Factors Affecting the Control of Chronic Rhinosinusitis With Nasal Polyps: A Comparison in Patients With or Without NERD

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Abstract
Objectives: The aim was to compare the control of chronic rhinosinusitis with nasal polyps (CRSwNP) after endoscopic sinus surgery (ESS), in patients with/without nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD).
Study Design: A retrospective hospital-based sample of CRSwNP patients with/without NERD with follow-up.
Setting: Tertiary rhinology centers.
Methods: Electronic patient record data from 116 CRSwNP patients (46 with NERD and 70 without NERD) undergoing ESS during 2001–17 were studied. Mean follow-up time was 9.9 years (range 1.1–15.3). Endpoints reflecting uncontrolled CRSwNP were revision ESS, and need for rescue/advanced therapy (e.g. antibiotics, oral corticosteroids and/or biological therapy) during follow-up. NERD was variable of interest and gender, age, asthma, allergic rhinitis (AR), smoking, Lund-Mackay (LM) score of sinus computed tomography scans previous ESS and baseline total ethmoidectomy were used as covariates.
Results: Twenty-one (49.7%) NERD patients and 18 (25.7%) non-NERD patients underwent revision ESS within a mean SD of 4.3 ± 2.8 and 3.7 ± 2.6 years, respectively (p = .013, by Logrank test). In Cox’s regression models, NERD, female gender, young age, asthma, AR, previous ESS, and lack of total ethmoidectomy were associated with revision-ESS. In adjusted model, only the total ethmoidectomy predicted revision-free survival. In adjusted logistic regression model, there was an insignificant trend that NERD and LM score were associated with the need for rescue/advanced therapy in the follow-up.
Conclusions: Patients with NERD had higher risk of uncontrolled CRSwNP than patient group without NERD, as measured by revision ESS and/or need for rescue/advanced therapy in the follow-up. In addition, baseline total ethmoidectomy was associated with revision-free survival.

Keywords
chronic rhinosinusitis, computed tomography, diagnostics, endoscopic sinus surgery, paranasal sinuses, sinusitis

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Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous group of inflammatory diseases of the nose and paranasal sinuses lasting for at least 12 weeks, with a prevalence varying between 3–11%. CRS has a severe impact on quality of life, which is comparable with asthma, chronic obstructive pulmonary disease, and diabetes. The costs of CRS are substantial. CRS phenotypes are CRS with nasal polyps (CRSwNP) and without (CRSsNP). Both have several molecular endotypes. CRSwNP affects 0.5-4.5% of the general population. Its pathogenesis is related to defects in the sinonasal epithelial cell barrier, increased exposure aberrant interactions between airway mucosa and microbiota/irritants. CRSwNP patients tend to have more extensive sinus disease than patients with CRSsNP as measured by the 22 item Sino-Nasal Outcome Test (SNOT-22) score, sinus computed tomography (CT) Lund-Mackay (LM) –scores, and endoscopic Lund-Kennedy-scores. Nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NERD) has been reported in 8–26% of patients with CRSwNP. NERD is characterized by severe eosinophilic hyperplastic inflammation of all sinuses and nasal passages as well as of the lower airways.

A sudden worsening of preexisting symptoms suggests an exacerbation of CRS. European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 proposed the first definition of control in rhinosinusitis, which was slightly elaborated upon in the 2020 version. It is based on a combined evaluation of symptom severity, nasal endoscopy and need for systemic medication (rescue treatment), and as such, CRS patients are defined as controlled, partly controlled or uncontrolled.

Several factors might associate with worsening of CRSwNP. CRSwNP patients have higher revision endoscopic sinus surgery (ESS) risk than CRSsNP patients. High serum and tissue eosinophilia values of CRSwNP have been shown to be associated with higher recurrence rates. In operated CRSwNP patients, higher preoperative endoscopic nasal polyp (NP) score, asthma, NERD, comorbid allergic sensitization, tissue interleukin-5 (IL-5) levels, and frontal sinus disease have higher risk for revision surgery. Smoking has been shown to decrease the time before revision surgery in CRSwNP. Postoperative SNOT-22 results can be used to predict the risk of revision surgery in CRS.

There is some evidence that recurrence rate of ESS is lower after ESS with extended approaches compared with limited one. A systemic Cochrane review showed that there is limited knowledge on whether isolated nasal polypectomy or more extensive sinus surgery is superior for CRSwNP. A multicenter cohort study showed no difference in terms of health-related quality of life improvement between polypectomy and ESS. However, some studies suggest that more extensive surgery (such as total ethmoidectomy) might be more effective than simple polypectomy or minimal invasive ESS.

The aim was to compare postoperative control of CRSwNP in patients with/without NERD. Disease control was measured by using revision ESS rate and, need for rescue/advanced therapy (e.g. antibiotics, oral corticosteroids (OCS) and/or biological therapy) during follow-up. We hypothesized that patients with NERD have higher risk of uncontrolled CRSwNP than patients without NERD.

Methods

Setting

A retrospective hospital-based sample of CRSwNP patients in Finland with follow-up.

Subjects

This retrospective follow-up study was carried out at the Skin and Allergy Hospital of Helsinki University Hospital, and Departments of Otorhinolaryngology – Head and Neck Surgery, at Helsinki and Tampere University Hospitals between 2001 and 2020. The study design (nro 31/13/03/00/2015) was approved by the Research Ethics Committee of the above mentioned hospital districts and a study permission was granted.

We used electronic health record data of in total 116 CRSwNP patients who underwent consultation for ESS between 2003 and 2017 in the above-mentioned hospitals. The inclusion criterion was ESS in /C20 year after the sinus CT scans taken for the baseline consultation visit (or the baseline visit, if CT data were not available) and this procedure was defined as the “baseline ESS”. Previous sinonasal surgery was allowed.

The group of CRSwNP with NERD involved a random sample of 46 patients undergoing baseline ESS between 2003–16. NERD data was obtained from patient records: a history of wheeze/cough/naso-ocular symptoms after ingestion of NSAID were considered a sign of NERD. NERD diagnosis was additionally based on a positive reaction (wheeze and/or naso-ocular reaction) after intake of acetylsalicylic acid (ASA) at the hospital in two patients.

The group of CRSwNP without NERD involved 70 patients undergoing baseline ESS between 2003–2017.
They were (i) twenty-six CRSwNP patients eligible (e.g., meeting with inclusion/exclusion criteria), from a random sample of 69 CRSwNP patients who had undergone nasal polyp biopsy during ESS consultation/ESS at Tampere University Hospital between 2005–2007; (ii) thirty-eight CRSwNP patients eligible from a random sample of 246 CRS patients who had undergone ESS consultation between 2002–2017 at the Helsinki and Tampere University Hospitals; (iii) six CRSwNP patients eligible form a random sample of 97 CRS/rhinitis patients who underwent sinus CT scans due to suspicion of CRS at Tampere University Hospital during 2006–2011.32

The exclusion criteria for both groups were age < 18 years, sinus CT signs of previous total ethmoidectomy in baseline CT scans, no patient record information of endoscopic NPs during baseline visit or baseline ESS, missing data of baseline operation or follow-up, ASA desensitization, eczematous granulomatosis with polyangiitis, primary ciliary dyskinesia, cystic fibrosis, acute fungal rhinosinusitis, or severe systemic disease such as active cancer. CRSwNP was diagnosed according to the EPOS 2012.33 Baseline and follow-up ESS were performed by eight surgeons. After surgery, patients were instructed to use topical corticosteroids (either sprays or drops) regularly to prevent polyp regrowth, but topical corticosteroid rinses were not used.

Outcomes and Covariates

The follow-up data were collected from patient records on average (min-max) 9.9 (1.1–15.3) years after the baseline visit, until the last follow-up visit and/or corresponding patient record data of CRSwNP control. Two outcome measurements reflecting uncontrolled CRSwNP, were formed from the data: survival time until revision ESS or the end of follow-up; and need for rescue/advanced therapy, e.g. at least one of the following: (1.) ≥2 purchased doctor-prescribed antibiotic courses/year (2.) ≥1 purchased doctor-prescribed OCS courses/year and/or continuous OCS (3.) initiation of biological therapy during the follow-up. Electronic prescription and/or patient record data (if available) of the visit at the time of prescription were used to confirm that courses were prescribed due to exacerbation of CRSwNP and/or asthma. The search for prescription data of the last two years was performed from the nation-wide electronic prescription database during 2018–2020, at least three years apart from the baseline ESS.

The data of covariates were collected from the hospitals patient records and sinus CT scans: gender, age, current smoking, allergic rhinitis (AR), asthma, previous ESS, and the extent of baseline ethmoidectomy. The definition of total ethmoidectomy was physician-reported opening of all ethmoidal cells ± additional operations (Table 1). Partial ethmoidectomy was defined as all other types of opening of ethmoidal cells ± additional operations. Polypectomy was defined as removal of NPs without opening of bony walls of ethmoidal cells ± middle meatal antrostomy. Asthma diagnosis was based on patient record documentation on typical history and asthma symptoms, and findings of lung function test (spirometry and peak expiratory flow (PEF)) of at least 15% improvement with bronchodilator test in spirometry (in forced expiratory flow volume in one second (FEV1) or in forced vital capacity (FVC)) and/or recurrent 20% diurnal variation in PEF monitoring or recurrent 15% bronchodilator response in PEF monitoring or positive methacholine challenge test (moderate to severe bronchial hyperresponsiveness). NERD diagnosis was based on a positive patient history of wheeze/cough or naso-ocular symptoms after intake of NSAID.34 A doctor-diagnosed AR was based on positive skin prick test or serum specific IgE results, in addition to typical symptoms.

Statistics

For the statistical analysis SPSS Base 24 Statistical Software Package (SPSS Inc., Chicago, IL, USA) was used. The associations between predictor/covariates and outcomes of uncontrolled CRSwNP during follow-up were estimated using Fisher’s exact test (dichotomous), and Kruskal-Wallis and Mann Whitney U test (continuous). Kaplan-Meier method and logrank test were used in revision-free survival models. Cox’s proportional hazards model was used to evaluate the hazard ratio (HR) of revision ESS rate between different background variables. Each predisposing factor was modelled separately. The background variables that were associated significantly with revision ESS, were entered into the multivariable model. P-values < 0.05 were considered statistically significant.

Results

Of the total of 116 CRSwNP patients, 53 (46%) were females, 50 (43%) had history of AR, 66 (57%) had asthma, 46 (40%) had NERD, and 23 (20%) were current smokers. At the baseline, the mean age ± SD was 48.6 ± 15.4 years. All patients underwent ESS within one year after the baseline consultation visit. Sixty patients (52%) did not have a history of previous ESS within one year after the baseline consultation visit. Patients with NERD were more often females and they had more often asthma diagnosis, higher median number of previous ESS, and higher median LM-score than patients without NERD (Table 1).
Table 1. Comparison Between Two Subject Groups: CRSwNP With NERD and CRSwNP Without NERD.

|                                | CRSwNP Without NERD | CRSwNP With NERD | P     |
|--------------------------------|---------------------|------------------|-------|
|                                | N = 70              | N = 46           |       |
| Gender, n (%)                  |                     |                  |       |
| Female                         | 23 (32.9)           | 30 (65.2)        | .001  |
| Male                           | 47 (67.1)           | 16 (34.8)        |       |
| Age, median (Q1–Q3)            | 48.8 (39.5–59.0)    | 50.0 (37.8–58.9) | .82   |
| Smoking, n (%)                 |                     |                  |       |
| No                             | 53 (77.9)           | 37 (82.2)        | .64   |
| Current                        | 15 (22.1)           | 8 (17.8)         |       |
| Asthma                         |                     |                  |       |
| No                             | 46 (65.7)           | 3 (6.7)          | <.001 |
| Yes                            | 24 (34.3)           | 42 (93.3)        |       |
| Allergic rhinitis              |                     |                  |       |
| No                             | 45 (64.3)           | 20 (44.4)        | .053  |
| Yes                            | 25 (35.7)           | 25 (55.6)        |       |
| ≥4 antibiotic courses /year    |                     |                  |       |
| No                             | 44 (74.6)           | 26 (70.3)        | .65   |
| Yes                            | 15 (25.4)           | 11 (29.7)        |       |
| ≥1 peroral corticosteroid course /year |   |                  |       |
| No                             | 41 (58.6)           | 23 (50.0)        | .45   |
| Yes                            | 29 (41.4)           | 23 (50.0)        |       |
| NP eosinophilia                |                     |                  |       |
| < 30%                          | 28 (49.1)           | 12 (37.5)        | .38   |
| ≥30%                           | 29 (50.9)           | 20 (62.5)        |       |
| Baseline NP score, median (Q1–Q3) | 4 (3–6)            | 5 (4–6)          | .076  |
| Total number of previous CRS surgeries, median (Q1–Q3) | 0 (0–1.25) | 1 (0–2) | .046 |
| A history of previous ESS     |                     |                  |       |
| No                             | 42 (58.6)           | 18 (40.0)        | .18   |
| Polypectomy (PP) ±middle/inferior meatal antrostomy (MMA/IMA) | 19 (27.1) | 15 (33.3) |       |
| PP + partial ethmoidectomy ± MMA ± frontal recess surgery (FRS) | 7 (10.0) | 9 (20.0) |       |
| PP + total ethmoidectomy ± MMA | 1 (1.4)            | 0 (0)            |       |
| MMA/IMA without PP             | 1 (1.4)             | 3 (6.7)          |       |
| Baseline sinus CT scans        |                     |                  |       |
| CT scans were available        | 58 (82.9)           | 40 (87.0)        | .61   |
| Total Lund-Mackay score, median (Q1–Q3) | 14 (12–17.5)    | 15 (14–21.5) | .010 |
| Sum of the ethmoid Lund-Mackay scores, median (Q1–Q3) | 4 (4–6) | 6 (4–8) | .025 |
| Previous ESS signs of the baseline sinus CT scans | 30 (51.7) | 30 (75.0) | .022 |
| Total removal of uncinated process | 7 (12.1)        | 11 (27.5)        | .066  |
| Opening of the infundibulum    | 8 (13.8)            | 10 (25.0)        | .19   |
| Opening of the bulla ethmoidalis | 6 (10.3)         | 4 (10.0)         | 1.0   |
| Opening of the basal lamella   | 1 (1.7)             | 1 (2.5)          | 1.0   |
| Full anterior ethmoidectomy (up to frontal recess) | 1 (1.7) | 1 (2.5) | 1.0   |
| Full posterior ethmoidectomy   | 0 (0)               | 0 (0)            | –     |
| Entrance of the frontal recess without performing adequate Draf 2a | 2 (3.4) | 0 (0) | .51   |
| Draf 2a                        | 2 (3.4)             | 0 (0)            | .51   |
| Opening of the sphenoid        | 0 (0)               | 0 (0)            | –     |
| Baseline ethmoidectomy         |                     |                  |       |
| No                             | 22 (31.4)           | 20 (43.5)        | .39   |
| Partial                        | 32 (45.7)           | 19 (41.3)        |       |
| Total                          | 16 (22.9)           | 7 (15.2)         |       |
| Baseline surgery performed in addition to ethmoidectomy |                 |                  |       |
| Polypectomy (PP)³              | 17 (24.6)           | 14 (31.1)        | .64   |
| PP + middle meatal antrostomy (MMA) ± inferior meatal antrost. (IMA) | 49 (71.0) | 27 (60.0) |       |
| PP + frontal recess surgery/balloon (FRS) ± MMA | 2 (2.9) | 2 (4.4) |       |
| PP + sphenoidectomy ± MMA ± FRS | 1 (1.4)            | 2 (4.4)          |       |

(continued)
Revision-Free Survival

Twenty-one (49.7%) NERD patients and 18 (25.7%) non-NERD patients underwent revision ESS within a mean ± SD of 4.3 ± 2.8 and 3.7 ± 2.6 years, respectively. The overall follow-up time was 9.6 ± 3.8 years in NERD group and 10.0 ± 3.2 years in non-NERD group. In the survival analyses the mean (min-max) follow-up time was 7.1 ± 3.8 years until the first revision surgery/2019, whichever came first. We formed a revision-free survival curve with logrank test, in which the predictor variables were NERD (Figure 1(A)) or, baseline polypectomy/partial/total ethmoidectomy in subgroups without/with NERD (Figure 1(B) and (C)). NERD was associated with increased revision ESS risk when comparing with the patients without NERD (Figure 1(A)). When observing the non-NERD group, baseline partial ethmoidectomy or baseline polypectomy was associated with increased revision ESS risk as compared with baseline total ethmoidectomy (Figure 1(B)). Yet in the NERD group, baseline total ethmoidectomy was not statistically significantly associated with revision-free survival (Figure 1(C)).

Cox’s proportional hazards model was used to investigate the association between the revision-free survival time until the revision ESS, and the predictors. In a univariate model, NERD, female gender, young age, asthma, AR, previous ESS, and lack of total ethmoidectomy were associated with revision-ESS in the follow-up (Table 2). In a multivariable model, only total ethmoidectomy at baseline was associated with revision-free survival (Table 2).

Table 1. Continued.

| CRSwNP Without NERD | CRSwNP With NERD |
|---------------------|------------------|
| N = 70              | N = 46           |
| **Revision ESS performed during the follow-up** |                  |
| No                  | 52 (74.3)        | 25 (54.3) | .016 |
| Polypectomy (PP) ± middle/inferior meatal antrostomy (MMA/IMA) | 6 (8.6) | 6 (13.0) |
| PP + partial ethmoidectomy ± MMA ± frontal recess surgery (FRS) | 10 (14.3) | 6 (13.0) |
| PP + total ethmoidectomy ± MMA | 2 (2.9) | 9 (19.6) |

NERD = nonsteroidal anti-inflammatory drug exacerbated respiratory disease; CRS = chronic rhinosinusitis; AR = allergic rhinitis; NP = nasal polyps; FRS = frontal recess surgery; MMA = middle meatal antrostomy; RFA = radiofrequency ablation. P values by Fisher's exact test (dichotomous variables) or Mann Whitney U test (continuous variables). Q1 = 25% percentile, Q3 = 75% percentile. Polypectomy = removal of polyps ± middle meatal maxillary antrostomy without ethmoidectomy Partial ethmoidectomy = anterior/partial ethmoidectomy in addition to polypectomy. Total ethmoidectomy = total ethmoidectomy in addition to polypectomy; ¹One patient had additional septoplasty and middle turbinate resection. ²Six patients had additional operations: inferior turbinate RFA (n = 4), septoplasty (n = 1), dental extractions (n = 1). All subjects underwent endoscopic sinus surgery (ESS) at baseline. Statistically significant p values (<.05) are in bold.

Figure 1. Revision-free survival models according to the Kaplan-Meier method. Predictive effect of (a) NERD and (b and c) extent of baseline ethmoidectomy to the time until revision endoscopic sinus surgery (ESS). P-values by log rank test. p1 = general; p2 = total ethmoidectomy vs. polypectomy or partial ethmoidectomy.
Rescue/Advanced Therapy in the Follow-up

Medication data for the follow-up period 2018–2020 were available for 112/116 (96.6%) patients. This patient group data was analyzed in univariate and multivariable logistic regression models to find background variables associating with the need for rescue/advanced therapy in the follow-up. In the univariate model, NERD, asthma, and high LM score at baseline were associated with the need for rescue/advanced therapy in the follow-up (Table 3). When entering these three variables into the multivariable model, there was an insignificant trend that NERD and LM score were associated with the need for rescue/advanced therapy in the follow-up (Table 3).

Discussion

The purpose of this retrospective follow-up study was to compare postoperative control of CRSwNP patients between NERD and non-NERD groups. We found that NERD group had higher risk of uncontrolled CRSwNP than non-NERD group. We used two outcome measurement variables for uncontrolled CRSwNP: revision ESS-rate and need for rescue/advanced therapy in the follow-up. This is in line with previous observations that have shown by using different outcome variables that CRSwNP patients with asthma or NERD have an increased risk for uncontrolled disease compared with CRSwNP without these comorbidities.18,21–23,31,35 CRSwNP patients with comorbid asthma and/or NERD patients have shown to benefit from ESS, yet long-term recurrence seems more common with these comorbidities.23,36,37

We also found in adjusted models that baseline total ethmoidectomy was associated with revision-free survival. This finding was more pronounced in the group without NERD than in the NERD group. This may reflect a more severe disease and a greater tendency for polyps to grow in NERD, despite the extent of baseline surgery. The literature has shown that CRSwNP patients with NERD have higher levels of serum and tissue eosinophils than CRSwNP without NERD, and both serum and tissue eosinophilia has been shown to predict polyps regrowth and ESS revisions.1,14–17

### Table 2. Unadjusted and Adjusted Cox’s Proportional Hazard Model for the Variables Analyzed Fitted for the Need for Revision Endoscopic Sinus Surgery (ESS) During the Follow-up of on Average 9.9 Years.

|                  | N All | N (%) | Events | HR (95% CI) | P-Value | Adjusted HR (95% CI) | P-Value |
|------------------|-------|-------|--------|-------------|---------|----------------------|---------|
| **NERD**         |       |       |        |             |         |                      |         |
| No               | 70    | 18 (25.7) | 1 |             |         |                      |         |
| Yes              | 46    | 21 (45.7) | 2.13 (1.13–4.00) | .019 | 1.15 (0.50–2.63) | .75     |
| **Gender**       |       |       |        |             |         |                      |         |
| Male             | 63    | 15 (23.8) | 1 |             |         |                      |         |
| Female           | 53    | 24 (45.3) | 2.25 (1.18–4.29) | .014 | 1.52 (0.73–3.17) | .26     |
| **Age**          |       |       |        |             |         |                      |         |
|                  | 90    | 31 (34.4) | 0.88 (0.40–1.91) | .75 | Not entered |         |
| **Current smoking** |     |       |        |             |         |                      |         |
| No               | 23    | 8 (34.8) | 1 |             |         |                      |         |
| Yes              | 66    | 28 (42.4) | 2.45 (1.22–4.95) | .012 | 1.89 (0.71–5.06) | .21     |
| **Asthma**       |       |       |        |             |         |                      |         |
| No               | 49    | 11 (22.4) | 1 |             |         |                      |         |
| Yes              | 66    | 28 (42.4) | 2.45 (1.22–4.95) | .012 | 1.89 (0.71–5.06) | .21     |
| **AR**           |       |       |        |             |         |                      |         |
| No               | 65    | 18 (27.7) | 1.91 (1.02–3.60) | .045 | 0.85 (0.38–1.87) | .68     |
| Yes              | 50    | 21 (42.0) | 1.91 (1.02–3.60) | .045 | 0.85 (0.38–1.87) | .68     |
| **LM score**     |       |       |        |             |         |                      |         |
|                  |       |       |        |             |         |                      |         |
| **Previous ESS** |       |       |        |             |         |                      |         |
| No               | 60    | 15 (25.0) | 1 |             |         |                      |         |
| Yes              | 56    | 24 (42.9) | 2.13 (1.12–4.08) | .022 | 1.69 (0.86–3.33) | .13     |
| **Baseline ethmoidectomy** | |       |        |             |         |                      |         |
| Total            | 23    | 3 (13.0) | 1 |             |         |                      |         |
| Partial          | 51    | 21 (41.2) | 3.75 (1.12–12.56) | .033 | 3.52 (1.03–11.98) | .044    |
| No (polypectomy) | 42    | 15 (35.7) | 3.30 (0.95–11.39) | .060 | 3.48 (0.99–12.23) | .052    |

NERD = nonsteroidal anti-inflammatory drug exacerbated respiratory disease; AR = allergic rhinitis; HR = Hazard ratio; CI = confidence interval. Only the variables that had significant p values (<.05, marked with bold font) in univariate model were entered into the multivariable model. Polypectomy = removal of polyps; Middle meatal maxillary antrostomy without ethmoidectomy; Partial ethmoidectomy = anterior/partial ethmoidectomy in addition to polypectomy; Total ethmoidectomy = total ethmoidectomy in addition to polypectomy.
limited knowledge of effect of extent of ethmoidal surgery on the revision ESS rate. Jankowski et al. has shown that more extensive surgery (nasalization of the ethmoids) was associated with lesser polyp recurrence.29 Browne et al. has concluded that nasal polypectomy with additional surgery seems to have no benefit over simple polypectomy in terms of health-related quality of life improvement.27 The study by Wu et al. has shown that the median time to revision surgery was longer in patients who underwent middle turbinate resection rather than preservation.24 Mastersson et al. has reported that extensive ESS had lower revision surgery rate compared to polyposis surgery limited to anterior ethmoids.30 Bassioni and Wormald has shown that Draf 3 frontal sinusotomy reduced the prevalence of polyp recurrence.21 Thus, most previous studies seem to be in line with the results presented in our study, which indicate that extended surgery might lead to better disease control in CRSwNP than limited surgery. However, a Cochrane review in 2014 has not identified any trials which would have met their inclusion criteria.26

Studies suggest that more extensive sinus surgery could be more effective than limited surgery in the treatment of CRSwNP.21,24,29,30 However, as mentioned in the EPOS 2020, the weight of evidence for extended approaches lies in revision cases, not in primary surgeries.1 When choosing between limited or extended surgery, the potential disadvantages and financial implications as well as the available hospital resources should be considered. A Japanese group showed in a database analysis of 50,734 patients, that the extent of ESS did not significantly affect the overall complication rate, but multiple sinus surgery was associated with a higher rate of orbital injury comparing with single sinus surgery or with surgery for all the sinuses.38 In future studies, it should be assessed whether the higher costs of extended surgery will lead to a reduction in subsequent healthcare costs.

In our study about a half of the patients had undergone one or more previous ESS, which was a
predictor of the need for revision ESS in the follow-up in unadjusted model. Yet previous ESS was not associated with recurrence-free survival in adjusted model. It has been reported earlier that revision rate is higher in CRSwNP if the patient has a history of previous surgery, but the finding has not been consistent in all reports.

We acknowledge that in order to reduce variables in statistical models, we focused on observing the extent of ethmoidectomy although also surgery of other paranasal sinuses could have had affected the results. Middle meatal antrostomy was performed in the most of baseline surgery cases yet, patient record data was not available of the extent of middle meatal antrostomy. Frontal surgery was performed in only a few baseline cases. Thus a prospective study with increased subject number would be warranted. Other limitations of this retrospective study include small sample size and lack of a standardized patient-reported outcome measurement. We acknowledge that due to retrospective nature of this study, proper data was not available if the patients had used intranasal corticosteroids postoperatively according to instructions, which could have affected the results. Our analysis of revision surgery may have been influenced by several factors unrelated to the recurrence of CRS, including waiting times for surgery, patients’ preferences to delay surgery for personal reasons, the patient’s tolerance of recurrent sinusitis symptoms, baseline operative technique, and the surgeon’s opinion as to when revision surgery is clinically warranted. It is also possible that a patient may have changed to private hospital leading to a slight possibility that no accurate follow-up data was available On the other hand, public medical care covers over 90% of operations in Finland and the patients who were no longer in hospital follow-up were followed up by reviewing electronic prescriptions, which would minimize this source of possible bias.

Conclusion
This retrospective cohort of CRSwNP patients showed that NERD group had higher risk of uncontrolled disease than patient group without NERD as measured by revision ESS and/or need for rescue/advanced therapy in the follow-up. In addition, baseline total ethmoidectomy was associated with revision-free survival.

Ethical Approval
This study was approved by our institutional review board.

Statement of Human and Animal Rights
This article does not contain any studies with human or animal subjects.

Statement of Informed Consent
There are no human subjects in this article and informed consent is not applicable.

Authors’ Contributions
Markus Jukka Lilja: Author has participated in study planning, data collection, data management, and manuscript preparation.
Anni Koskinen: Author has participated in study planning, data collection, data management, and manuscript preparation.
Paula Virkkula: Author has participated in study planning, data collection, data management, and manuscript preparation.
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