

Surgical treatment for nasal polyposis: predictors of outcome

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Abstract Nasal polyps recur in approximately one-third of patients after surgical treatment. It would be beneficial to be able to predict the patients in whom we might expect recurrence and to predict the clinical outcome after surgery. The study included 30 patients operated for nasal polyps. Removed polyps were analyzed by immunohistochemical analysis for IL-5, IgE, vascular endothelial growth factor and eosinophilic infiltration. These parameters together with preoperative CT score were used as independent variables, and subjective score improvement after 2 years was used as a dependent variable in multiple linear regression analysis. Furthermore, the patients were divided into two groups: low and high polyp tissue immunoreactivity. The Chi-squared test was used to determine whether polyp immunoreactivity influences polyp recurrence and subjective score. Preoperative CT score had a slightly positive correlation with subjective score after 2 years. High eosinophil infiltration significantly predicted a higher risk for polyp recurrence. High IL-5 positivity was related to greater risk for polyp recurrence than low IL-5 reactivity but not significantly. IgE and VEGF reactivity in polyp specimens did not have any effect on polyp recurrence. High eosinophilic infiltration in polyps can predict worse outcome after surgical treatment of chronic rhinosinusitis with nasal polyposis. IgE and

VEGF do not have prognostic significance to polyp recurrence after surgery. The preoperative extent of disease measured by CT score had a slightly positive correlation with worse outcome after surgery.

Keywords Nasal polyps · Interleukin-5 · Vascular endothelial growth factors · Immunoglobulin E · Nasal surgical procedures · CT score · Eosinophil infiltration

Introduction

Nasal polyps (NP) are usually part of an entity called chronic rhinosinusitis with nasal polyposis (CRSwNP). According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012) [1], CRSwNP is defined as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip); ± facial pain/pressure; ± reduction or loss of smell; lasting for ≥12 weeks; and bilateral polyps which should be endoscopically visualized in the middle meatus. Although the exact etiology of NP is still unknown, there are several mediators and factors that have an apparent role in the growth and development of NP. Eosinophils are predominant cells found in the majority of NP [2] in Caucasians, suggesting that they have an important role in polyp growth. NP are found more frequently in some conditions such as aspirin intolerance and allergic fungal rhinosinusitis [3]. Contrary to common belief, NP are not more common in immunoglobulin-E (IgE)-mediated diseases such as allergic rhinitis and extrinsic asthma than in their non-allergic counterparts. These data led some authors to propose the hypothesis of IgE-mediated nasal disease without systemic manifestations [4]. IgE is, however,

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related to local eosinophilic inflammation [5] and is probably involved in the etiology of NP. A mediator with an undisputable (but still not entirely clear) role in the development of eosinophilic NP is IL-5. Several studies have shown increased IL-5 levels in NP compared to the surrounding mucosa or healthy controls [6, 7]. There are data showing that an increased level of IL-5 could occur after infection with *Staphylococcus aureus* [8]. Staphylococcal exotoxins have been detected in NP [9], possibly acting as superantigens, but only in half of the specimens of NP. Interestingly though, these exotoxins have not been found in control mucosa. Furthermore, another study [10] did not show evidence of bacterial DNA in NP specimens, thus making the role of bacterial infection in NP etiology questionable.

Another interesting mediator with a putative role in NP formation is vascular endothelial growth factor (VEGF). VEGF is involved in angiogenesis and tumor invasion. It increases vascular permeability and is expressed in inflamed nasal and middle ear mucosa. Increased expression of VEGF and its receptor has been found in NP compared to normal mucosa [11]. Another study [12] showed increased VEGF production by nasal fibroblasts under anaerobic conditions enhanced by TNF-alpha and endotoxins. The authors concluded that VEGF is locally produced in sinonasal mucosa and that production is increased in patients with chronic rhinosinusitis. Another contribution to the importance of VEGF in NP growth was a study that showed a correlation between VEGF expression and polyp size in children with NP [13].

Tissue eosinophilia has already been correlated with worse outcome after surgical therapy for CRSwNP [14]. The authors even proposed a new classification of CRSwNP according to mucosal eosinophilia.

Finally, it would be logical to expect that the extent of disease has a prognostic value in surgical outcome, so we decided to include that parameter in our study as well.

It is, however, undisputable that CRSwNP has a strong and negative impact on quality of life [15]. Current treatment of CRSwNP begins with medical therapy which comprises intranasal corticosteroids and short courses of oral steroids. If the response to medical treatment is not satisfactory, surgery is indicated. Polyp recurrence can be expected in roughly one-third of patients [16], but this percentage is probably much higher with longer follow-up. Fortunately, not all of those patients will require reoperation. It would be beneficial to be able to predict the outcome of surgery in terms of disease recurrence, for both the patient and surgeon.

In this study, we analyzed the levels of IL-5, VEGF, IgE and eosinophilic infiltration in nasal polyps as well as the preoperative CT score in predicting the outcome of surgical treatment of CRSwNP patients.

Materials and methods

This study was designed as a prospective trial. It included 30 adult (age ≥ 18 years) patients with CRSwNP who had been surgically treated for their disease. All patients have been operated by the same surgeon (first author) to minimize bias in surgical technique. All patients gave their informed consent and the study was approved by the Ethics Committee of the institution. We excluded patients with antrochoanal polyps, cystic fibrosis, inverted papilloma and diseases that clinically mimic nasal polyposis but histologically represent other diagnoses (e.g. tumors). We also excluded patients with perennial allergic rhinitis whose symptoms would overlap those examined in the questionnaire. Patients with mild seasonal rhinitis with positive skin prick test were not excluded from this study, but we tried to avoid scheduling their questionnaires during the allergy season. In this study, there were no patients with asthma. Asthmatic patients were not actively excluded from the study, but by coincidence, none of the patients in our cohort had asthma.

Indication for surgery was failure of medical treatment in patients with more extensive disease (clinical grade II or III—described later in the text).

Before the operation, every patient was examined clinically (endoscopically) and underwent a CT scan. The clinical classification of disease severity was estimated using a questionnaire containing 20 questions on symptoms and functions. In this questionnaire proposed by Baudoin and colleagues [17, 18], each symptom and functional disturbance is scored according to severity and frequency. The following symptoms and functions were questioned: nasal obstruction, anterior and posterior discharge, itching, sneezing, headache, olfaction, cough, facial swelling, taste, overall handicap, everyday activity, recreation, frustration, feebleness, sleep, communication, confusion, concentration and socialization. The questionnaire that was used in our study is similar to SNOT-22 in that most of the questioned parameters overlap, and scoring for each parameter can give a maximal value of six, compared to five in SNOT-22. Our questionnaire has been used since 2000 on more than 500 patients. It has been checked for internal consistency (Cronbach alpha = 0.852) and other parameters recommended by Terwee et al. [19].

Endoscopic grading yielded four grades of nasal polyps based on the Davos scoring system: 0, no visible polyps; I, polyps within the ostiomeatal complex; II, polyps occupy more than the ostiomeatal complex reaching the convexity of the lower turbinate, but not the whole nasal cavity; and III, extent of polyps is below the lower turbinate convexity. [20] Preoperative CT score was assessed according to the Lund-Mackay grading [21].

All patients were operated endoscopically. The operation included polyp removal, and anterior and posterior ethmoidectomy. Surgery on the frontal, maxillary or sphenoid sinus was not performed in this group of patients, apart from removing secretions through natural ostia and sometimes enlargement of the maxillary natural ostium. Frontal sinus opacification was addressed by removing disease from the ethmoid infundibulum and removing the uncinata process and ethmoidal bulla. This is actually a Draf type 1 operation, but we did not remove mucosa or polyps from the frontal sinus itself. Care was taken not to injure the frontal sinus ostium which might result in post-operative scarring. No complications were recorded in this group of patients.

Postoperatively, all patients were given mometasone intranasal spray (200 µg daily) for 1 month, as well as regular saline nasal douching. Nasal steroid was discontinued after 1 month but was reintroduced if a recurrence was found. Postoperative control included one visit weekly in the first month, one visit monthly in the 2nd to 6th months, then every 3 months to the end of the first year. After the first year, controls were scheduled once a year or more frequently if needed.

Histological and immunohistochemical analysis was performed on specimens fixed in formaldehyde, embedded in paraffin, cut into 3–5 µm slices and dyed with hematoxylin-eosin staining. Eosinophil infiltration was measured as the eosinophil count per high power magnification field (hpmf) (400×). Ten non-overlapping fields were counted and the average count calculated. According to cell count, the eosinophil infiltration was scored as follows: I, <10 Eo/hpmf; II, 10–20 Eo/hpmf; and III, >20 Eo/hpmf.

The presence and quantity of immunoglobulin-E (IgE), IL-5 and VEGF were analyzed by respective monoclonal IgG antibodies in a 1:100 dilution (Santa Cruz BioTechnology). The scoring (semi-quantitative analysis) was done according to the percentage of immunoreactive cells, resulting in four grades: –, no immunoreactivity detected; +, weak reaction (<10 % immunoreactive cells); ++, moderate reaction (10–25 % immunoreactive cells) and; +++, strong reaction (>25 % immunoreactive cells) [22].

Postoperative clinical controls for this study were performed after 1 month, after 6 months and after 1 and 2 years. Postoperative assessment included endoscopic grading and questionnaire.

Results

Among 30 patients, 23 were males and seven females. Average age was 47.8 years (18–72). Average duration of disease before operation was 8 years (4 months to 40 years). Three patients had been previously operated, all

of them three or more years before, and all other patients had not yet been operated. Eighteen patients had proven allergy to one or more allergens (mostly dust mites and pollen), while 12 did not have any allergy in their medical history. Five patients were smokers. Endoscopic polyp grade was two in 15 patients and three in the remaining 15 patients. The average CT score was 8.6 (range from 5 to 12). All of the patients had peak CT score for the ostiomeatal complex.

Histological analysis revealed a high percentage of eosinophil infiltration. According to the previously described grading system, 22 specimens were rated as +++, three specimens as ++ and five specimens as +. The immunoreactivity to IL-5 was more evenly distributed: seven specimens showed a strong reaction (+++); seven had a moderate reaction; 11 a weak reaction; and in five, no immunoreactivity to IL-5 was detected (Table 1).

The IgE reactivity was high in 19 specimens, moderate in 10 and only one specimen had weak reactivity. The VEGF reactivity was also high in the majority of specimens—20 specimens were highly positive, nine were moderately reactive and one showed a weak reaction. It should be mentioned that VEGF reactivity was only analyzed in stromal cells, and not in endothelial cells where it was uniformly high as expected.

The results of subjective scores for symptoms and functions were as follows: The average preoperative scores for symptoms and functions were 2.7 and 1.8, respectively, giving 4.5 as the average overall score, which represents moderate chronic rhinosinusitis (CRS). One month post-operatively, the average scores for symptoms and functions were 0.5 and 0.2, respectively, which gives an overall score of 0.7, correlating with mild CRS. After 2 years, a moderate deterioration of scores was observed. The average scores for symptoms and functions were 0.9 and 0.6, respectively, thus yielding 1.5 as the average score after 2 years (Table 2). It can be seen that the major complaint among all observed symptoms was nasal obstruction (average 4.8) and that symptom showed the greatest improvement after surgery. Two years after surgery, the average score for obstruction was 1.6. Subjective score was significantly improved after surgery, shifting the patients'

Table 1 Number of specimens (patients) according to histomorphometry and immunohistochemical analysis

Parameter	Reactivity			
	0	1+	2+	3+
Eosinophils	0	5	3	22
IL-5	5	11	7	7
IgE	0	1	10	19
VEGF	0	1	9	20

Table 2 Results of subjective score questionnaires preoperatively and 2 years after the operation

Symptom/function	Average preoperatively	Average after 24 months
Nasal obstruction	4.8	1.6
Anterior nasal discharge	3.7	1.4
Postnasal discharge	3.1	1.2
Nasal itching	2.0	0.8
Sneezing	3.3	1.0
Headache	2.3	0.6
Olfactory disturbance	3.9	1.3
Cough	2.4	0.9
Facial swelling	0.4	0.2
Taste disturbance	1.4	0.5
Average	2.7	0.9
I feel handicapped	1.7	0.6
Everyday activity compromised	2.5	0.8
Difficulty in recreation	2.3	0.9
I feel frustrated	1.8	0.7
I feel feebleness	2.2	0.9
Sleep disturbances	2.4	0.9
Stress in communication	1.3	0.3
I feel confused	1.3	0.3
Difficult concentration	1.4	0.4
I avoid socializing	0.3	0.0
Average	1.8	0.6

average symptoms from moderate to mild, but over time, a slight deterioration was observed, as seen in Fig. 1.

Two years after surgery, 19 patients had no recurrence (endoscopic grade = 0), while 11 patients had recurring nasal polyps (endoscopic grade ≥ 1). Among patients with recurrence, three had small polyps (grade 1), six moderate (grade 2) and two had massive recurrent polyposis (grade 3).

Data analysis

We used multiple linear regression analysis to determine whether the preoperative extent of disease and the histologic/immunohistochemical parameters could predict the outcome of surgical treatment after 2 years measured by an improvement in subjective score. Preoperative CT score, eosinophilic infiltration, IL-5, VEGF and IgE immunoreactivity were used as independent variables, and the subjective score after 2 years was used as a dependent variable. A higher score after 2 years meant deterioration in condition. The results of multiple linear regression analysis are shown in Table 3. It can be noted that, by using this kind of analysis, only CT was found to be predictive in that there was a positive correlation between preoperative CT score and subjective score after 24 months ($r = 0.558$, $p = 0.003$) (Table 3). All of the other observed parameters (eosinophils, IL-5, IgE and VEGF)

did not show a positive correlation with end results (Table 3).

In order to analyze the influence of the observed histologic parameters on the risk of polyp recurrence, we divided the patients into two groups: one group included 19 patients without polyp recurrence (endoscopic grade = 0 after 12 months) and the other group included 11 patients with any level of polyp recurrence (grade ≥ 1). Every patient was then evaluated according to each observed parameter and classified as either low or high grade of reaction as follows: according to the histologic score of eosinophilic infiltration, patients with a score of 1 or 2 were rated as “low eosinophil infiltration” and patients with a score of 3 were rated as “high eosinophil infiltration”. In the same manner, according to immunohistochemical staining, the patients were assigned either to a “low reactivity” group or a “high reactivity” group. Thus, 2×2 tables were generated for every parameter and these were analyzed using the χ^2 test. The relative risk of recurrence for each parameter is shown in Table 4. It can be noted that the only parameter that reached statistical significance ($p < 0.05$) was eosinophilic infiltration. Patients whose removed polyps had more than 20 eosinophils per hpmf had recurrent disease more often (41 %) than patients with low eosinophil infiltration (12 % recurrence).

In a similar manner, we correlated the above parameters with improvement in subjective score. The percentage of

Fig. 1 Subjective score preoperatively and postoperatively after 6, 12 and 24 months

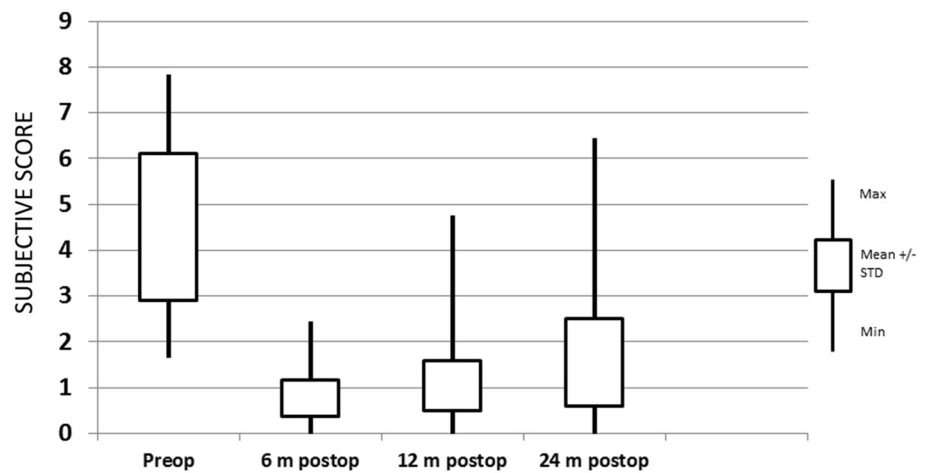


Table 3 Results of multiple linear regression analysis

Variable	Beta in	Partial correlation	Tolerance	R ²	t(24)	p value
CT score	0.567145	0.557810	0.869357	0.130643	3.292534	0.003067
Eosinophils	0.030442	0.033280	0.740697	0.259303	0.163128	0.871783
IgE	-0.014679	-0.017535	0.883734	0.116266	-0.085918	0.932245
IL-5	0.176219	0.187884	0.729486	0.270514	0.937128	0.358028
VEGF	-0.035864	-0.044305	0.946658	0.053342	-0.217265	0.829838

Partial correlation between predictors and subjective score after 12 months

Table 4 Risk of recurrence for different parameters

Histologic or immunohistochemical parameter	Risk of recurrence (%)
Eosinophil infiltration low (1 or 2)	12*
Eosinophil infiltration high (3)	41*
IgE positivity low (1 or 2)	35
IgE positivity high (3)	37
IL-5 positivity low (1 or 2)	31
IL-5 positivity high (3)	43
VEGF positivity low (1 or 2)	40
VEGF positivity high (3)	35

* *p* < 0.05

subjective score improvement dependent on histologic/immunohistochemical analysis is shown in Table 5. The average improvement in subjective score after 2 years was 66 %. As expected, patients without recurrence had a higher percentage of improvement (88 % according to the subjective score questionnaire) compared to patients with recurrence who rated their improvement as 30 % on average. The higher preoperative endoscopic score was not a predictor for recurrence.

Discussion

CRSwNP is still an unresolved problem with growing list of putative mediators and genes involved in NP etiology [23].

The growing list of probable mediators in CRSwNP might lead to confusion, rather than understanding of this disease. According to recently published data [24], CRSwNP is just a phenotype of CRS and may include several different endotypes. This means that different patients with CRSwNP, although presenting with a similar clinical picture, may harbor different pathogenetic mechanisms of polyp formation. If true, this concept might lead to targeted treatment of CRSwNP in future. At present, the cornerstone of therapy for CRSwNP remains steroid therapy (topical or systemic) and surgery when medical therapy is not satisfactory.

Other attempts to treat CRSwNP have included antibiotics, capsaicin, furosemide, antimycotics, proton pump inhibitors and several other medications [25], but with limited benefit. Some recent attempts at targeted therapy,

Table 5 Influence of different parameters on subjective score improvement

Histologic/immunohistochemical parameters	Subjective score improvement (%)
Eosinophil infiltration low (1 or 2)	92*
Eosinophil infiltration high (3)	62*
IgE positivity low (1 or 2)	71
IgE positivity high (3)	62
IL-5 positivity low (1 or 2)	67
IL-5 positivity high (3)	67
VEGF positivity low (1 or 2)	55
VEGF positivity high (3)	73

* $p < 0.05$

such as anti IL-5 [26] or anti IgE [27], may sound promising, but still have to prove their value when tested in randomized placebo-controlled trials. Furthermore, such targeted therapy (e.g. anti IL-5 or anti IgE) might only be effective on appropriate endotypes of CRSwNP. Regardless of that, at present, none of the therapeutic options can eliminate the possibility of recurrence of NP after surgery, so after surgical removal, a proportion of patients will have recurrence, and some of them will require another operation or even multiple operations. A recent study [16] has shown that postoperative steroids can reduce the need for repeat surgery in patients with CRSwNP and increase the interval before reoperation. Although the difference was statistically significant, the actual numbers were not so impressive, because the need for reoperation was postponed for just 76 days on average, and the percentage of steroid users who needed a second operation was 4.1 % compared to 7.8 % of steroid non-users. Furthermore, that study only included reoperations between the first and fourth year postoperatively, so the number of repeat polypectomies is obviously higher, especially taking into account the high percentage of NP recurrence (the same study is quoting up to 40 %). Interestingly, a study performed in our institution [28] showed a better response to steroid and antibiotic therapy among patients with higher levels of IL-5 in maxillary sinus lavages, but that study analyzed patients with chronic maxillary sinusitis.

There are other studies that have shown the benefit of postoperative steroids, but mainly until 4 years postoperatively [29]. A corollary here is that we cannot guarantee a cure for many CRSwNP patients. Every patient should be informed about the possible results of surgery, so we attempted to identify clinically applicable parameters that could serve as predictors of outcome after surgery. We expected that all of the parameters analyzed in this study might have had some predictive value. However, only two of them showed prognostic value for predicting the results of surgical treatment after 2 years. The first was

preoperative CT (which is a measure of the extent of disease) which was found to be a prognostic factor in that patients with a worse preoperative CT score showed less improvement after 2 years. We did not find a correlation between preoperative endoscopic score and recurrence. Although this is surprising at first, it can be explained by the fact that all of our patients had a preoperative score II or III and that the difference in scoring is not particularly discriminative. On the other hand, there is better discrimination in scoring between score 0 and any positive score when we analyzed recurrence. The second parameter that significantly influenced postoperative score and recurrence was eosinophilic infiltration. This result is in agreement with other published data [14, 30] although there is some disagreement with regard to the predictive value of CT. Kim et al. [31] have found CT score (they limited their study to the olfactory cleft) to be predictive for worse olfactory outcome, and Wu et al. [32] did not find any correlation between preoperative CT score and long-term outcomes of sinus surgery.

The extent of surgery is certainly an important parameter that influences outcome. Contrary to many other surgical procedures, there is no consensus regarding the extent of surgery for both CRSsNP and CRSwNP. We agree with the concept of functional endoscopic sinus surgery described by Messerklinger and Stammberger. Therefore, apart from polyp removal, we performed a complete ethmoidectomy in all patients, but without removing mucosa from the frontal, sphenoidal and/or maxillary sinus. Furthermore, despite the high endoscopic grading score (half of the patients had score 2 and the other half had score 3), the total Lund-Mackay score was not that high (average 8) and most of the sinus opacifications in our cohort were due to swollen sinus mucosa and/or retained secretions and not to polyps that had formed. Therefore, we believe that our level of surgery was appropriate for most, if not all, of the patients. Another factor that supports our surgical philosophy is the result of an English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis, which did not show a significantly higher recurrence rate, even between snare polypectomy and polypectomy + ESS, which was 21.2 vs. 20.0 %, respectively [33].

Contrary to our expectations, we did not find a statistically significant correlation between immunohistochemical reactivity to IL-5, VEGF and IgE and postoperative outcome in our series of patients, although the high reactivity to IL-5 was connected with a higher percentage of recurrence. There may be several explanations for such a result including non-heterogeneous cellularity of the polyp tissue, imperfect methodology of tissue immunostaining or incorrect set-up of cut-off values for semiquantitative scoring of the specimens. Regarding the latter, we had

chosen previously defined cut-off point values because of their simplicity for use. Namely, we did not use computer-assisted cell counting methods, so the cut-off values that we used enabled relatively fast scoring of each specimen. Perhaps the exact count of every immunoreactive cell in a specimen could produce a different, statistically significant result, but at present, we cannot apply such a method for routine use.

The finding that eosinophilic infiltration significantly affects the outcome might be explained by recent data published by Payne et al. [34] They suggested that eosinophilic and non-eosinophilic polyps may represent two distinct entities, not only just by histologic appearance but also by genetic and protein expression patterns, which might require different therapeutic interventions. According to that, eosinophilic NP would be one of the CRSwNP endotypes. Our results would fit this theory, indicating that this particular endotype is related to worse prognosis after surgical treatment. However, the present state of knowledge regarding CRSwNP etiology is not sufficient to apply endotype concept on a cohort of 30 or even lot more patients.

Some data collected in the questionnaire with regard to symptoms were expected. For example, the symptom that was the highest ranked before the operation was nasal obstruction, followed by secretion and olfactory disturbance. As expected, the same symptoms were the ones most affected by surgery. Interestingly, headache as a preoperative symptom was not so highly rated although it is one of the major symptoms in CRS diagnosis according to EPOS2012 [1]. Our clinical observations on patients with CRSwNP which were not included in this study are in agreement with that, as is a recently published study by Eweiss et al. [35]. Those authors have proven that significant facial pain is uncommon in patients with CRSwNP which should be taken into account when counseling them before surgery. It should be mentioned here that SNOT22 contains questions about facial and ear pain and not headache, and our questionnaire had just one question about headache. It should also be noted that patients can sometimes confuse pain, fullness, malaise and even dizziness when asked about headache. This is sometimes a matter of terminology and occurs especially in the Croatian language due to the many existing dialects. We speculate that the significant improvement that our patients reported in headache (Table 2) might be partly for that reason.

Polyp recurrence is just one among several factors that should be taken into account when one estimates the surgical outcome in treating CRSwNP. Although the recurrence strongly correlates with symptom improvement, we have to be aware that different CRSwNP patients may have different symptoms as the leading complaints that made them seek medical help. Our results have also confirmed that surgical treatment improves not just major CRSwNP

symptoms (obstruction, secretion, olfaction, pain) but also overall function and everyday activity. Our study was designed to assess the prognostic value of several parameters on outcome after surgical treatment of NP.

When analyzing our results in the light of the ‘endotype concept’ of CRSwNP, there are several conclusions that can be drawn. First of all, although that concept could best explain our present knowledge about CRSwNP, the list of particular endotypes has not been proposed yet. Some of the endotypes proposed in the recently published PRAC-TALL consensus report [24] are, for example, IL-5 and IgE endotypes. Although the design and number of patients in our study do not allow us to draw conclusions about different endotypes among CRSwNP patients, the results of immunohistochemical analyses on our specimens showed overlap but not regularity in reactivity. For example, among the highly eosinophilic specimens, we could find both IgE-positive and IgE-negative specimens, as well as IL-5-positive and IL-5-negative specimens. This observation suggests that, in future, a large number of patients and parameters should be included to more precisely define specific endotypes in terms of pathogenesis and probable therapeutic response. Based on our results, and speaking just in terms of predicting surgical outcome, we may conclude that eosinophilic infiltration of polyp tissue may be used as a predictor of surgical outcome. Further studies and improvement in methodology might determine whether IL-5 can also be a predictor of surgical outcome. Preoperative CT score could be used cautiously as a predictor as our results are not in agreement with other published data [32]. The important contribution of this study is the simultaneous research on IgE, IL-5 and VEGF in polyp tissue with the potential impact of each mediator on recurrence and the potential impact of their interaction. The fact that we have shown that eosinophil infiltration is a significant negative prognostic factor is already known, but a more important finding is that IgE, IL-5 and VEGF are not important prognostic factors although each has been claimed to be an important factor in the pathogenesis of CRSwNP and, because of that, a potential negative prognostic factor. All of these mediators have been shown to be upregulated in asthmatic and Acetyl-salicylic acid (ASA) intolerant patients [5, 36]. VEGF was shown to be upregulated in polyp patients compared to controls and specifically upregulated in endotypes with asthma intolerance [37]. As ASA intolerance with asthma is a poor prognostic factor, it may be suggested that VEGF may be one of the contributors.

What is also important is that we have found that, in the population of non-asthmatic, non-ASA intolerant polyp patients (although it was not the intention to exclude them), high tissue upregulation of IL-5 might be a negative prognostic factor for polyp recurrence, while IgE is not. It

is possible that, in a much larger patient population, the Chi-squared difference [43 % recurrence in high IL-5 (grade 2 and 3) vs 31 % in low IL-5 score (grade 1)] may reach statistical significance. However, this may indicate that IL-5 is not the only cytokine/chemokine responsible for eosinophilia. It is also important to note that VEGF in this study population (without asthma and ASA intolerance) is not a prognostic factor for recurrence.

Conclusion

The aim of this study was to identify a clinically applicable way to predict surgical outcome after CRSwNP surgery, in terms of subjective improvement and also recurrence. The number of patients in this study was rather small, allowing the possibility of a type II error in our conclusions. The fact is that, even with this possibility, for a single patient to have a parameter that could be regarded as prognostic, it should be easily visible using the available diagnostic methods. To make a parameter clinically useful, a difference should be visible in most of the patients in that particular practice. Therefore, we have to conclude that IL-5, VEGF and IgE are not predictors of surgical outcome. On the other hand, from our results, we can conclude that high eosinophilic infiltration in polyp tissue and greater extent of preoperative disease (i.e. higher CT score) do correlate with a higher percentage of polyp recurrence and lower postoperative subjective improvement.

Conflict of interest The authors declare that they have no conflict of interest.

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