, total SNOT-22 scores in the nonsurgical group increased from 14 to 18, which was statistically insignificant ($p = 0.7476$) and did not meet the MCID. In terms of subdomain scores, the surgical group demonstrated a statistically significant improvement in the rhinologic subdomain ($p = 0.0059$), while the nonsurgical group did not show a statistically significant improvement in any subdomain scores at follow-up. Following these changes, the initial observed difference in the total SNOT-22 score between the 2 groups lost significance ($p = 0.3687$). Similarly, the differences in the baseline rhinologic, extranasal, and ear/face subdomain scores between the 2 groups resolved ($p = 0.1461$, 0.3131, and 0.3401, respectively).

The difference in the change in the total SNOT-22 scores between the groups at the different time points was statistically significant ($p = 0.0040$). For the changes in subdomain scores, only the rhinologic component achieved significance (3-point decrease in the surgical group and 1-point increase in the nonsurgical group, $p = 0.0047$). Although the surgical group demonstrated postoperative improvements in the extranasal, sleep, and rhinologic subdomain scores, and the nonsurgical group did not, these differences were not

TABLE 1. Baseline patient characteristics*

Characteristic	Surgical (n = 13)	Nonsurgical (n = 13)	p
Age completed RT, median	43.8	46.3	0.3622
Gender, n (% female)	4 (30.8)	7 (53.9)	0.4283
Comorbidities/complications of RT, n (%)			
Asthma	2 (15.4)	0	0.4800
Chronic obstructive pulmonary disease	0	0	1.000
Obstructive sleep apnea	1 (7.7)	0	1.000
Allergy (skin prick or RAST)	0	0	1.000
Depression	4 (30.8)	1 (7.7)	0.3217
CRS	13 (100)	0	<0.0001
Choanal atresia	0	0	1.000
Epiphora	1 (7.7)	0	1.000
Otitis media	8 (61.5)	6 (53.9)	0.6951
Osteoradionecrosis	5 (38.5)	4 (30.8)	1.000
History of smoking, n (%)	6 (46.2)	1 (10.0)	0.0730
Radiation dose (Gy), median [range]	70 [66 to 72]	66 [60 to 70]	0.6699
Concurrent chemotherapy, n (%)	12 (92.3)	12 (92.3)	1.000
T stage, n (%)			
1, 2	2 (15.4)	7 (53.8)	0.0968
3, 4	9 (69.2)	4 (30.8)	0.1152
Unknown	2 (15.4)	2 (15.4)	1.000

*Demographics and baseline characteristics of patients comprising the surgical and nonsurgical CRS groups, with corresponding p values in the right column; bold p value is significant. T stage for NPC was divided into low (1 or 2) and high (3 or 4).

CRS = chronic rhinosinusitis; NPC = nasopharyngeal carcinoma; RAST = radioallergosorbent assay; RT = radiation therapy.

TABLE 2. Sinusotomies performed in surgical cohort of 13 patients

Sinus	Right	Left
Maxillary, n	11	13
Anterior ethmoid, n	11	11
Posterior ethmoid, n	6	7
Sphenoid, n	5	7
Frontal, n	3	5

statistically significant ($p = 0.0861$, 0.0670 , and 0.0635 , respectively).

Discussion

Radiotherapy with or without chemotherapy is the primary treatment modality for NPC, but it often induces unintended sinonasal morbidity that significantly harms quality of life and necessitates long-term care. Although the

long-term effects of chemotherapy on the sinonasal mucosa have not been clearly delineated, radiation has been shown to trigger pathologic changes in the macroscopic and ultrastructural features of sinonasal cells and glands, including altered mucociliary function, adhesions, prolonged crusting, and poor wound healing.⁹ Prior studies have illustrated the efficacy of saline irrigation in the management of typical sinonasal symptoms in this group, but a subset of patients may develop acute or chronic rhinosinusitis and require more aggressive management.^{7,14} Surgery is a feasible option when medical therapies fail to adequately control symptoms of CRS, but the efficacy of ESS in reducing CRS-related symptoms is still uncertain.

Appropriate treatment of NPC requires irradiation of the posterior nasal cavity, sphenoid sinuses, and ethmoid sinuses.⁷ Histologically, post-irradiated sinonasal mucosa shows evidence of epithelial metaplasia and sloughing, reduced cytoplasmic volume, collagen deposition in the lamina propria, ciliary dysmorphism, and ciliary loss.^{3,9,15} Saccharin transit time is delayed following irradiation, indicating disturbance of mucociliary clearance.¹⁶ These pathologic findings remain evident even decades after

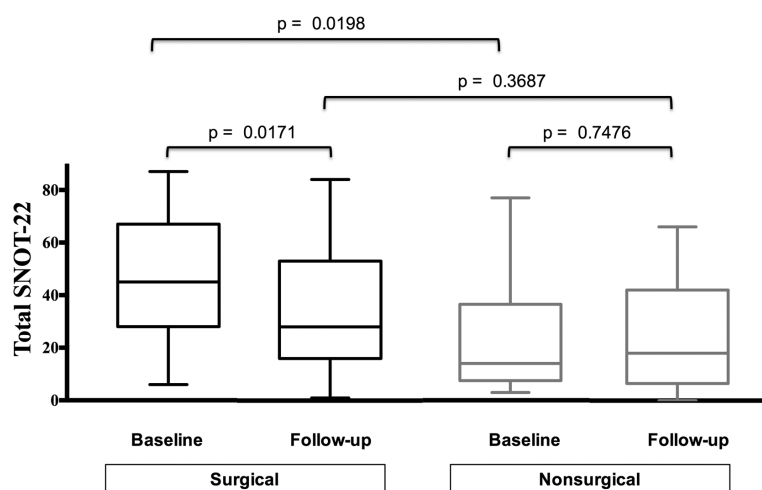


FIGURE 1. Absolute preoperative and postoperative SNOT-22 scores. Box-and-whisker plots of the baseline and follow-up total SNOT-22 scores for the surgical and control groups. SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 3. Absolute total and subdomain SNOT-22 scores at baseline and 6-month to 12-month follow-up for the surgical and nonsurgical groups*

SNOT-22 total and subdomains	SNOT-22 scores		p
	Surgical	Nonsurgical	
Baseline (median)			
Total	45	14	0.0198
Rhinologic	17	4	0.0010
Extranasal	7	2	0.0179
Ear face	9	3	0.0068
Sleep	10	3	0.2126
Psychological	12	5	0.2126
6 to 12 months postsurgery (median)			
Total	28	18	0.3687
Rhinologic	12	6	0.1461
Extranasal	6	3	0.3131
Ear face	6	6	0.3401
Sleep	4	7	0.7864
Psychological	3	2	0.8683

*Bold p values are significant.
SNOT-22 = 22-item Sino-Nasal Outcome Test.

radiotherapy, and may be predisposing factors that lead to the development of CRS.⁹ The addition of concurrent chemotherapy to radiotherapy treatment has been thought to further hinder sinonasal mucosal function, but the long-term histological effects of chemotherapy on sinonasal mucosa independent of radiation therapy have

not been well studied. Studies of radiographic changes in the paranasal sinuses after chemoradiation for NPC suggest that mucosal thickening may be observed for more prolonged periods (>30 months) when patients receive chemoradiation compared to radiation therapy alone.¹⁷

Given these known deleterious effects of treatment for NPC, there is concern that sinonasal mucosa may be irreversibly damaged. If true, then surgery may not be able to overcome the effects of these pathologic changes or provide adequate symptomatic relief. However, ESS has proven benefits in patients with cystic fibrosis, primary ciliary dyskinesia, and other ciliary disorders, indicating that sinonasal disease can improve despite underlying structural and functional liabilities.^{18,19} One study in a group of patients who underwent radiotherapy for NPC, additionally demonstrated improvements in the ultrastructural properties of sinonasal mucosa, including increased ciliary density and reduced saccharin transit time, following ESS for CRS.¹⁸ Thus, the facilitation of sinus drainage and improved access for topical therapy following ESS may facilitate recovery of microscopic properties of the sinus mucosa, with improved mucociliary function.¹⁸

Our nonsurgical group represents a suitable control group because the patients underwent radiation therapy but did not develop CRS. The similarity in baseline characteristics between the 2 groups additionally suggests that it was CRS, rather than another sinonasal comorbidity, that contributed to the higher SNOT-22 scores in the surgical group. While normative SNOT-22 scores have been established for the general population and for patients with CRS, they have not been determined for patients following radiation therapy for NPC.²⁰ Based on a classification scheme that stratifies SNOT-22 scores in patients with CRS by severity of overall symptom burden, the control group in this study would be classified into the mild category (mild range: 8 to 20 points), and the surgical group into the moderate category (moderate range: 20 to 50 points).²¹ Surgical

TABLE 4. Comparison of the total and subdomain SNOT-22 scores within each group between baseline and 6-month follow-up*

SNOT-22 total/subdomain	Surgical			Nonsurgical		
	Baseline SNOT-22 score (preoperative)	6-month follow-up SNOT-22 score (postoperative)	<i>p</i>	Baseline SNOT-22 score	6 month follow-up SNOT-22 score	<i>p</i>
Total	45	28	0.0171	14	18	0.7476
Rhinologic	17	12	0.0059	4	6	0.3379
Extranasal	7	6	0.1406	2	3	0.5039
Ear/face	9	6	0.4346	3	6	0.1602
Sleep	10	4	0.1484	3	7	0.9590
Psychological	12	3	0.0645	5	2	0.2383

*Bold *p* values are significant.

SNOT-22 = 22-item Sino-Nasal Outcome Test.

treatment of CRS resulted in a statistically significant and clinically meaningful improvement in the total SNOT-22, indicated by a greater than 8.9-point decrease in the total score.¹² In contrast, the control group experienced no change in overall symptom burden. The observed postsurgical improvement normalized the CRS/surgical group to a similar level of symptoms as the control group of NPC patients without CRS. These data suggest that ESS appears to be beneficial in the management of CRS-related symptoms in patients with prior exposure to radiotherapy or concurrent chemoradiation for NPC. Rudmik et al.²² showed that patients who undergo ESS with a preoperative SNOT-22 score above 30 demonstrate a 45% improvement in SNOT-22 scores following ESS. While our patients did not quite experience such an improvement (33.3%), the long-term effects of radiotherapy may have prevented additional resolution of CRS-related symptoms.

Given that NPC patients often suffer from multiple post-treatment comorbidities, the factors that prompt them to elect to pursue ESS are unclear. At baseline, patients in the surgical group suffered from more severe symptoms within the rhinologic (need to blow nose, sneezing, runny nose, thick nasal discharge, nasal obstruction, and loss of smell or taste), extranasal (cough, postnasal discharge, and thick nasal discharge), and ear/face (sneezing, ear fullness, dizziness, ear pain, and facial pain or pressure) subdomains. These specific symptoms may represent driving factors in the decision to pursue sinus surgery in this population. At follow-up, these subdomain scores closely matched those in the control group, suggesting that ESS is effective in reducing the symptoms that most significantly hamper sinonasal quality of life. Given the relatively limited number of patients, this study may have had insufficient power to detect relative improvements in all subdomain scores between the 2 groups.

The development of CRS following radiation is associated with more advanced T stage, tumor invasion into the nasal cavity, and failure to regularly irrigate with saline

following radiation treatment.⁴ The incidence of sinusitis, moreover, has been shown to increase during the first 9 months following radiotherapy, and then stabilize after 1 year.⁴ Because the time from radiotherapy to baseline SNOT-22 in our study was over 6 years, our findings assume that control group patients were medically stable with respect to their risk of developing radiation-associated CRS.


As with any retrospective review, there are limitations to this study, including sampling and survivorship bias. Due to variability in record keeping over the years, the medical management of CRS, such as frequency of nasal irrigations, could not be clearly assessed in these patients. Only subjective, and not objective, improvements in sinonasal disease were thus assessed, as prior studies have already illustrated the objective benefit of ESS for CRS in this patient population.^{15,18} The identical use of chemotherapy treatment between the 2 groups also did not allow for an independent comparison of the effects of chemotherapy on sinonasal symptoms. Although no patients were diagnosed with CRS prior to radiotherapy, the baseline SNOT-22 score prior to radiation was not known for these patients. Thus, the trend of SNOT-22 scores during and immediately following radiation is unclear from this data but would be an interesting focus of future studies. The longer-term outcomes of ESS for CRS in this population also require further evaluation.

We considered performing a comparative analysis with patients who underwent treatment for NPC and subsequently developed CRS, but did not undergo ESS. However, only 3 eligible patients were identified; therefore, there was an insufficient number of patients to pursue this additional analysis. A multicenter study would likely be necessary to recruit sufficient patients for this type of comparison.

Additionally, while this study demonstrates the benefits of ESS in the post-irradiated NPC population, offering surgery for these patients should be approached with

care and prudence. No patients in our study experienced intraoperative or postoperative complications, but in 1 published case series of 6 patients, 3 experienced complications, slow healing, or recurrence of symptoms.²³ Radiation may result in friable mucosa, bony dehiscence, and altered surgical landmarks, any of which may complicate ESS.^{16,23} The pathologic changes in the mucosa may delay healing and therefore require meticulous surgery and stringent, regular postoperative care.

Conclusion

Patients who undergo radiotherapy or concurrent chemoradiation for nasopharyngeal carcinoma may develop CRS, among other posttreatment complications. Our findings suggest that in those who fail appropriate medical therapy for CRS, ESS may effectively reduce CRS-related symptoms in a durable manner. ESS is therefore a rational treatment option to consider for radiation-associated CRS following treatment for NPC. 

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