The Journal of Laryngology & Otology

cambridge.org/jlo

Usefulness of post-operative endoscopic score for optimal treatment selection in recurrent eosinophilic chronic rhinosinusitis

Takahiro Saito, Ken Okazaki, Katsuya Fushimi and Kenzo Tsuzuki

Department of Otorhinolaryngology – Head and Neck Surgery, Hyogo Medical University, Nishinomiya, Japan

Abstract

Objective. This study retrospectively analysed post-operative endoscopic scores to determine the optimal post-operative treatment in patients with eosinophilic chronic rhinosinusitis undergoing functional endoscopic sinus surgery.

Methods. In total, 339 adults who underwent initial bilateral functional endoscopic sinus surgery for eosinophilic chronic rhinosinusitis were enrolled. Patients were divided into group A, which required no additional post-operative treatment; group B, which required local/systemic steroids post-operatively; and group C, which further required dupilumab and/or revision surgery.

Results. Sixty-five per cent of patients could be treated with initial functional endoscopic sinus surgery (group A). Post-operative steroids were required in 35 per cent of patients with a post-operative endoscopic score of 30 per cent (group B). Further advanced treatments with dupilumab and/or revision functional endoscopic sinus surgery were required in 10 per cent of patients with a post-operative endoscopic score of 65 per cent (group C).

Conclusion. The post functional endoscopic sinus surgery endoscopic score can be used as an index to determine treatment at the time of eosinophilic chronic rhinosinusitis recurrence.

Introduction

Chronic rhinosinusitis with nasal polyps is a chronic inflammatory disease involving the sinonasal area; it is associated with a high symptom burden and poor health-related quality of life.[1] Eosinophilic chronic rhinosinusitis is characterised by diffuse bilateral chronic rhinosinusitis due to the presence of type 2 inflammation, with the involvement of type 2 cytokines, such as interleukin (IL)-4, IL-13 and IL-5, and high levels of tissue immunoglobulin E in its pathophysiology.[2–4] The disease is clinically often intractable, with frequent relapse of nasal polyps.[2]

Based on the recent pharmacological strategy of suppressing type 2 cytokines, biological products (biologics), in addition to conventional medicines, mainly corticosteroids (steroids), have emerged as the treatment for eosinophilic chronic rhinosinusitis.[5–7] Dupilumab, a fully human monoclonal antibody that inhibits the signalling of the IL-4 and IL-13 pathways, is one of the newer biologics used for intractable chronic rhinosinusitis with nasal polyps.[8] In order to relieve patients' symptoms early, functional endoscopic sinus surgery (FESS) is also useful for removing the lesions and opening the paranasal drainage pathway. This approach is further advocated when medical treatment fails,[9–12] particularly in cases of relapsed disease. Treatments that successfully combine pharmacotherapy (local and systemic steroids, and biologics) and surgery (FESS) should be carefully selected.

It is important to clarify the definition of relapse of eosinophilic chronic rhinosinusitis to determine an accurate treatment strategy for treating this condition. However, no such definition has been unequivocally established. A scoring system is a useful method in this regard. The endoscopic scoring system is a simple and useful real-time evaluation method. In particular, the post-operative endoscopy score, which is an index that suggests the ratio of relapse in the sinonasal area, is useful.[13]

This study aimed to clarify: (1) risk factors for relapse; (2) relapse ratios; and (3) an index for deciding on treatment at the time of relapse using the endoscopic scoring system, in patients with eosinophilic chronic rhinosinusitis who have undergone FESS. We also evaluated the appropriate timing of the decision for an optimal post-operative treatment strategy for relapsed eosinophilic chronic rhinosinusitis.

Materials and methods

Patients

The subjects in this study were 339 adults who underwent bilateral initial FESS for eosinophilic chronic rhinosinusitis, diagnosed based on the criteria of the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study,[14] from

Main Article

Takahiro Saito takes responsibility for the integrity of the content of the paper

Cite this article: Saito T, Okazaki K, Fushimi K, Tsuzuki K. Usefulness of post-operative endoscopic score for optimal treatment selection in recurrent eosinophilic chronic rhinosinusitis. *J Laryngol Otol* 2024;**138**: 162–168. https://doi.org/10.1017/S0022215123000798

Received: 20 June 2022
Revised: 6 April 2023
Accepted: 29 April 2023
First published online: 24 May 2023

Keywords:
Eosinophilia; operative procedures; recurrence; risk factors; steroids

Corresponding author:
Takahiro Saito;
Email: t-saito@hyo-med.ac.jp

April 2007 to July 2021. There were 193 male and 146 female patients, with a median age of 52 years (range = 22–82 years).

Depending on the post-operative treatment, all patients were initially divided into two groups, A and B. Group A required no additional treatments, except for a basic treatment with steroid nasal spray and anti-leukotrienes, after FESS, and acted as a control group with a good clinical course. Group B required additional steroid treatment (sinonasal topical steroid treatment and/or systemic (oral prednisolone ≥ 5 mg/day) steroids). Patients in group B were further divided into those who required dupilumab and/or revision surgery because of resistance to additional steroid treatment after the initial FESS, in whom eosinophilic chronic rhinosinusitis could not be controlled with steroids (group C).

Patients with chronic rhinosinusitis were excluded from this study if they: did not fulfil the criteria for eosinophilic chronic rhinosinusitis, had a history of previous sinonasal surgery, had traumatic sinonasal lesions or had paranasal cysts.

Initial full-house FESS was performed on all patients under general anaesthesia, after informed consent was obtained in accordance with the guidelines of the Ethics Committee of Hyogo Medical University. This study used a retrospective case series design, and complied with the regulations of the Ethics Committee of Hyogo Medical University (approval numbers: 1512 and 3308). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Diagnosis

Chronic rhinosinusitis was diagnosed when nasal respiratory and olfactory symptoms (including nasal obstruction, anterior rhinorrhoea, postnasal drip, facial pain or headache, cough, sputum, and/or loss of smell) were observed for more than three months, based on the guidance provided by the Japan Rhinologic Society and previous reports from Europe[1] and the USA.[15] The presence of bilateral nasal polyps were observed on nasal endoscopy, and evidence of paranasal sinus lesions was detected on computed tomography (CT). Surgical management in the form of initial FESS was indicated for patients with chronic rhinosinusitis when nasal symptoms and physical findings did not improve despite intensive medical therapy for at least three months.[15]

Eosinophilic chronic rhinosinusitis was diagnosed when the total score of the following 4 items was 11 points or more: (1) bilateral lesions (3 points); (2) nasal polyps (2 points); (3) dominant ethmoid sinus involvement or pansinusitis on CT (2 points); and (4) percentage of blood eosinophils of more than 2 per cent and up to 5 per cent (4 points), over 5 per cent and up to 10 per cent (8 points), or over 10 per cent (10 points), based on the criteria reported by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study.[14]

The severity of eosinophilic chronic rhinosinusitis was determined based on factors A and B. Factor A consisted of two items: 5 per cent or more eosinophils in peripheral blood and ethmoid-dominant opacification on CT. Factor B included the co-morbidity of bronchial asthma, aspirin intolerance and/or non-steroidal anti-inflammatory drug intolerance. Patients with eosinophilic chronic rhinosinusitis were classified into three grades: mild when one or no factor A items were present, without the presence of any factor B items; moderate when both factor A items were present, but no factor B item was present, or one or no factor A item and/or one factor B item was present; and severe when both factor A items were present with any factor B item.

Post-operative treatments

All patients with eosinophilic chronic rhinosinusitis received post-operative basic treatment with nasal spray (mometasone furoate (200 µg/day) or fluticasone furoate (110 µg/day), once a day in each nasal cavity) and oral leukotriene receptor antagonists (montelukast, 10 mg/day) after the initial FESS. Patients received steroid treatment as the first therapeutic choice for relapse after the initial FESS (group B). In group C, biologics (dupilumab) and/or revision FESS were required after steroid treatment failed.

Additional steroid treatment

Sinonasal topical steroid treatment

Sinonasal topical steroid treatment using a bioabsorbable device consisting of oxidised regenerated cellulose (Surgicel Absorbable Haemostat; Johnson and Johnson, Tokyo, Japan) and triamcinolone acetonide (Kenacort, 40 mg/ml vial; Bristol Myers Squibb, Tokyo, Japan) was used, based on previous reports.[16,17] First, cotton swabs impregnated with 4 per cent xylocaine and 5000-fold diluted adrenaline were bilaterally inserted into the surgically opened ethmoid sinuses and olfactory clefts, to shrink the nasal mucosae, for 5–10 minutes. Second, a moderate amount of oxidised regenerated cellulose was inserted bilaterally into the ethmoid sinuses and olfactory clefts. Third, triamcinolone acetonide in a half vial (20 mg/0.5 ml) was dripped onto the oxidised regenerated cellulose on each side.

Systemic steroid treatment

Oral prednisolone at a dose of 5 mg per day or more was administered when patients' symptoms and multiple nasal polyps persisted even after sinonasal topical steroid treatment. The median total dose of oral steroids was 70 mg (range = 25–140 mg).

Biologic treatment

Dupilumab, a biologic consisting of a fully human monoclonal anti-interleukin-4Rα antibody, was indicated for patients with bilateral chronic rhinosinusitis with nasal polyps who fulfilled the following conditions: bilateral total polyps score of ≥ 5 points (score of ≥ 2 in each nasal cavity);[6,18] the requirement of systemic steroids for chronic rhinosinusitis with nasal polyps within the past two years; no contraindications or intolerance to systemic steroids; a history of sinonasal surgery; and the most severe symptoms of nasal obstruction, olfactory disorders, and nasal discharge persisting for more than eight weeks before screening, according to the guidelines for the promotion of optimal use by the Pharmaceuticals and Medical Devices Agency in the Ministry of Health, Labour and Welfare in Japan. Dupilumab (Dupixent, 300 mg per syringe; Sanofi, Tokyo, Japan) was injected subcutaneously every two weeks.

Revision functional endoscopic sinus surgery

Revision FESS was indicated particularly for patients with eosinophilic chronic rhinosinusitis with: nasal obstruction, multiple polyposis with adhesion in the sinonasal area on endoscopy, and residual cells on CT. Full-house FESS was performed to remove the residual, adhesive and relapsed lesions, under general anaesthesia.

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press

Post-operative endoscopic appearance score

The post-operative endoscopic appearance of the operated sinuses and olfactory clefts was scored as follows: 0 points = normal appearance; 1 point = only partially observable given the presence of polyps, oedematous mucosa or discharge; and 2 points = unobservable because the sinuses are completely filled with swollen mucosae, polyps or discharge.[12] When the polyps occupied and prevented observation of the posterior part of the sinuses, a score of 2 points was assigned to the part of the sinuses that had undergone surgery. Sinuses not included in the surgery were excluded from scoring. The percentage of the total score relative to the maximum possible worst score for the operated sinuses and olfactory clefts was rated as the post-operative endoscopic appearance score. Higher scores indicated a worse status. The post-operative endoscopic appearance score indicated the endoscopic relapse ratio of inflamed lesions in the sinonasal area.

Computed tomography score

Sinonasal CT findings were scored to evaluate the degree of chronic rhinosinusitis severity, based on the Lund and Mackay scoring system, which is one of the most widely accepted methods in otorhinolaryngology.[19] The frontal, maxillary, anterior/posterior ethmoid and sphenoid sinuses were scored as: 0 points = no opacification, 1 point = partial opacification, or 2 points = complete opacification. The ostiomeatal complex was scored as: 0 points = without opacification, or 2 points = with opacification. The CT score was calculated as the sum of the scores for each site. The CT score ranged from 0 to 12 points per side (bilateral range = 0–24 points).

Olfactory evaluation

Self-administered odour questionnaire

The self-administered odour questionnaire consisted of 20 items (steamed rice, miso, seaweed, soy sauce, baked bread, butter, curry, garlic, orange, strawberry, green tea, coffee, chocolate, household gas, garbage, timber, stercus (faeces), sweat, flower and perfume), as suggested by the Japan Rhinologic Society.[20] Patients answered the 20 items using the following responses: 1 – I can perceive the smell (2 points); 2 – I can sometimes perceive the smell (1 point); 3 – I cannot perceive the smell at all (0 points); and 4 – I have not smelled it recently or before (unevaluable). The self-administered odour questionnaire score was calculated by dividing the total score of the evaluable items (responses 1–3) by the number of evaluable items, multiplied by two, and then converting the result into a percentage. Lower percentages indicated a worse status. If patients answered 11 or more items with response 4 (unevaluable items), they were considered 'invalid' cases.

Olfactory recognition threshold test

A standard olfactory test using a T&T (Takagi and Toyota) olfactometer, which is covered by health insurance in Japan, was used to evaluate olfactory acuity.[20,21] The T&T olfactometer test consists of five odorants: A = β-phenyl ethyl alcohol, which smells like a rose; B = methyl cyclopentenolone, which has a burnt smell; C = isovaleric acid, which smells like sweat; D = γ-undecalactone, which smells like fruit; and E = skatole, which smells like refuse waste (Daiichi Yakuhin Sangyo, Tokyo, Japan). Reagents A, C, D and E have eight concentration levels (from −2 to 5), whereas B has seven concentration levels (from −2 to 4). The maximum concentrations of A5, B4, C5, D5, and E5 are 631 mg/ml, 25.1 mg/ml, 100 mg/ml, 795 mg/ml and 79.5 mg/ml, respectively. Each reagent was serially 10-fold-diluted up to the most diluted stage (−2).

Patients were given a paper filter (width, 7 mm; length, 140 mm), one tip of which had been dipped in an odorous reagent. Patients sniffed the paper filter at a distance of 10–20 mm from the nostrils. This test kit was used to determine the recognition threshold for each odorant by using increasingly higher concentration levels. The recognition threshold was defined as the lowest concentration at which the odour could be identified for each odorant. Subsequently, the recognition thresholds for the five odorants were averaged, and the mean values were used to evaluate olfactory acuities.

Statistical analysis

In order to clarify the risk factors for relapse, we retrospectively investigated the patients' backgrounds, self-administered odour questionnaire findings, mean olfactory recognition thresholds, polyp (post-operative endoscopic appearance) scores and pre-operative CT scores among the groups. Comparisons of between-group results were performed using the Mann–Whitney U test. Fisher's exact test was used to compare sex differences, the presence or absence of asthma, and the severity of eosinophilic chronic rhinosinusitis.

The post-operative endoscopic appearance score was analysed using a conventional receiver operating characteristic curve, in order to determine the cut-off points that yielded the highest combined sensitivity and specificity with respect to distinguishing patients who required additional treatments at the time of relapse from those who did not, at the stage of selecting the post-operative treatment. The positive and negative predictive values were also calculated, given the cut-off points and the area under the curve. The optimum cut-off values were set using the Youden index, where (sensitivity + specificity − 1) is the maximum value under the receiver operating characteristic curve.[22]

Data are presented as median (range) values, unless otherwise indicated. All p-values were two-sided, and values of $p < 0.05$ were considered significant. All statistical analyses were performed using Stat Flex version 6.0 software (Osaka, Japan).

Results

Post-operative treatment requirements

Of the 339 patients with eosinophilic chronic rhinosinusitis, 65.2 per cent did not require additional treatment after the initial FESS (221 out of 339 patients, group A) (Figure 1). The remaining 34.8 per cent (118 out of 339 patients) were additionally treated with steroids for a median of five months (range = 1–68 months) after the initial FESS (group B). In group B, additional steroid treatment consisted of sinonasal topical steroids (106 out of 118, 89.8 per cent) and systemic steroids (47 out of 118, 39.8 per cent), with 43 patients receiving both treatments. Of these, the eosinophilic chronic rhinosinusitis was controlled by additional steroid treatment in 68.6 per cent of patients (84 out of 118). In the remaining patients (34 out of 118, 28.8 per cent), further treatment with dupilumab (19 out of 118, 16.1 per cent) and/or revision FESS (18 out of 118, 15.3 per cent) was required at a median of 69 months (range = 57–81 months) after the initial FESS (group

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press

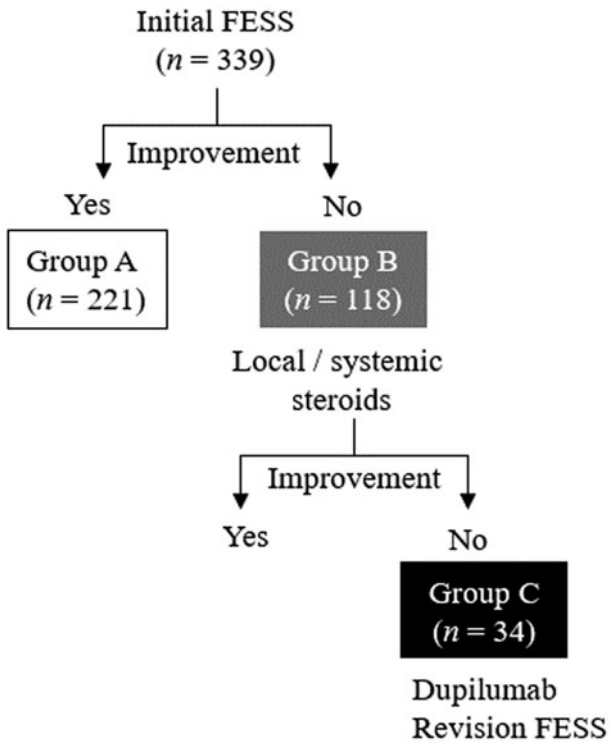

Figure 1. Post-operative course of patients with eosinophilic chronic rhinosinusitis. Initial functional endoscopic sinus surgery (FESS) was treatable in 65 per cent of patients with eosinophilic chronic rhinosinusitis (group A). In the remaining 35 per cent of patients, steroid treatment with topical sinonasal ($n = 106$) and/or oral administration ($n = 47$) was the first choice for relapse (group B). Even after steroid treatment, biologics (dupilumab, $n = 19$) and/or revision FESS ($n = 18$) were required (group C).

C). Consequently, the ratios of additional treatments required after the initial FESS, for local and systemic steroids, dupilumab, and revision FESS, were 31.3 per cent (106 out of 339), 13.9 per cent (47 out of 339), 5.6 per cent (19 out of 339) and 5.3 per cent (18 out of 339), respectively.

Group A significantly differed from group B in terms of age, diagnostic score, peripheral blood eosinophil count, presence of bronchial asthma, self-administered odour questionnaire score, mean olfactory recognition threshold and pre-operative CT score ($p < 0.01$) (Table 1). There were significant differences between groups A and C in terms of diagnostic score, peripheral blood eosinophil count, presence of bronchial asthma, self-administered odour questionnaire score, mean olfactory recognition threshold and CT score ($p < 0.01$).

There were significant differences in the distribution of degrees of eosinophilic chronic rhinosinusitis severity between groups A and B (Table 2). The proportions of mild and moderate patients were significantly higher in group A than in group B, whereas the proportion of severe patients was significantly higher in groups B and C.

Determination of post-operative treatments

In order to analyse the impact of intranasal conditions on the determination of post-operative treatment, we examined the post-operative endoscopic appearance scores. Receiver operating characteristic analysis of groups A and B demonstrated that the requirement for steroid treatment after the initial FESS (group B) could be predicted with a sensitivity of 0.8118 and specificity of 0.7971 by using an optimal cut-off post-operative endoscopic appearance score value of 30 per cent at a median of five months after the initial FESS (Figure 2). The post-operative endoscopic appearance score of 50.0 per cent (range = 33.3–83.3 per cent, $n = 106$) improved to 12.5 per cent (range = 0–25.0 per cent, $n = 106$) after sinonasal topical steroid treatment.

Furthermore, receiver operating characteristic analysis of groups A and C demonstrated that the requirement for dupilumab and/or revision surgery (group C) could be predicted with a sensitivity of 0.8947 and specificity of 0.4762 by using a cut-off post-operative endoscopic appearance score of 65 per cent at a median value of 69 months after initial FESS (Figure 3). The post-operative endoscopic appearance score of 83.3 per cent (range = 50.0–100 per cent, $n = 19$) improved to 25.0 per cent (range = 0–66.7 per cent, $n = 19$) after treatment with dupilumab.

Discussion

This study demonstrated risk factors for relapse, relapse ratios, and appropriate timing of the decision for post-operative optimal treatment using the post-operative endoscopic scoring system in patients with eosinophilic chronic rhinosinusitis after FESS.

Table 1. Baseline characteristics of patients with eosinophilic chronic rhinosinusitis

Characteristics	Group A	Group B	Group C	*P*-values	
				A *vs* B	A *vs* C
Age (median (range); years)	53 (23–82)	50 (22–75)	51 (29–75)	0.00345*	0.2640
Sex, male/female (*n*)	126/95	67/51	21/13	0.5701	0.7102
JESREC diagnostic score (median (range))	15 (11–17)	15 (11–17)	15 (9–17)	0.00001*	0.00179*
Peripheral blood eosinophils (median (range); %)	6.9 (1.5–38)	9.2 (2.2–27)	8.7 (2.3–27)	0.00005*	0.02945*
Presence of bronchial asthma, yes/no (*n*)	87/134	80/38	24/10	0.00001*	0.0008*
Severity of eosinophilic chronic rhinosinusitis, moderate/severe (*n* (%))	170/221 (76.9)	104/118 (88.1)	30/34 (88.2)	0.0136*	0.0418*
SAOQ score (median (range); %)	27.0 (0–97.5)	5.0 (0–97.5)	36 (0–80)	0.00022*	0.00082*
Mean olfactory recognition threshold (range)	5.6 (0–5.8)	5.8 (0–5.8)	5.8 (0–5.8)	0.00390*	0.02049*
CT score (median (range))	14 (3–24)	16 (0–28)	18 (0–28)	0.00030*	0.00093*

Group A – no additional post-operative treatment required, $n = 221$. Group B – local/systemic steroids required post-operatively, $n = 118$. Group C – dupilumab and/or revision surgery required, $n = 34$. *$p < 0.05$. JESREC = Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; SAOQ = self-administered odour questionnaire; CT = computed tomography

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press

Table 2. Post-operative treatment requirements according to eosinophilic chronic rhinosinusitis severity

Severity	Group A (*n* (%))	Group B (*n* (%))	Group C (*n* (%))	*P*-values	
				A *vs* B	A *vs* C
Mild	51 (23.1)	14 (11.9)	4 (11.8)	0.0136*	0.1794
Moderate	106 (48.0)	41 (34.7)	12 (35.3)	0.0216*	0.1978
Severe	64 (28.9)	63 (53.4)	18 (52.9)	0.00001*	0.0094*

Group A – no additional post-operative treatment required, $n = 221$. Group B – local/systemic steroids required post-operatively, $n = 118$. Group C – dupilumab and/or revision surgery required, $n = 34$. *$p < 0.05$.

For post-operative management aiming to avoid relapsed inflammation, it is important to predict the post-operative disease course. Younger age, severe levels of eosinophilia in the peripheral blood, olfactory dysfunction, rhinosinusitis, and complications of bronchial asthma were found to be risk factors for the requirement of additional treatments in groups B and C. Significant differences in the distribution of degrees of eosinophilic chronic rhinosinusitis severity, determined based on a criteria algorithm, suggested that greater severity required more advanced treatment.

In terms of the post-operative treatment strategy, regular post-operative follow up is required to allow early intervention for exacerbations. In particular, in cases of relapsed eosinophilic chronic rhinosinusitis, an accurate therapeutic strategy should be carefully selected. Although steroid nasal spray and leukotriene receptor antagonists are used to control eosinophilic chronic rhinosinusitis, their medical effects were insufficient in some patients in our study. As a recent pharmacological strategy, steroids and biologics that suppress type 2 inflammation have mainly been used for patients with intractable, relapsed eosinophilic chronic rhinosinusitis.[23,24] However, because these medicines are relievers rather than curative medicines, the condition will worsen if the treatment is discontinued.[6,25,26] Long-term administration is required for maintenance. Adverse effects must also be considered, even at low doses in the short term.[27,28]

Dupilumab improves the outcomes of chronic rhinosinusitis with nasal polyps, irrespective of surgery history, with greater improvements in endoscopic outcomes seen in patients with a shorter duration since the last surgery.[29] Dupilumab certainly improved the sinonasal condition of patients in this study. While biologics could help to avoid the adverse effects caused by long-term steroid administration, cost remains an issue.[9] Revision surgery (FESS) is indicated for patients with sufficient pharmacological effects and post-operative inflamed lesions in the residual tissue and/or adhesions in the sinonasal area. By removing the lesions and re-opening the ventilation routes of the paranasal sinuses using revision FESS, patients' symptoms can be relieved early. Particularly, polyps in the frontal sinus, which predict an adverse post-operative outcome, should be safely and completely removed and irrigated.[30]

In order to determine the appropriate post-operative treatment, it is important to define the relapse of eosinophilic chronic rhinosinusitis, as this definition has not been established. Therefore, we used the post-operative endoscopic appearance score, which is a simple and validated scoring system for clinical, real-time evaluation of the sinonasal condition.[13] Adverse symptoms and the presence of nasal polyps are included as risk factors for eosinophilic chronic rhinosinusitis relapse.[14] The rates of recurrence were 12.7 per cent for non-eosinophilic chronic rhinosinusitis, and 23.4 per cent

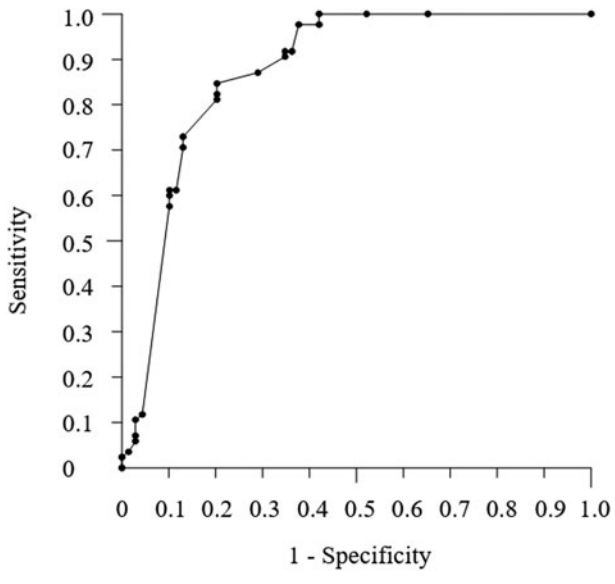

Figure 2. Requirement of steroids. The optimal cut-off value for the post-operative endoscopic appearance score in group B, which required post-operative steroid treatment, was 30 per cent ($p < 0.001$). Receiver operating characteristic – area under the curve value = 0.8725; cut-off value = 30 per cent; sensitivity = 0.8118; specificity = 0.7971; positive predictive value = 0.8313; negative predictive value = 0.7747.

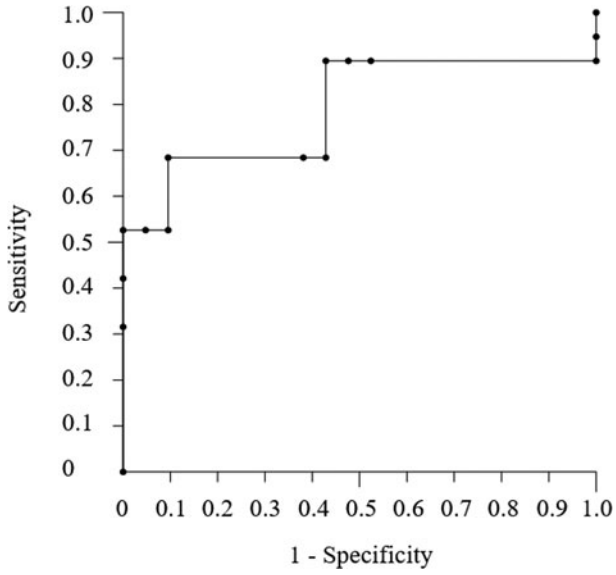

Figure 3. Requirement of advanced treatments. The optimal cut-off for the post-operative endoscopic appearance score in group C, for patients in whom the condition was resistant to steroid treatment and who required dupilumab and/or revision surgery, was 65 per cent ($p < 0.05$). Receiver operating characteristic – area under the curve value = 0.7895; cut-off value = 65 per cent; sensitivity = 0.8947; specificity = 0.4762; positive predictive value = 0.6296; negative predictive value = 0.8462.

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press

for mild, 31.1 per cent for moderate and 51.8 per cent for severe eosinophilic chronic rhinosinusitis.

It was desirable to increase both the positive and negative predictive values in order for the post-operative endoscopic appearance score to be used as a screening tool for treatment selection at the time of eosinophilic chronic rhinosinusitis relapse. In the receiver operating characteristic and area under the curve analysis, the relapsed ratios after initial FESS were 35 per cent (118 out of 339 patients) when the relapse was defined based on the requirement for steroids, with intranasal relapse ratios of 30 per cent based on the post-operative endoscopic appearance score. Thus, the data indicated that 65 per cent of patients with eosinophilic chronic rhinosinusitis could be treated successfully with FESS.

The rate of requirement for even more advanced treatment, with dupilumab and/or revision FESS, was 10 per cent (34 out of 339), in cases with a post-operative endoscopic appearance score of 65 per cent. Although the cut-off value of the post-operative endoscopic appearance score for dupilumab after FESS was analysed, the curve was almost a straight line; therefore, an effective cut-off value could not be determined by receiver operating characteristic analysis. Patients only underwent revision FESS before the time when dupilumab was indicated for chronic rhinosinusitis with nasal polyps, and were covered by health insurance. The advent of the biologic dupilumab might mean that revision FESS can be avoided in some patients who would have required revision FESS prior to the availability of dupilumab, as previously reported.[29]

This study had some limitations. We could not follow up all patients because they did not return for post-operative treatment unless we strongly recommended regular follow up after the initial FESS. Patients with more severe disease and with worse disease courses tended to return for follow-up assessments. It is necessary to educate patients on the necessity of continuing follow up to maintain favourable conditions and improve therapeutic outcomes further, particularly in patients with intractable eosinophilic chronic rhinosinusitis.

- Eosinophilic chronic rhinosinusitis is a refractory chronic rhinosinusitis caused by type 2 inflammation
- Defining eosinophilic chronic rhinosinusitis relapse is important for determining appropriate post-operative treatments
- The post-operative endoscopic scoring system can be used to determine post-operative treatment in eosinophilic chronic rhinosinusitis patients
- Younger age, severe eosinophilia, olfactory dysfunction, rhinosinusitis and bronchial asthma are risk factors for additional post-operative treatment
- The more severe the intranasal findings, the more advanced the treatment required

Our future work will involve the analysis of more patients within prospective multicentre studies, in order to understand the current therapeutic situation for intractable chronic rhinosinusitis and to contribute to medical advances in this field.

Conclusion

Post-operative treatment is essential for avoiding relapse in patients with eosinophilic chronic rhinosinusitis who undergo FESS. The more severe the intranasal findings, the more advanced the treatment required. It is necessary to develop treatment methods that consider the degree of relapse in post-operative eosinophilic chronic rhinosinusitis patients.

Acknowledgements. The authors gratefully acknowledge the help of their technical assistants Ms Yumi Kida and Ms Midori Tanide. We would also like to thank Editage (www.editage.com) for the English language editing. This work was financially supported by the Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research ('JSPS KAKENHI' grant number: 20K09700), and a Health Labour Sciences Research Grant (number: H30-Nantitou(nan)-Ippan-016).

Competing interests. None declared

References

1 Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S *et al.* European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020;**58**:1–464
2 Fujieda S, Imoto Y, Kato Y, Ninomiya T, Tokunaga T, Tsutsumiuchi T *et al.* Eosinophilic chronic rhinosinusitis. *Allergol Int* 2019;**68**:403–12
3 Ho J, Earls P, Harvey RJ. Systemic biomarkers of eosinophilic chronic rhinosinusitis. *Curr Opin Allergy Clin Immunol* 2020;**20**:23–9
4 Kato A. Immunopathology of chronic rhinosinusitis. *Allergol Int* 2015;**64**:121–30
5 Eschenbacher W, Straesser M, Knoeddler A, Li RC, Borish L. Biologics for the treatment of allergic rhinitis, chronic rhinosinusitis, and nasal polyposis. *Immunol Allergy Clin North Am* 2020;**40**:539–47
6 Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE *et al.* Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;**394**:1638–50
7 Fokkens FW, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J *et al.* EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy* 2019;**74**:2312–19
8 Fujieda S, Matsune S, Takeno S, Ohta N, Asako M, Bachert C *et al.* Dupilumab efficacy in chronic rhinosinusitis with nasal polyps from SINUS-52 is unaffected by eosinophilic status. *Allergy* 2022;**77**:186–96
9 Scangas GA, Wu AW, Ting JY, Metson R, Walgama E, Shrime MG *et al.* Cost utility analysis of dupilumab versus endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. *Laryngoscope* 2021;**131**:26–33
10 Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of disease in chronic rhinosinusitis with nasal polyps. *J Asthma Allergy* 2021;**14**:127–341
11 Matsunaga K, Katoh N, Fujieda S, Izuhara K, Oishi K. Dupilumab: basic aspects and applications to allergic diseases. *Allergol Int* 2020;**69**:187–96
12 Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W *et al.* Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013;**131**:110–16
13 Tsuzuki K, Hinohira Y, Takebayashi H, Kojima Y, Yukitatsu Y, Daimon T *et al.* Novel endoscopic scoring system after sinus surgery. *Auris Nasus Larynx* 2014;**41**:450–4
14 Tokunaga T, Sakashita M, Haruna T, Asaka D, Takeno S, Ikeda H *et al.* Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy* 2015;**70**:995–1003
15 Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M *et al.* Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg* 2015;**152**:1–39
16 Konno W, Kashiwagi T, Tsunemi Y, Goto K, Haruna S. Long-term postoperative control of eosinophilic chronic rhinosinusitis recurrence by inserting a steroid-eluting, sinus-bioabsorbable device reduces the dosage of oral steroid. *Auris Nasus Larynx* 2019;**46**:365–73
17 Saito T, Okazaki K, Hamada Y, Hashimoto K, Tsuzuki K. Therapeutic indications for sinonasal topical steroid treatment and its effects on eosinophilic chronic rhinosinusitis after endoscopic sinus surgery. *J Laryngol Otol* 2021;**135**:858–63
18 Tsetsos N, Goudakos JK, Daskalakis D, Konstantinidis I, Markou K. Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review. *Rhinology* 2018;**56**:11–21
19 Lund VJ, Mackay IS. Staging in rhinosinusitus. *Rhinology* 1993;**31**:183–4
20 Takebayashi H, Tsuzuki K, Oka H, Fukazawa K, Daimon T, Sakagami M. Clinical availability of a self-administered odor questionnaire for patients with olfactory disorders. *Auris Nasus Larynx* 2011;**38**:65–72
21 Oka H, Tsuzuki K, Takebayashi H, Kojima Y, Daimon T, Sakagami M. Olfactory changes after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Auris Nasus Larynx* 2013;**40**:452–7
22 Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cut-off point. *Biom J* 2005;**47**:458–72

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press

23 Shah SA, Ishinaga H, Takeuchi K. Pathogenesis of eosinophilic chronic rhinosinusitis. *J Inflamm* (*Lond*) 2016;**13**:11
24 Takabayashi T, Schleimer RP. Formation of nasal polyps: the roles of innate type 2 inflammation and deposition of fibrin. *J Allergy Clin Immunol* 2020;**145**:740–50
25 Akiyama K, Makihara S, Uraguchi K, Samukawa Y, Oka A, Hoshikawa H. Impact of preoperative systemic corticosteroids on the histology and diagnosis of eosinophilic chronic rhinosinusitis. *Int Arch Allergy Immunol* 2019;**179**:81–8
26 Hong SJ, Lee JK, Lee HS, Lee JY, Pyo JS, Lee KC. Availability of preoperative systemic steroids on endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Yonsei Med J* 2014;**55**:1683–90
27 Grennan D, Wang S. Steroid side effects. *JAMA* 2019;**322**:282
28 Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C *et al*. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;**71**:339–46
29 Hopkins C, Wagenmann M, Bachert C, Desrosiers D, Han JK, Hellings PW *et al*. Efficacy of dupilumab in patients with a history of prior sinus surgery for chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol* 2021;**11**:1087–101
30 Tsuzuki K, Hashimoto K, Okazaki K, Nishikawa H, Sakagami M. Predictors of disease progression after endoscopic sinus surgery in patients with chronic rhinosinusitis. *J Laryngol Otol* 2019;**133**:678–84

https://doi.org/10.1017/S0022215123000798 Published online by Cambridge University Press