Corticosteroid responsive olfactory dysfunction in chronic rhinosinusitis: what does it mean?

Kaete A. Archer[1], Jess C. Mace[2], Timothy L. Smith[2], Zachary M. Soler[3], Rodney J. Schlosser[3], Jeremiah A. Alt[4], Jose Mattos[5], Vijay R. Ramakrishnan[1]

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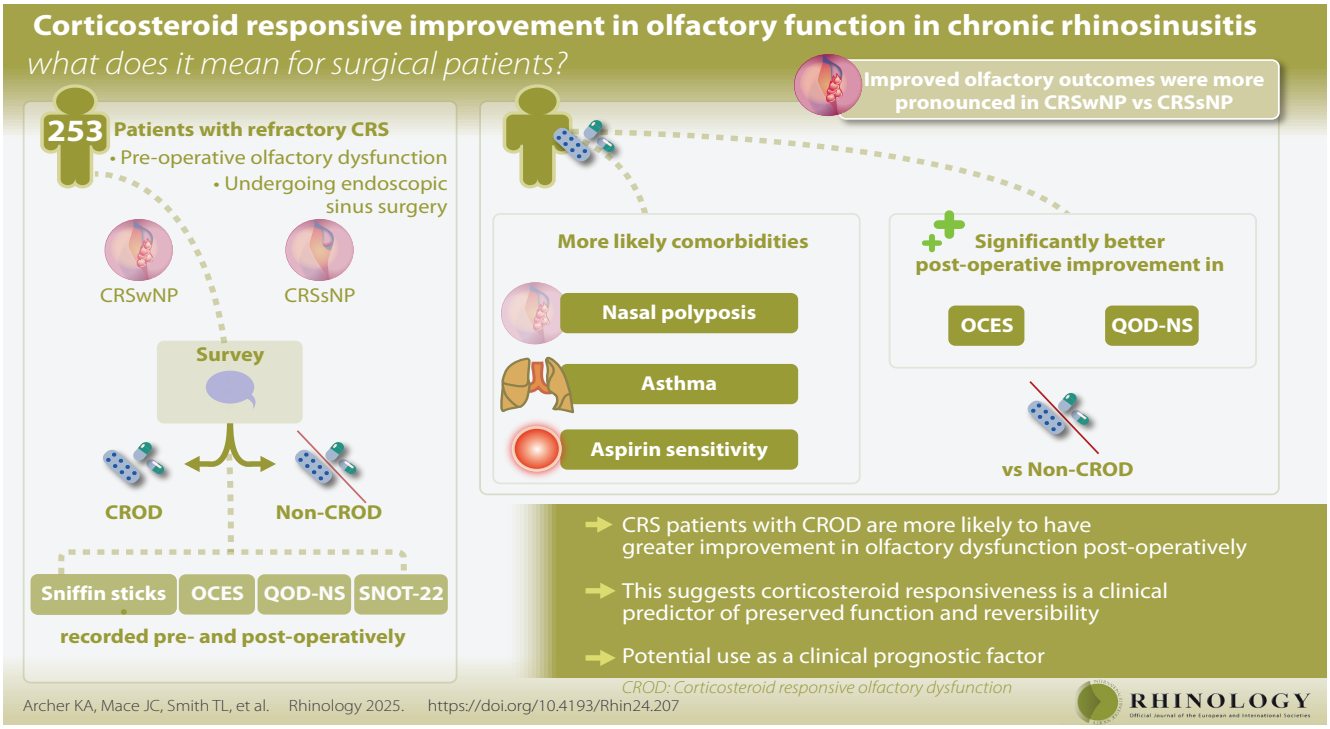

Abstract

Background: In the setting of chronic rhinosinusitis (CRS), olfactory improvement with corticosteroids suggests reversibility and preserved function. While self-rated olfactory function does not replace psychophysical measures of olfactory function, our goal is to investigate if self-reported pre-operative corticosteroid-responsive olfactory dysfunction (CROD) is a predictor of post-operative olfactory improvement in patients with CRS undergoing sinus surgery.

Methodology: We performed a prospective, observational study of patients with refractory CRS with and without nasal polyposis and pre-operative olfactory dysfunction undergoing sinus surgery. Patients were characterized into corticosteroid-responsive and non-corticosteroid-responsive based on a survey response. Patient outcome measures for Sniffin Sticks, Olfactory Cleft Endoscopy Score (OCES), Questionnaire of Olfactory Disorders (QOD-NS), and Sino-nasal Outcomes Test (SNOT-22) were recorded pre- and post-operatively.

Results: A total of 253 participants were included. Patients with CROD were more likely to have comorbid nasal polyposis, asthma, and aspirin sensitivity. Patients with CROD had significantly better post-operative improvement in OCES total scores and QOD-NS total scores compared to patients without CROD.

Conclusions: In conclusion, patients with CRS and CROD are more likely to have a greater improvement in olfactory dysfunction post-operatively by several measures of olfactory outcomes. This suggests that corticosteroid responsiveness is a clinical predictor of preserved function and reversibility and can be used as a simple clinical prognostic factor.

Key words: rhinosinusitis, olfaction disorder, outcome assessment, quality of life, self report

Introduction

Although common, olfactory dysfunction (OD) is not a universal symptom of chronic rhinosinusitis (CRS), affecting 78% of patients with CRS and 94% of patients with CRS with nasal polyposis (CRSwNP) [1]. Despite this prevalence, the mechanisms of OD in CRS are incompletely understood. A sensorineural contribution may exist from decreased neuronal function, a conductive problem may result from loss of odorant delivery to the olfactory sensory neurons, and a reduction in the olfactory bulb volume may occur [2]. The basis is thought to be the inflammatory processes of CRS, suggesting that corticosteroids should improve CRS related OD (CRS-OD); however, this is not evident for all patients [3]. "Reversibility" suggests preservation of underlying function without severe disease progression to an irreversible pathologic state.

Treatment for CRS includes both medical and surgical management. The CRS endotype classification can guide medical management as type 2 and non-type 2 pathways have different sensitivities to steroid treatment. Patients with CRSwNP are more likely to have type 2 inflammation and have success with corticosteroid therapy, similar to patients with asthma [4]. Endoscopic sinus surgery (ESS) is offered for medically refractive CRS. Because of the heterogeneity in CRS symptoms, impacts on quality-of-life and underlying disease pathophysiology, surgeons are often stymied from precise counseling for expected surgical outcomes. Specifically, for a patient with CRS-OD, the expected improvement in OD is uncertain. Prior investigation has shown that ESS improves measures of olfaction to varying degrees [5], however, patients are frequently counseled that OD may not improve, and may even worsen, postoperatively.

Expectations for improvement in specific symptoms is important in the decision-making process for ESS. For patients with CRS-OD, clinical predictors of OD improvement would be helpful for patient counseling. Bogdanov et al. reported that patients with CRSwNP who did not respond to preoperative systemic steroids did not respond to subsequent ESS, in terms of olfactory outcomes [3]. We hypothesized that patients who had improvement in CRS-OD with oral corticosteroids should have better postoperative olfactory outcomes compared to patients who did not improve with oral steroids, as ESS not only addresses the suspected underlying inflammatory process but also improves topical steroid delivery to the nose, olfactory cleft and sinuses. Our goal is to investigate the frequency of self-reported preoperative corticosteroid responsive OD (CROD), and if this clinical observation predicts postoperative olfactory improvement in patients with CRS undergoing ESS.

Materials and methods

Sample population

A prospective, observational study of adult patients undergoing ESS for medically refractory CRS was completed. Study participants were recruited from academic, rhinology care facilities in the United States including: Oregon Health & Science University (Portland, OR), the Medical University of South Carolina (Charleston, SC), the University of Utah (Salt Lake City, UT), the University of Colorado (Aurora, CO), and the University of Virginia (Charlottesville, VA). The Institutional Review Board at each performance site provided regulatory review and oversight for study protocols.

Subjects were recruited between November 2016 and February 2020 with confirmed diagnoses of symptomatic CRS with nasal polyposis (CRSwNP), or without nasal polyposis (CRSsNP), from a fellowship-trained rhinologist following criteria established by current practice guidelines [6]. Participants were screened for completion of prior appropriate medical therapy for symptoms of CRS consisting of, but not limited to, saline irrigations and topical corticosteroid sprays at least QD, broad-spectrum or culture-directed antibiotics, and oral corticosteroid therapy. Participants elected to pursue ESS following patient counseling for treatment options provide by the enrolling clinician/surgeon. All study participants provided written, informed consent after baseline enrollment meetings to ensure voluntary participation (Figure 1).

Exclusion criteria

Due to possible disparities in treatment approach and postoperative management, study participants with comorbid pulmonary ciliary dyskinesia/cystic fibrosis or immunodeficiency were excluded from final cohort selection, regardless of comorbid disease status. Additional exclusions included subjects who declined to complete preoperative olfactory assessments or provide responses to anchor questions of corticosteroid responsiveness. Patients with neuropsychiatric diagnoses, such as dementia or traumatic brain injury, were excluded while unrecognized mild cognitive dysfunction or preclinical dementia disorders were not screened for exclusion. The study was completed prior to the wide availability and adoption of biologic therapies for CRSwNP.

Endoscopic sinus surgery

Surgical approach was determined after review of preoperative computed tomography (CT) image findings, endoscopic examinations, and consideration of patient history and comorbidity. Surgical intervention consisted of outpatient primary or revision ESS, under general anesthesia, potentially involving maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, and frontal sinusotomy for optimal sinonasal ventilation. Inferior turbinate reduction and/or septoplasty was also completed, if indicated. Patients were prescribed postoperative oral corticosteroid tapers or broad-spectrum antibiotics, as indicated, to facilitate postoperative healing, and further topical saline and corticosteroid therapies for maintenance.

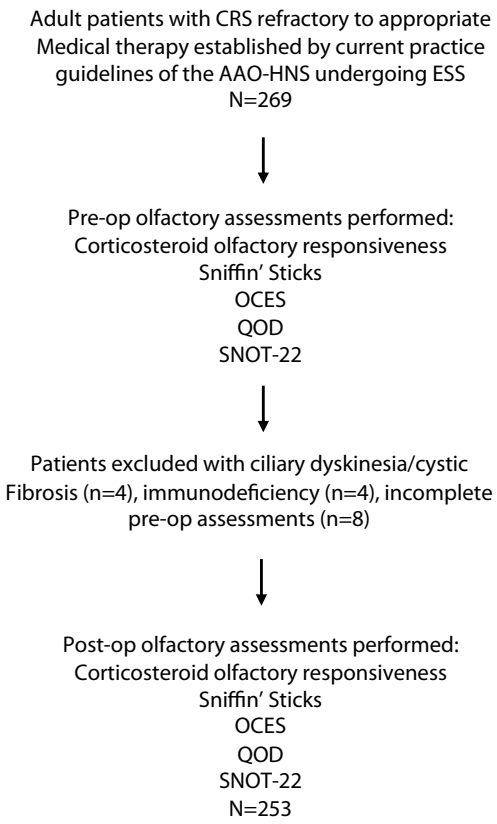

Figure 1. Prospective, observational study design of refractory CRS patients. ESS, endoscopic sinus surgery. OCES, Olfactory Cleft Endoscopy Score. QOD-NS, Questionnaire of Olfactory Disorders. SNOT-22, sinonasal outcome test.

Corticosteroid responsiveness

While several patient-reported outcome measures exist to assess olfactory function, there is not a widely available, standardized, clinical definition that defines corticosteroid responsiveness in CRS. The primary independent exposure of interest to this investigation was defined using an anchor-based question as part of preoperative evaluation/surveys for which study respondents were asked to recall "*Does your sense of smell improve when you take oral steroids*?" Predetermined survey response options of "*Yes*"/"*No*"/"*Don't know/unknown*" directed the categorization of patient-based experiences with CROD.

Additional clinical measures of disease severity

Sinonasal disease severity was evaluated using standard clinical diagnostic procedures including bilateral, rigid endoscopy and high-resolution CT. Diagnostic imaging was quantified by each enrolling physician using the Lund-Kennedy (LK) staging system (range: 0-20) and Lund-Mackay staging system (range: 0-24), respectively [7,8].

Pathology of the olfactory cleft (OC) was evaluated simultaneously during bilateral endoscopy examinations and staged by each enrolling clinician/surgeon using the Olfactory Cleft Endoscopy Score (OCES)[9]. The OCES quantifies the severity of pathologic attributes in the OC including: discharge, nasal polyposis, edema, crusting, and scarring (range: 0-20). Higher summarized OCEStotal scores also reflect worse overall disease. Postoperative LK and OCES measures were collected on participants approximately 6-months after ESS during routine clinical follow-up appointments. Postoperative CT imaging was not collected due to elevated radiation exposure risk and divergence from routine standard of care. Bilateral visualization and staging were not possible for some subjects with severe preoperative septal deviation or polyposis.

Patient outcome measures

For the primary outcome, bilateral olfactory function was measured using Sniffin' Sticks (Burghart Messtechnik, Wedel, Germany). Olfactory threshold (T), discrimination (D), and identification (I) scores were recorded, as well as a composite TDI total score whereas higher scores reflect better olfactory function. The summarized total score is interpreted by a diagnostic category of anosmia (range: 1-15), hyposmia (range: 16-30), and normosmia (range: 31-48) [10-12]. Olfactory testing was completed both preoperatively and during post-treatment follow-up appointments approximately 6-months after ESS. The Bogdanov et al. definition of the minimal clinically important difference (MCID) of a post-treatment change of >6.0 points was adopted; however, this MCID value has not been validated in a CRS population [3]. Study participants also completed two surveys designed to evaluate the perceived impact of OD on respondent's daily function. First, the Questionnaire of Olfactory Disorders contains 17 negatively termed statements (QOD-NS) using Likert scale responses from 0 ("Disagree") to 3 ("Agree"). Higher summarized total scores (range: 0-51) represent worse overall OD [13]. Previous literature employing the QOD-NS within an outpatient population with smell and taste disorders has previously identified total scores of 12.5 or higher to confirm a diagnosis of symptomatic OD [14]. Postoperative improvements of at least 5.2 points have been defined as a MCID in patients with CRS undergoing ESS [15]. Case subjects were asked to complete the QOD-NS both preoperatively and ~6 months postoperatively either during clinical follow-up or using surveys mailed to study participants at regular intervals.

Second, the 22-question SinoNasal Outcomes Test (SNOT-22) is a validated survey designed to quantify the severity of symptoms associated with sinonasal disorders using Likert scale (item score range: 0-5) response options (©Washington University, St. Louis, MO) [16]. Validated factor analysis of SNOT-22 scores in a patient population with CRS identified symptom subdomains which can be categorized and summarized into: rhinologic (range: 0-30), extranasal rhinologic (range: 0-15), ear and/or facial (range: 0-25), psychological dysfunction (range: 0-35), and sleep dysfunction (range: 0-25) (17). One specific survey question of

Table 1. Omnibus comparisons of preoperative measures between study participants with and without corticosteroid responsive olfactory dysfunction within CRS (n=253).

Demographics	CROD Categories			Test statistics	Omnibus p-value
	CROD (n=70)	Don't know / Unknown (n=124)	on-CROD (n=59)		
Age at enrollment (years) Mean±SD	49.6 ± 14.7	46.2 ± 16.3	52.6 ± 16.1	F=3.47	**0.033**
Male N (%)	33 (47.1%)	64 (51.6%)	32 (54.2%)	χ2=0.68	0.711
Female	37 (52.9%)	60 (48.4%)	27 (45.8%)		
White/Caucasian	66 (94.3%)	104 (83.9%)	52 (88.1%)	χ2=4.53	0.104
African American	4 (5.7%)	15 (12.1%)	4 (6.8%)	χ2=2.70	0.259
Asian	0 (0.0%)	3 (2.4%)	1 (1.7%)	χ2=1.69	0.430
American Indian/Alaska native	0 (0.0%)	2 (1.6%)	1 (1.7%)	χ2=1.16	0.559
Hispanic/Latino ethnicity	5 (7.1%)	8 (6.5%)	3 (5.1%)	χ2=0.24	0.889
				Disease characteristics and comorbidity	
Nasal polyposis	49 (70%)	55 (44.4%)	31 (52.5%)	χ2=11.84	**0.003**
Septal deviation	23 (32.9%)	44 (35.5%)	21 (35.6%)	χ2=0.16	0.924
Previous sinus surgery / ESS	38 (54.3%)	45 (36.3%)	37 (62.7%)	χ2=13.02	**0.001**
Asthma	43 (61.4%)	49 (39.5%)	31 (52.5%)	χ2=9.08	**0.011**
ASA sensitivity / AERD	21 (30.0%)	8 (6.5%)	11 (18.6%)	χ2=19.10	**<0.001**
Migraine	13 (18.6%)	18 (14.5%)	17 (28.8%)	χ2=5.33	0.070
Diabetes mellitus (Type I/II)	4 (5.7%)	8 (6.5%)	5 (8.5%)	χ2=0.42	0.812
Depression	16 (22.9%)	36 (29.0%)	20 (33.9%)	χ2=1.96	0.376
Anxiety	17 (24.3%)	32 (25.8%)	13 (22.0%)	χ2=0.31	0.856
Obstructive sleep apnea	11 (15.7%)	31 (25.0%)	13 (22.0%)	χ2=2.27	0.321
Smoking / tobacco use (current)	1 (1.4%)	7 (5.6%)	2 (3.4%)	χ2=2.16	0.340
Smoking / tobacco use (former)	21 (30.0%)	23 (18.5%)	22 (37.3%)	χ2=8.05	**0.018**
Alcohol use (current)	40 (57.1%)	60 (48.4%)	25 (42.4%)	χ2=2.90	0.235
Alcohol use (former)	4 (5.7%)	12 (9.7%)	9 (15.3%)	χ2=3.28	0.194
Allergic rhinitis	37 (52.9%)	60 (48.4%)	35 (59.3%)	χ2=1.93	0.380
Positive allergy test (mRast/skin prick)	35 (50.0%)	62 (50.0%)	37 (62.7%)	χ2=2.94	0.231
GERD	19 (27.1%)	31 (25.0%)	29 (49.2%)	χ2=11.61	**0.003**
Autoimmune disease, NOS	6 (8.6%)	11 (8.9%)	11 (18.6%)	χ2=4.49	0.106
Oral corticosteroid dependency	7 (10.0%)	10 (8.1%)	2 (3.4%)	χ2=2.12	0.346
				Measures of disease severity and outcome: Median [IQR]	
Lund-Kennedy endoscopy score	9.0 [6.0]	6.0 [4.0]	7.0 [6.0]	KW=16.14	**<0.001**
Lund-Mackay CT score	16.0 [10.0]	13.0 [8.75]	14.0 [8.0]	KW=8.39	**0.015**
OCES total score	6.0 [8.0]	2.0 [4.75]	4.0 [8.0]	KW=17.27	**<0.001**
Sniffin' Sticks total score	19.0 [18.81]	26.0 [15.25]	23.0 [18.25]	KW=11.89	**0.003**
-Threshold score	1.0 [4.75]	4.5 [5.75]	2.5 [4.75]	KW=11.40	**0.003**
-Discrimination score	8.0 [7.0]	10.0 [5.0]	8.0 [7.0]	KW=10.92	**0.004**
-Identification score	8.0 [8.0]	11.0 [6.0]	9.0 [9.0]	KW=8.57	**0.014**
Diagnosis: Normosmia	14 (20.0%)	39 (31.5%)	10 (16.9%)	χ2=5.74	0.057
Diagnosis: Hyposmia	23 (32.9%)	58 (46.8%)	28 (47.5%)	χ2=4.13	0.127
Diagnosis: Anosmia	33 (47.1%)	27 (21.8%)	21 (35.6%)	χ2=13.68	**0.001**
QOD-NS total score	18.0 [19.0]	10.0 [16.0]	12.0 [19.0]	KW=21.27	**<0.001**
-Normal olfaction (<12.5)	21 (30.0%)	76 (61.3%)	32 (54.2%)	χ2=17.85	**<0.001**
-Abnormal olfaction (>12.5)	49 (70.0%)	48 (38.7%)	27 (45.8%)		
SNOT-22 total score	48.5 ± 19.5	48.3 ± 20.5	48.6 ± 23.5	F=0.01	0.994

Table 1 *continued*. Omnibus comparisons of preoperative measures between study participants with and without corticosteroid responsive olfactory dysfunction within CRS (n=253).

Demographics	CROD Categories			Test statistics	Omnibus p-value
	CROD (n=70)	Don't know / Unknown (n=124)	on-CROD (n=59)		
Rhinologic symptoms	17.0 ± 6.3	15.8 ± 6.4	17.4 ± 7.2	F=1.50	0.226
Extranasal rhinologic symptoms	7.5 ± 3.8	7.6 ± 3.3	7.5 ± 4.2	F=0.01	0.996
Ear/facial symptoms	8.4 ± 5.0	8.4 ± 5.6	8.8 ± 5.7	F=0.11	0.898
Psychological dysfunction symptoms	13.2 ± 7.6	14.1 ± 8.6	12.8 ± 9.0	F=0.62	0.538
Sleep dysfunction symptoms	12.5 ± 6.1	12.6 ± 7.4	11.9 ± 7.4	F=0.25	0.783
Item: "Sense of smell/taste"	4.0 [2.0]	3.0 [3.0]	4.0 [4.0]	KW=19.01	**<0.001**

CRS, chronic rhinosinusitis; CROD, corticosteroid responsive olfactory dysfunction; SD, standard deviation; N, sample size; ESS, endoscopic sinus surgery; ASA, acetylsalicylic acid; AERD, aspirin exacerbated respiratory disease; GERD, gastroesophageal reflux disease; mRAST, modified radioallergosorbent testing; NOS, not otherwise specified; CT, computed tomography; OCES, olfactory cleft endoscopy score; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements survey; SNOT-22, 22-item SinoNasal Outcome Test survey; F-test statistic associated with one-way analysis of variance for Gaussian distributed data; χ2, chi-square test statistic associated with 2x3 contingency tables. KW, Kruskall-Wallis asymptotic test statistic for non-Gaussian distributed data; IQR, interquartile range.

the SNOT-22 (Q#21) queries respondents to rank their 'Sense of smell/taste'. Higher SNOT-22 total score (range: 0-110) domain, and item scores reflect and overall worse symptom severity. A MCID of >8.9 points in SNOT-22 total scores post-treatment has been historically described for patients with CRS using distribution-based scoring methodology [16,18,19].

Data collection and biostatistics

Data security was ensured through unique study identification number assignment for study participants and removal of patient identifiers prior to electronic data capture (Access; Microsoft Corporation; Redmond, WA, USA). Biostatistical analyses were completed using SPSS (ver.29.0; IBM Corporation, Armonk, NY, USA). Continuous study data was evaluated for parametric distributions using Q-Q plots and Shapiro-Wilk tests of normality. Independent, between-group comparisons were conducted using either one-way analysis of variance (F-tests), likelihood ratio chi-square (χ2) testing, or Kruskall-Wallis testing, to identify significant differences between mean or frequency counts, respectively. Global significance was further evaluated between all pair-wise comparisons using α-adjusted Bonferroni corrections (adj.p-values). Within-subject, postoperative differences were evaluated using paired sample t-testing, McNemar's χ2 or Wilcoxon signed rank standardized testing. Unadjusted, effect estimates (Δ) were determined with associated 95% confidence intervals (CIs) with unadjusted type-I error rate probabilities (p-values).

Results

Final cohort characteristics

A total of 269 study participants with CRS met study inclusion criteria and provided informed consent between November 2016 and February 2020. Subjects were excluded from final analyses due to a comorbid diagnosis of comorbid pulmonary ciliary dyskinesia/cystic fibrosis (n=4) or immunodeficiency (n=4), while additional subjects elected to not complete preoperative Sniffin' Stick evaluations (n=2) or failed to provide responses to preoperative corticosteroid responsiveness anchor questions (n=6). A total of 63 subjects were identified as having preoperative normosmia via Sniffin' Sticks total scores. Out of the 63 normosmic subjects, 14 (22%) reported CROD, 39 (61.9%) were Don't know/unknown, and 10 (15.9%) were non-CROD. For the final cohort (total n=253; CRSwNP n=135; CRSsNP n=118) study participant demographics, comorbidity, and preoperative study measures are described and compared between CROD subgroups (Table 1). The prevalence of interventional surgical procedures is similarly described in Table 2 between CROD subgroups.

Omnibus testing identified significant bivariate differences in study subject demographics, disease characteristics, comorbidities, and preoperative scores of disease severity and quality-of-life impact between CROD categories (Table 1). Between study participants who indicated either CROD (n=70) or non-CROD (n=59), the only statistically significant differences were found in the prevalence of both comorbid GERD (adj.p=0.030) and abnormal olfaction as indicated by higher QOD-NS total scores (adj. p=0.015) after adjustment for multiple comparisons. Between study participants who indicated either CROD and those who were unsure of CROD (n=124), statistically significant differences were identified in in the prevalence of nasal polyposis (adj.

Table 2. Frequency of bilateral endoscopic sinus surgery procedures completed for subgroups with and without corticosteroid responsive olfactory dysfunction (n=253).

	CROD (n=70)		
Surgical procedures:	**Unilateral Left Side N (%)**	**Unilateral Right Side N (%)**	**Bilateral N (%)**
Maxillary antrostomy	0 (0.0%)	5 (7.1%)	62 (88.6%)
Partial ethmoidectomy	0 (0.0%)	1 (1.4%)	1 (1.4%)
Total ethmoidectomy	0 (0.0%)	1 (1.4%)	66 (94.3%)
Sphenoidotomy	1 (1.4%)	2 (2.9%)	63 (90.0%)
Middle turbinate resection	2 (2.9%)	3 (4.3%)	34 (48.6%)
Inferior turbinate reduction	1 (1.4%)	1 (1.4%)	5 (7.1%)
Frontal sinusotomy (Draf 2a)	0 (0.0%)	1 (1.4%)	45 (64.3%)
Frontal sinusotomy (Draf 2b)	1 (1.4%)	0 (0.0%)	7 (10.0%)
Frontal sinusotomy (Draf 3)	---	---	10 (14.3%)
Septoplasty		17 (24.3%)	
Image guidance		67 (95.7%)	
Surgical procedures: Don't know / unknown (n=124)			
Maxillary antrostomy	10 (8.1%)	6 (4.8%)	105 (84.7%)
Partial ethmoidectomy	5 (4.0%)	1 (0.8%)	16 (12.9%)
Total ethmoidectomy	6 (4.8%)	6 (4.8%)	91 (73.4%)
Sphenoidotomy	4 (3.2%)	5 (4.0%)	90 (72.6%)
Middle turbinate resection	6 (4.8%)	9 (7.3%)	35 (28.2%)
Inferior turbinate reduction	0 (0.0%)	0 (0.0%)	26 (21.0%)
Frontal sinusotomy (Draf 2b)	3 (2.4%)	1 (0.8%)	13 (10.5%)
Frontal sinusotomy (Draf 3)	---	---	11 (8.9%)
Septoplasty		52 (41.9%)	
Image guidance		106 (85.5%)	
Surgical procedures: Non-CROD (n=59)			
Maxillary antrostomy	5 (8.5%)	2 (3.4%)	52 (88.1%)
Partial ethmoidectomy	2 (3.4%)	0 (0.0%)	5 (8.5%)
Total ethmoidectomy	1 (1.7%)	2 (3.4%)	48 (81.4%)
Sphenoidotomy	0 (0.0%)	4 (6.8%)	44 (74.6%)
Middle turbinate resection	1 (1.7%)	4 (6.8%)	23 (39.0%)
Inferior turbinate reduction	0 (0.0%)	1 (1.7%)	7 (11.9%)
Frontal sinusotomy (Draf 2a)	0 (0.0%)	4 (6.8%)	27 (45.8%)
Frontal sinusotomy (Draf 2b)	2 (3.4%)	0 (0.0%)	7 (11.9%)
Frontal sinusotomy (Draf 3)	---	---	8 (13.5%)
Septoplasty		19 (32.2%)	
Image guidance		51 (86.4%)	

N, sample size; CROD, corticosteroid responsiveness olfactory dysfunction.

p=0.003), previous ESS (adj.p=0.045), asthma (adj.p=0.009), ASA sensitivity/AERD (adj. p<0.001), anosmia as diagnosed using Sniffin' Sticks total scores (adj.p<0.001), and abnormal olfaction as indicated by higher QOD-NS total scores (adj.p<0.001) after adjustment. Significant differences in scaled measures between those same two groups were also identified for OCES total scores (adj.p<0.001), Sniffin' Sticks total scores (adj.p=0.006), threshold (adj.p=0.003), discrimination (adj.p=0.008), identification scores (adj. p=0.019), QOD-NS total scores (adj.p<0.001), and responses to the "Sense of smell/taste" item of the SNOT-22 survey (adj.p<0.001).

Additionally, between participants who indicated either

Table 3. Within-subject comparisons of disease severity and outcome measures for all study participants with postoperative follow-up.

Measures of disease severity and outcome: Median [IQR]	N	Preop.	Postop.	Δ	95% CI	Test statistic	p-value
Lund-Kennedy endoscopy score	129	7.0 [6.0]	2.0 [4.0]	-4.0 [4.0]	----	WSR= -7.62	<0.001
OCES total score	88	4.0 [8.0]	0.0 [4.0]	-2.0 [5.0]	----	WSR= -4.50	<0.001
Sniffin' Sticks total score Mean±SD	120	22.4 ± 9.2	25.9 ± 8.3	3.6 ± 7.9	2.1 – 5.0	t= 4.93	<0.001
-Threshold score	120	3.7 ± 3.1	4.5 ± 3.0	0.8 ± 3.3	0.2 – 1.4	t= 2.63	0.010
-Discrimination score	120	9.1 ± 3.5	10.7 ± 3.2	1.5 ± 3.8	0.9 – 2.2	t= 4.52	<0.001
-Identification score	120	9.6 ± 4.0	10.8 ± 3.5	1.2 ± 3.3	0.6 – 1.8	t= 4.06	<0.001
Diagnosis: Normosmia N (%)	120	29 (24.2%)	48 (40.0%)	19 (15.8%)	----	χ2= 10.45	0.001
Diagnosis: Hyposmia	120	53 (44.2%)	54 (45.9%)	1 (1.7%)	----	χ2= 0.01	>0.999
Diagnosis: Anosmia	120	38 (31.7%)	18 (15.0%)	-20 (16.7%)	----	χ2= 11.28	0.001
QOD-NS total score Mean±SD	155	13.2 ± 10.5	7.6 ± 8.0	5.6 ± 8.7	4.2 – 7.0	t= 8.05	<0.001
-Normal olfaction (<12.5) N (%)		82 (52.9%)	124 (80.0%)	42 (27.1%)	----	χ2=5.72	<0.001
-Abnormal olfaction (>12.5)		73 (47.1%)	31 (20.0%)				
SNOT-22 total score Mean ± SD	157	48.1 ± 20.7	24.0 ± 19.7	24.1 ± 19.9	20.9 - 27.2	t=15.14	<0.001
Rhinologic symptoms	157	16.5 ± 6.6	7.6 ± 6.0	8.9 ± 6.6	7.8 - 9.9	t= 16.71	<0.001
Extranasal rhinologic symptoms	157	7.5 ± 3.5	3.9 ± 3.4	3.6 ± 3.7	3.0 – 4.2	t= 12.10	<0.001
Ear/facial symptoms	157	8.5 ± 5.3	3.8 ± 4.0	4.7 ± 4.6	4.0 – 5.4	t= 12.88	<0.001
Psychological dysfunction symptoms	157	13.3 ± 8.3	6.9 ± 7.9	6.4 ± 7.6	5.2 – 7.6	t= 10.60	<0.001
Sleep dysfunction symptoms	157	12.2 ± 6.9	6.8 ± 6.5	5.4 ± 6.8	4.3 – 6.4	t= 9.93	<0.001
Item: "Sense of smell/taste"	157	3.0 ± 1.8	1.9 ± 1.7	1.1 ± 2.0	0.8 – 1.4	t= 7.28	<0.001

N, sample size; Δ, postoperative change value; CI, confidence interval; OCES, olfactory cleft endoscopy score; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements survey; SNOT-22, 22-item SinoNasal Outcome Test survey; t-test statistic associated with dependent, paired samples with Gaussian distributed change data; χ2, McNemars chi-square test statistic associated with pre-post testing with continuity correction. WSR, Wilcoxon signed rank standardized test statistic for non-Gaussian distributed change data; IQR, interquartile range; SD, standard deviation.

non-CROD and those unsure of CROD, statistically significant differences were found in the prevalence of previous ESS (adj.p=0.003), ASA sensitivity/AERD (adj.p=0.033), former smoking/tobacco use (adj.p=0.018), and GERD (adj.p=0.003). Significant differences in scaled measures between those same two groups were also identified for age (adj.p=0.033), Sniffin' Sticks total scores (adj.p=0.040), and responses to the "Sense of smell/taste" item of the SNOT-22 survey (adj.p=0.009).

Overall postoperative follow-up and olfactory improvements

Due to the observational study design, a variable number of study participants were evaluated postoperatively for both olfactory function and CRS symptom severity using Lund-Kennedy endoscopy scores, OCES, Sniffin' Stick pens, QOD-NS and SNOT-22 surveys after an average 6.0 [SD ± 1.9] months after ESS (20). A total of ~62% of participants provided follow-up responses to the QOD-NS and SNOT-22 surveys while ~47% of participants were able to complete postoperative bilateral olfactory function testing (Table 3). Statistically significant improvement was reported across all measures of disease severity and olfactory outcomes following ESS, with the exception of the prevalence of hyposmia. The prevalence of responses equal to at least one MCID for both QOD-NS and SNOT-22 total scores were 65/155 (41.9%) and 123/157 (78.3%), respectively. Overall, out of the 120 subjects with postoperative olfactory testing, 42 (35%) were found to have improvements equal to or exceeding the MCID of 6.0 points.

Comparisons of postoperative differences between CROD subgroups

Outcomes were stratified across CROD categories, with variable sample size, to identify whether olfactory corticosteroid responsiveness is a general prognostic factor associated with postoperative differences within those measures. Additional omnibus testing identified significant bivariate differences in postoperative improvement in measures of disease severity between CROD categories (Table 4).

Between study participants who indicated either CROD or non-CROD, after multiple pairwise comparisons the only significant differences were identified for median values of postoperative improvement in OCES total scores (adj.p=0.002), QOD-NS total scores (adj.p=0.006), and the number of participants reporting

Table 4. Omnibus comparisons of postoperative changes in disease severity and outcome measures between study participants with and without corticosteroid responsive olfactory dysfunction.

Demographics	CROD Categories			Test statistics	Omnibus p-value
	CROD (n=70)	Don't know / Unknown (n=124)	on-CROD (n=59)		
Lund-Kennedy endoscopy score	-5.0 [6.0]	-4.0 [5.0]	-3.0 [4.3]	KW= 5.70	0.058
OCES total score	-4.0 [6.5]	-2.0 [4.0]	0.0 [5.0]	KW=11.89	**0.003**
Sniffin' Sticks total score	5.3 [14.0]	2.6 [10.8]	2.8 [10.0]	KW=2.36	0.308
-Threshold score	0.0 [4.0]	0.3 [4.5]	0.0 [3.0]	KW=0.13	0.936
-Discrimination score	2.0 [6.0]	0.0 [5.0]	2.0 [6.0]	KW=2.73	0.255
-Identification score	2.0 [6.0]	1.0 [3.0]	1.0 [5.0]	KW=4.74	0.093
Diagnosis: Normosmia N (%)	5 (16.1%)	9 (15.5%)	5 (16.1%)	$\chi2$=0.01	0.996
Diagnosis: Hyposmia	7 (22.5%)	-5 (8.6%)	-1 (3.2%)	----	----
Diagnosis: Anosmia	-12 (38.7%)	-4 (6.9%)	-4 (12.9%)	----	----
QOD-NS total score	-8.0 [8.5]	-2.0 [13.0]	-1.0 [9.0]	KW=11.29	**0.004**
-Normal olfaction (<12.5)	19 (38.8%)	17 (25.4%)	6 (15.4%)	$\chi2$=6.19	**0.045**
SNOT-22 total score	-23.5 [28.5]	-23.0 [26.8]	-22.0 [29.0]	KW=0.81	0.667
Rhinologic symptoms	-11.0 [10.8]	-8.0 [8.0]	-8.0 [11.0]	KW=1.97	0.373
Extranasal rhinologic symptoms	-3.0 [4.0]	-4.0 [5.0]	-3.0 [7.0]	KW=0.54	0.765
Ear/facial symptoms	-4.0 [5.8]	-4.0 [7.0]	-5.0 [6.0]	KW=0.18	0.915
Psychological dysfunction symptoms	-6.0 [9.0]	-6.5 [12.0]	-5.0 [10.0]	KW=2.71	0.257
Sleep dysfunction symptoms	-5.0 [8.0]	-5.0 [9.3]	-4.0 [9.0]	KW=1.56	0.459
Item: "Sense of smell/taste"	-2.0 [3.8]	-1.0 [2.0]	0.0 [2.0]	KW=7.18	**0.028**

CROD, corticosteroid responsive olfactory dysfunction; N, sample size; Δ, postoperative change value; OCES, olfactory cleft endoscopy score; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements survey; SNOT-22, 22-item SinoNasal Outcome Test survey; $\chi2$, chi-square test statistic associated with 2x3 contingency tables; KW, Kruskall-Wallis asymptotic test statistic for non-Gaussian distributed data; IQR, interquartile range.

normal olfactory symptoms using the QOD-NS threshold values (38.8% vs. 15.4%, respectively; adj.p=0.048). The only additional significant pairwise comparisons were identified between subjects with CROD and those who were unsure of CROD for both median values of QOD-NS total scores (adj.p=0.019) and the "Sense of smell/taste" survey item of the SNOT-22 (adj.p=0.047). Between CROD subgroups, no difference in the percent of MCID improvement of Sniffin' Sticks scores was found between any two groups (p=0.197).

Further comparing differences in postoperative improvement in study subjects with CROD, between those with and without CRSwNP, also identified statistically significant differences in postoperative improvement in Sniffin' Stick total scores (p=0.007; Figure 2), but not with improvements in QOD-NS total scores (p=0.073; Figure 3). The prevalence of subjects reporting postoperative improvement equal to at least one MCID for QOD-NS total scores was however significantly higher for study subjects with CROD (32/49; 65.3%) compared to both non-CROD (11/39; 28.2%; adj.p=0.003) and those unsure of CROD (22/67; 32.8%; adj.p=0.003) after adjustment for multiple comparisons.

Discussion

Although OD is an incompletely understood feature of CRS, corticosteroids are of value in many cases and a recommended first line treatment for CRSwNP [21]. Self-reported ratings of olfactory function and psychophysical measures of olfactory function are established measurements of olfactory function with varying degrees of subjectiveness. Our goal was to explore the frequency of self-reported preoperative CROD in CRS, and if this simple clinical observation could be used to prognosticate olfactory improvement after ESS. Because there is not a standardized definition of corticosteroid responsiveness in CRS, the single, anchor-based question to define corticosteroid responsiveness was designed to mimic clinical practice, be easily implemented, and sensitive enough to capture a preoperative olfactory response to corticosteroids.

Patients with CROD had greater postoperative improvement in olfactory measures compared to non-CROD patients, independent of polyp status. CROD status was not associated with overall SNOT-22 improvement after ESS. Taken together, CROD as a preoperative feature, suggests some preservation of the

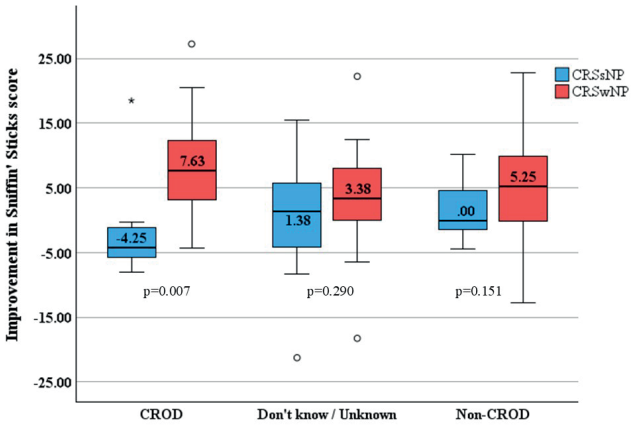

Figure 2. Comparison of median postoperative improvement in Sniffin' Sticks total scores between CROD categories with and without nasal polyposis. CROD, corticosteroid responsive olfactory dysfunction. The subgroup of CROD subjects consists of 31 total cases, CRSsNP (n=7), and CRSwNP (n=24). Data outliers are indicated by "o" and "*" notation.

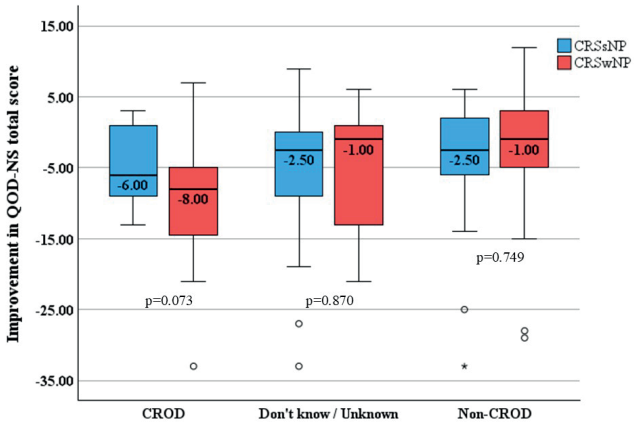

Figure 3. Comparison of median postoperative improvement in QOD-NS total scores between CROD categories with and without nasal polyposis did not identify significant differences in postoperative improvement. CROD, corticosteroid responsive olfactory dysfunction; QOD-NS, Questionnaire of Olfactory Dysfunction-negative statements survey. The subgroup of CROD subjects consists of 49 total cases, CRSsNP (n=13), and CRSwNP (n=36). Data outliers are indicated by "o" and "*" notation.

olfactory system's functional and regenerative capacity, and potential reversibility with successful treatment. However, it may not be useful in counseling for anticipated sinonasal quality-of-life improvements after ESS.

Prior investigations have consistently associated OD more commonly in patients with CRSwNP compared to those with CRSsNP. Other risk factors for CRS-OD include eosinophilic CRS, aspirin-exacerbated respiratory disease (AERD), central compartment atopic disease (CCAD), current smoking, serum IgE >400IU/ml, ethmoid opacification and asthma [2,22,23]. Although oral corticosteroids are the main treatment of CRS-OD, it is established that not all patients with CRS-OD will respond to oral corticosteroids therapy or ESS[24]. Prior meta-analyses by Zhao et al. and Kohli et al. demonstrated that ESS may be beneficial for CRS-OD in general, with objective and patient reported measures improving in CRSwNP to a greater degree than in CRSsNP [5,24]. Another study by Bogdanov et al. evaluated preoperative corticosteroids and postoperative olfaction in patients with CRSwNP. They showed that after preoperative corticosteroids, TDI score significantly improved in 57% of patients but unchanged in 43%. Patients whose olfaction did not improve after corticosteroids did also not benefit from surgery [3].

Not surprisingly, on presentation, patients with nasal polyposis exhibited a significantly higher rate of CROD compared to non-CROD. Similarly, patients with asthma and ASA sensitivity/AERD showed a higher rate of CROD also consistent with likely underlying type 2 inflammatory pathogenesis. This is in alignment with the presumed inflammatory cause of OD in patients with CRSwNP and known literature demonstrating benefit of corticosteroids and anti-type 2 medical therapies in this phenotype [25,26]. However, we also found that patients with a history of prior ESS or with prior tobacco use, have a higher prevalence of non-CROD compared to CROD. This may suggest that ESS, especially near the olfactory epithelium, could result in fibrosis or irreversible change in the epithelium leading to non-CROD. Alternatively, CRS patients who had prior surgery could represent a category with the most refractory or prolonged disease, and would be least likely to respond to medical management. Yee et al. studied olfactory respiratory epithelium biopsies in smoking and nonsmoking patients with CRSsNP and found epithelial and neuronal changes associated with increased tobacco exposure, specifically that tobacco exposure was associated with increased squamous metaplasia and abnormal olfactory sensory neuron morphology [27].

This study data showed no significant difference between the number of patients with preoperative CROD and non-CROD with postoperative normosmia. This may suggest that even when corticosteroids do not benefit OD preoperatively, ESS may still benefit CRS-OD by multiple mechanisms including clearance of inflammatory disease burden, improvement of topical drug delivery to the sinuses and olfactory cleft, improved airflow, improved mucus characteristics, enhanced odorant delivery to the olfactory epithelium, or other indirect effects not identified by corticosteroids responsiveness alone.

Patients with CROD were significantly more likely to have nasal polyposis compared to patients with non-CROD and it may seem that the postoperative improvement outcomes are driven by collinearity with nasal polyps (Table 4). However, the results actually demonstrate that differences in postoperative improvement by CROD category according to the presence or absence of polyposis did not identify significant differences in postoperative improvement in Sniffin Sticks total scores (adj. p>0.336) or

QOD-NS total scores (adj. p>0.213) for any independent CROD group. This suggests that polyp status did not significantly confound or influence the results of Table 4 findings.

Phenotyping and endotyping CRS are now established means to understand the heterogeneous groups within CRS. However, these divisions have known limitations, and may not be widely accessible to all providers caring for CRS patients. We propose the addition of "theratyping" as a consideration in the classification of CRS, similar to asthma, as a potential clinical feature that could aid in understanding disease pathophysiology and treatment selection [28]. For instance, in asthma, inhaled corticosteroids have long been the mainstay for maintenance therapy, but not all patients are corticosteroid responsive, and it is increasingly recognized that different treatment algorithms are required for such patients [4].

Even though our specific aim was to examine postoperative CROD improvement compared to non-CROD improvement, we retained subjects who responded "Don't Know/unknown" in their response to oral steroid effectiveness in some analyses. This reflects the real-world clinical setting in which many patients were unsure of their steroid response. Future research could focus on CROD vs non-CROD, but a formal definition of CROD would first be required.

Study limitations include the heterogeneity of CRS disease, the variability of surgical technique, and unstandardized perioperative care in an academic, tertiary care setting. Duration and weight-dependent dose of oral corticosteroid are not standardized in current CRS guidelines. The corticosteroid dosing approximated the recommended 0.5mg-1mg/kg/day of prednisone tapering down over 1-2 weeks. Short course OCS is known to provide significant benefit to patients, particularly in CRSwNP, and given individualized side effect risk profiles specifics were left to the discretion of each prescribing physician(29). Another limitation is the presumption that in patients with CRS and OD, the OD is caused by CRS, not a primary smell disorder. Patients were not excluded with an upper age threshold, on medications that may alter olfactory function or with neuro-degenerative disorders which we acknowledge can affect olfactory presentation. If patients with neurologic disorders were unable to complete accurate pre-operative assessments however, they were excluded. As with longitudinal outcomes, some subjects were lost to follow-up which may contribute to selection bias and a smaller sample size for additional multivariate analysis. Further studies with larger sample sizes that examine obesity, smoking, GERD, pollution exposure, severity of pre-operative OD, and ethnicity/race should be explored. Lastly, importantly to such research, defining success and perhaps creating a definition of corticosteroid responsiveness would be useful to further define these groups for clinical and pathophysiological studies.

Conclusions

Self-reported corticosteroid responsiveness in patients with CRS-OD appears to be a positive prognostic indicator for improvement in olfaction with surgical intervention and continued medical therapies, suggesting that the clinical response to corticosteroid therapy may indicate underlying preservation of tissue function with maintained capacity for return of olfactory function. Conversely, corticosteroid nonresponse in CRS indicates a lower likelihood of olfactory return, perhaps due to particular inflammatory characteristics and/or irreversible tissue damage. Corticosteroid responsiveness can be used as a simple clinical prognostic factor in the shared decision making for ESS in medically refractory CRS.

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Authorship contribution

KAA: manuscript preparation and editing; JCM: data collection, manuscript preparation, statistical analyses; TLS: participant recruitment, data collection, manuscript editing; ZMS, RJS, JAA, JLM, VRR: patient recruitment, data collection, manuscript editing.

Conflict of interest

No conflicts of interest by the authors.

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Vijay R. Ramakrishnan, MD
Department of Otolaryngology
Head and Neck Surgery
Indiana University School of Medicine
1130 W Michigan Street
Fesler Hall 400
Indianapolis, IN 46202
USA

Tel: +1-317-278-1440
E-mail: vrramakr@iu.edu

Kaete A. Archer[1], Jess C. Mace[2], Timothy L. Smith[2], Zachary M. Soler[3], Rodney J. Schlosser[3], Jeremiah A. Alt[4], Jose Mattos[5], Vijay R. Ramakrishnan[1]

[1] Department of Otolaryngology-Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, IN, USA
[2] Department of Otolaryngology-Head and Neck Surgery, Oregon Health Sciences University, Portland, OR, USA
[3] Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA
[4] Department of Otolaryngology-Head and Neck Surgery, University of Utah, Salt Lake City, UT, USA
[5] Department of Otolaryngology-Head and Neck Surgery, University of Virginia, Charlottesville, VI, USA

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