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Long-term evaluation of nasal polyposis recurrence: a focus on multiple relapses and nasal cytology

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Abstract

Purpose. Recurrence of chronic rhinosinusitis with nasal polyps (CRSwNP) is highly variable, reaching 55-60% of cases. Different results about clinical parameters as recurrence predictors has been reported. The aim of this retrospective study was to evaluate CRSwNP recurrence risk after a long-term follow-up (up to 20 years). Moreover, the role of nasal cytology was assessed.

Materials and methods. Sixty-one patients who underwent functional endoscopic sinus surgery for CRSwNP were enrolled. Clinical parameters were recorded. Nasal cytology was performed at follow-up examinations. The Kaplan-Meier method was used to obtain the recurrence-free survival curves. The median number of recurrences per year was evaluated.

Results. Five- and 10-year recurrence rates were 30.29% and 66.06%, respectively. Median recurrence-free survival was 106 months. Asthma and Aspirin-Exacerbated Respiratory Disease represented predictors of multiple recurrences ($p<0.05$). Intranasal steroids were the main treatment to prevent relapses ($p<0.05$). Patients with normal cytology at follow-up evaluation had a lower probability to have first recurrence within 10 years (59% of cases), compared to neutrophil or eosinophil infiltrate (100% and 88% of cases, respectively) ($p<0.05$).

Conclusions. CRSwNP has a high recurrence risk, also more than 10 years after surgery. Nasal cytology may identify subjects with a higher risk of early recurrence.

Key words: Nasal polyposis; Chronic rhinosinusitis; Recurrences; Endoscopic sinus surgery; Intranasal steroids; Nasal cytology

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex disease, whose etiology is not completely understood [1]. Genetic predisposition and immunologic mechanisms are involved in CRSwNP pathogenesis [2-4]. Allergy, asthma, and Aspirin-Exacerbated Respiratory Disease (AERD) seems to have a role as predisposing factors for CRSwNP [1]. Medical and surgical treatments have been proposed. Intranasal and systemic corticosteroids are the mainly used medical therapies, while Functional Endoscopic Sinus Surgery (FESS) is performed when patients are refractory to medical treatment [1].

Several studies analyzed recurrence risk after endoscopic surgery [5-22]. Their results were heterogeneous, reporting a highly variable recurrence risk that reached 55-60% in some case series [9-15]. Some authors found that allergy, asthma, AERD, and eosinophils at histological exam were risk factor for recurrence, while other failed to find a correlation. Agreement was achieved about post-operative intranasal corticosteroids that reduced recurrence risk, as showed in two meta-analyses [23,24].

The main limitation of these studies was a short follow-up. In particular, most authors limited evaluations at 1-5 years after surgery. Only three studies had a follow-up interval that reached 10-12 years [9,14,22]. Another limitation was the type of statistical analysis that was performed. In the majority of papers, the authors evaluated the percentage of recurrence during follow-up without indications about the time to recurrence. The latter was assessed only by Brescia et al. in 60 patients [8], while recurrence-free survival curves obtained with the Kaplan-Meier estimator were analyzed only in two studies by Wu et al. and Calus et al [12,22]. Finally, the number of recurrences per each subject has never been evaluated.

The aim of this retrospective study was to evaluate CRSwNP recurrences after a long-term follow-up (up to 20 years). The role of risk factors was assessed. Moreover, besides recurrence rate and time to first recurrence, we also analyzed the median number of recurrences

per year and time interval among them for each subject included in the study. Finally, the role of nasal cytology was assessed.

2. Materials and methods

Sixty-one patients who underwent follow-up examination and nasal cytology at our Division between 2019 and 2020 after FESS for CRSwNP were enrolled in the study. All the participants underwent their first endoscopic surgical procedure between 1999 and 2017. Exclusion criteria were: age <18 years; follow-up <3 years; antrochoanal polyps; mycotic rhinosinusitis; cystic fibrosis; primary ciliary dyskinesia; sinonasal cancer; systemic chemotherapy and/or radiation therapy on head and neck; frequent administration of systemic steroids for other diseases. A chart review was performed to collect clinical data (age, sex, smoking, comorbidities, number and time of recurrences, treatment for recurrences). In particular, we collected data about allergy, asthma, and Aspirin-Exacerbated Respiratory Disease (AERD). The type of inflammatory infiltrate at histologic exam after the first surgical procedure and nasal cytology results from follow-up evaluation were recorded. Mean follow-up after the first FESS was 126.49 ± 60.92 months (range 39-267 months). All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval by the Institutional Review Board was not needed because of the retrospective nature of the study. All the participant gave their informed consent.

Diagnosis of CRSwNP was based on the European Position Paper on Chronic Rhinosinusitis and Nasal Polyps (EPOS) 2020 [1]. Indication for first and revision surgery was symptomatic CRSwNP refractory to systemic steroid therapy. All the procedures were performed by the same surgeon (GP) for bilateral nasal polyposis with the involvement of at

least ethmoidal cells and maxillary sinuses. Pre-operative Lund-Mckay radiologic score was between 10 and 24. All post-operative evaluations were performed by the same physician (GR).

Nasal scraping for cytological exam was performed to assess nasal mucosa inflammation with particular attention to the type of inflammatory infiltrate. Cytological samples were collected from the medial portion of the inferior turbinate, by scraping with a Rhino-pro® Curette (ASI Arlington Scientific Inc, Springville, UT, USA). The material was laid on a microscope slide, fixed in 95° alcohol for 4 s and stained by the May-Grünwald-Giemsa method. Observation was performed by a common optical microscope, able of a 1000x magnification, analyzing at least 50 microscopic fields. A semi-quantitative scale from 0 to 4+ was used to assess inflammatory infiltrate, as previously described [25].

All statistical analyses were carried out using the Statistical Package for Social Sciences, version 20.0, and Graphpad Prism for Windows, version 5. A descriptive analysis of all data was performed, and they were reported as means, medians, or percentages and standard deviations or interquartile range (IQR). The Kolmogorov-Smirnov test demonstrated a non-Gaussian distribution of variables, so non-parametric tests were used. The Mann-Whitney U test and the Kruskal-Wallis test were used to assess differences among groups in the mean of continuous variables. The chi-squared test was used for categorical variables. Spearman's test was used to assess the correlations between continuous variables. The Kaplan-Meier method was used to obtain the recurrence-free survival curves and the Log-rank test was used for comparisons. A $p<0.05$ was considered statistically significant.

3. Results

Mean age at follow-up examination was 57.57 ± 10.92 years (range 23-74 years), while mean age at first FESS was 47.05 ± 11.24 years (range 20-64 years). Clinical data are reported in table 1. Daily nasal washings with isotonic saline solution were performed by 77.0% of

patients, while regular treatments with nasal steroids (mometasone furoate nasal spray 50 mcg in each nostril once a day for at least 2 months, 1 or 2 times per year) were reported in 26.2% of cases. Nasal cytology at follow-up examination (with prior steroid suspension lasting at least 10 days) highlighted eosinophil inflammation in 22 patients (36.1%) and neutrophil inflammation in 11 cases (18.0%). Normal cytology was observed in 28 cases (45.9%).

A total number of 94 recurrences were reported. Fifty-two out of 94 (55.3%) recurrences were treated with medical therapy (oral or intramuscular systemic steroids), while revision endoscopic sinus surgery was performed in 42 cases (44.7%). Five- and 10-year recurrence rates were 30.29% and 66.06%, respectively (Figure 1). Median recurrence-free survival was 106 months. Awaiting a sufficiently long time (20 years), Kaplan-Meier estimator showed that all the patients seemed to have polyposis recurrence. The log-rank test did not show any statistically significance for patients' characteristics (Figure 2, Table 2). However, asthma, AERD, and eosinophil inflammation at histological exam seemed to represent risk factors for polyposis recurrence (Figure 2). A statistically significant difference about recurrence rate curves was found for regular use of nasal steroids (p=0.018) with and hazard ratio of 0.375 (95% IC 0.166-0.850) (Figure 2). Median recurrence-free survival was 118.00 months for patients who regularly used nasal steroids and 61.50 months for the other subjects. Frequent nasal irrigation seemed to prevent recurrence, but without statistical significance.

Median time between first surgical procedure and first recurrence, between first and second recurrences, and between second and third ones were 71.50 (IQR 79), 60 (IQR 70), and 29.50 (IQR 71.25) months, respectively. A near significant trend toward decrease of time interval between recurrences was observed (p = 0.074, Figure 3). Median number of recurrences per subject was 0.11 per year (IQR 0.55). Therefore, we can expect a recurrence every 9.09 years (i.e., 109 months) on average, similar to median recurrence-free survival obtained with the Kaplan-Meier method (106 months).

Analyzing the role of risk factors on median time to first recurrence and median number of recurrences per year, we found a statistically significant difference for regular use of nasal steroids (Table 2). In particular, median time to first recurrence was 73 (IQR 122.75) and 25 (IQR 81.75) months, respectively for patients who regularly used nasal steroids or not (p=0.008), while median number of recurrences was 0.27 (IQR 0.25) and 0.25 (IQR 0.19) per year, respectively (p=0.010). Asthma and AERD showed a role as risk factors only for median number of recurrences per year (p=0.045 and p=0.035, respectively). Clinical characteristics, like age, sex, smoking, and Lund-Mackay score did not show any correlation with recurrences (p>0.05).

Concerning nasal cytology at follow-up evaluation, a favorable trend at Kaplan-Meier estimator curves was observed for patients with normal nasal cytology (p=0.217, Figure 4A). Median time to first recurrence was 106 (IQR 99), 61.50 (IQR 29.50), and 52 (IQR 89.50) months, respectively for normal cytology, neutrophil, and eosinophil inflammation (p=0.128, Figure 4B), whereas median number of recurrences per subject was 0.08 (IQR 0.15), 0.17 (IQR 0.25), and 0.17 (IQR 0.31) per year, respectively (p=0.186, Figure 4C). Inflammatory infiltrate at follow-up evaluation did not correlate with other clinical features (p>0.05). Finally, we compared nasal cytology in patients who had first recurrence within 10 years and those who had after, because this time interval is near our median recurrence-free survival. Patients with normal cytology at follow-up evaluation had a lower probability to have first recurrence within 10 years (59% of cases), compared to neutrophil or eosinophil infiltrate (100% and 88% of cases, respectively) (p=0.029).

4. Discussion

Recurrence represents one major problem treating CRSwNP.[1] Relapses after endoscopic surgery may reach 60% during follow-up [15]. Several studies tried to identify clinical

predictors after endoscopic surgery [5-22]. Despite advances in our knowledge of CRSwNP pathogenesis, recurrence risk often remains unpredictable. Different results about clinical parameters as recurrence predictors were observed in different studies. In particular, allergy, asthma, AERD, and Lund-Mackay score seemed to be related to a higher risk of recurrence in some case series [9,10,12,16], while other authors found that they were not associated to recurrence [7,13,19,21]. Greater agreement has been observed among studies concerning tissue eosinophilia and IL-5, serum IgE and eosinophil cationic protein (ECP) as predictors of recurrence [6,7,14-16,19-22]. Moreover, Boztepe et al. and Brescia et al. showed that other serological parameters, such as neutrophil-, eosinophil-, and basophil-to-lymphocyte ratios, correlated with relapses [5,11]. Finally, two meta-analyses demonstrated that post-operative topical intranasal steroids reduce recurrence risk [23,24].

Previous studies that evaluated clinical predictors of CRSwNP recurrence have some limitations: (1) near all the studies have a short follow-up, usually less than 5 years; (2) some case series include less than 50 patients; (3) in the majority of papers, the authors evaluated the recurrence rate during follow-up without indications about time to recurrence; (4) the number of recurrences per each subject has never been evaluated.

Concerning follow-up interval, long-term evaluations after 10-12 years were included in only three studies [9,14,22]. On the other hand, Kaplan-Meyer method was used to better analyze the recurrence rate only in two studies [12,22]. Indeed, the evaluation of recurrence-free survival curves inserts the time parameter in the analysis. In particular, it allows to better assess how much time elapses between surgery and first relapse. Finally, patients with CRSwNP usually experience multiple recurrences. Such evolution during time has never been assessed and adequately reported.

Our study on a large sample of 61 patients detected 94 recurrences that underwent revision endoscopic sinus surgery in almost 50% of cases. Kaplan-Meier estimator showed that

5- and 10-year recurrence rates were 30.29% and 66.06%, respectively, with a median recurrence-free survival of 106 months. Analyzing the survival curve, it may be observed that, awaiting a sufficiently long time (20 years), all the patients seemed to have nasal polyposis recurrence. Log-rank tests on recurrence-free survival rates highlighted that no clinical parameter (allergy, asthma, AERD, tissue eosinophilia) may be considered a predictor of recurrence. However, asthma, AERD, and eosinophil inflammation at histological exam seemed to represent risk factors for polyposis relapse, showing a higher recurrence in the first 5 years without reaching statistical significance. Since Kaplan-Meyer curves took into account only first relapses, comparisons among times to first recurrence obtained the same results.

Analyzing next CRSwNP relapses, a near significant trend toward decrease of time interval between recurrences was observed. Our case series highlighted a median number of recurrences per subject of 0.11 per year. Therefore, we could expect a recurrence every 9.09 years (i.e., 109 months) on average, similar to median recurrence-free survival obtained with the Kaplan-Meier method (106 months). Evaluating the number of recurrences per year, we found that asthma and AERD became predictors of multiple recurrences.

Regular use of intranasal steroids reduced the risk of first and next relapses, while nasal irrigation did not. These results are in agreement with previous meta-analyses [23,24]. Therefore, a regular use of topical steroids should be recommended to all the patients who undergo FESS.

Looking for clinical and non-invasive predictors of recurrence, we analyzed nasal cytology at long-term evaluations. Indeed, cytological examination of nasal mucosa is a safe and effective tool to evaluate inflammatory infiltrate in allergic and non-allergic rhinitis, chronic rhinosinusitis and other nasal diseases [26-29]. Although the limitation of the absence of a pre-operative examination, we found that subjects with normal cytology at follow-up evaluation had a lower probability to have first recurrence within 10 years (59% of cases),

compared to neutrophil or eosinophil infiltrate (100% and 88% of cases, respectively). These results suggest a role of nasal cytology in the evaluation of patients with CRSwNP in order to identify those with a higher risk of early recurrence.

The strengths of this study were the assessment of time to recurrence in addition to percentage of patients with relapses and not to limit the analyses to the first event. The assessment of the number of recurrences per year allowed us to identify asthma and AERD as predictors of multiple relapses, while their role in favoring the first recurrence was less clear. Moreover, our results showed that nasal cytology may play an important role in predicting early recurrence. The main limitation of this study is the lack of cytological examinations before surgery.

5. Conclusions

CRSwNP has a high recurrence risk, being 66% at 10 years after surgery. Asthma and AERD represents predictors of multiple recurrences. Therefore, such patients should undergo more careful follow-up evaluations in order to early identify recurrences. Intranasal steroids are the main treatment to prevent or postpone relapses. Finally, further studies with large samples and long follow-up are mandatory to investigate the role of nasal cytology in daily practice in order to identify subjects with a higher risk of early recurrence and that need more intensive post-operative treatment to prevent it.

Author contributions: Giuseppe Riva: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - original draft; Marco Tavassoli: Investigation; Ester Cravero: Investigation; Matteo Moresco: Investigation; Andrea Albera: Writing - original draft; Andrea Canale: Writing - review & editing; Giancarlo Pecorari: Project administration, Resources, Supervision, Writing - review & editing.

No color should be used for any figures in print.

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Figure legends

Figure 1. Recurrence rate curve obtained with Kaplan-Meier method. Five- and 10-year recurrence rates were 30.29% and 66.06%, respectively.

Figure 2. Recurrence rate curves for clinical characteristics and regular use of nasal irrigations and steroids. The log-rank test did not show any statistically significance for patients' characteristics. However, asthma, AERD, and eosinophil inflammation at histological exam seemed to represent risk factors for polyposis recurrence.

Figure 3. Median time between first surgical procedure and first recurrence (1), between first and second recurrences (2), and between second and third ones (3). A near significant trend toward decrease of time interval between recurrences was observed (p = 0.074).

Figure 4. The role of nasal cytology at follow-up evaluation: (A) recurrence rate curves obtained with Kaplan-Meier method; (B) median time to first recurrence; (C) median number of recurrences per year. A favorable trend at Kaplan-Meier estimator curves was observed for patients with normal nasal cytology (p=0.217, Figure 4A). Median time to first recurrence was 106 (IQR 99), 61.50 (IQR 29.50), and 52 (IQR 89.50) months, respectively for normal cytology, neutrophil, and eosinophil inflammation (p=0.128, Figure 4B), whereas median number of recurrences per subject was 0.08 (IQR 0.15), 0.17 (IQR 0.25), and 0.17 (IQR 0.31) per year, respectively (p=0.186, Figure 4C).

Tables

Table 1. Clinical characteristics.

	Number (%)
Sex	
Male	42 (68.9)
Female	19 (31.1)
Smoking	9 (14.8)
Allergy	29 (47.5)
Asthma	22 (36.1)
AERD	10 (16.4)
Eosinophil inflammation at histologic exam	35 (57.4)

AERD = Aspirin-Exacerbated Respiratory Disease

Table 2. Different evaluations for risk factors (p values).

	Recurrence rate curve	**Time to first recurrence**	**Number of recurrences per year**
Allergy	0.688	0.252	0.473
Asthma	0.480	0.743	**0.045**
AERD	0.162	0.942	**0.035**
Eosinophil inflammation at histologic exam	0.881	0.940	0.446
Regular nasal irrigation	0.152	0.738	0.281
Regular use of nasal steroids	**0.018**	**0.008**	**0.010**

AERD = Aspirin-Exacerbated Respiratory Disease

Bold p values show statistical significance ($p<0.05$).

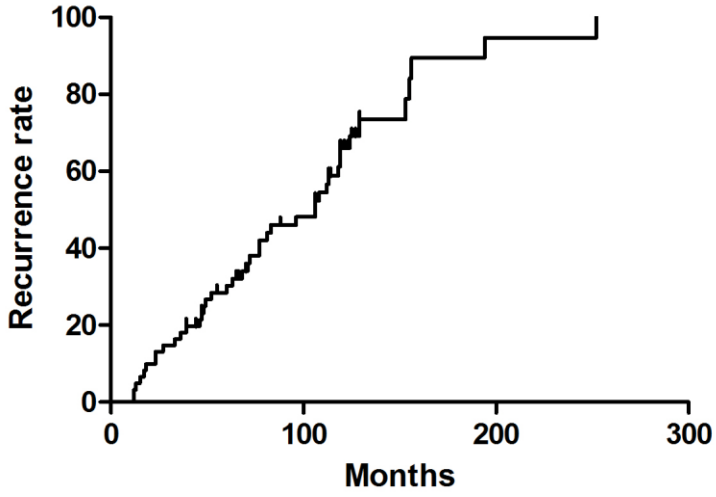

Figure 1

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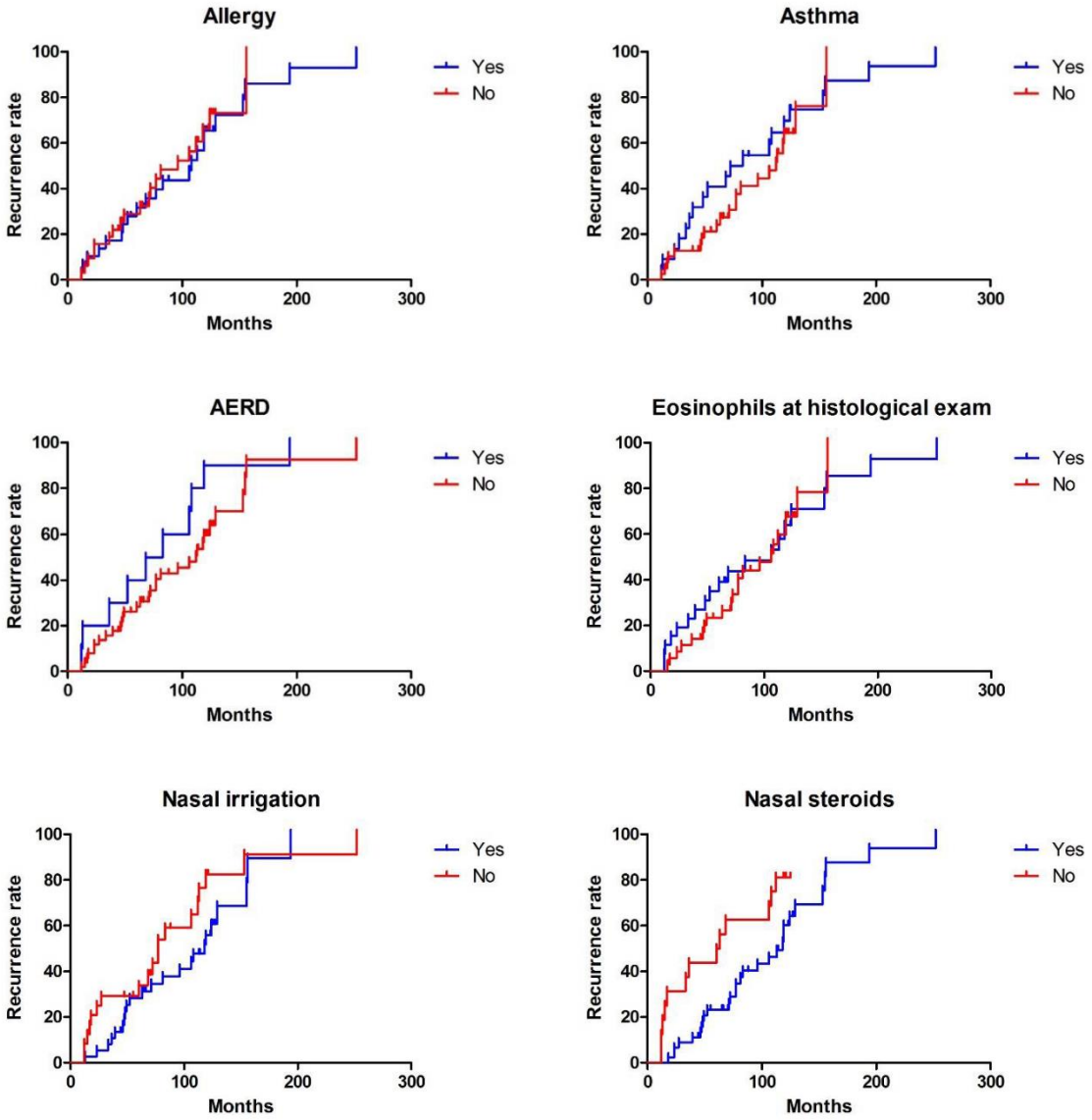
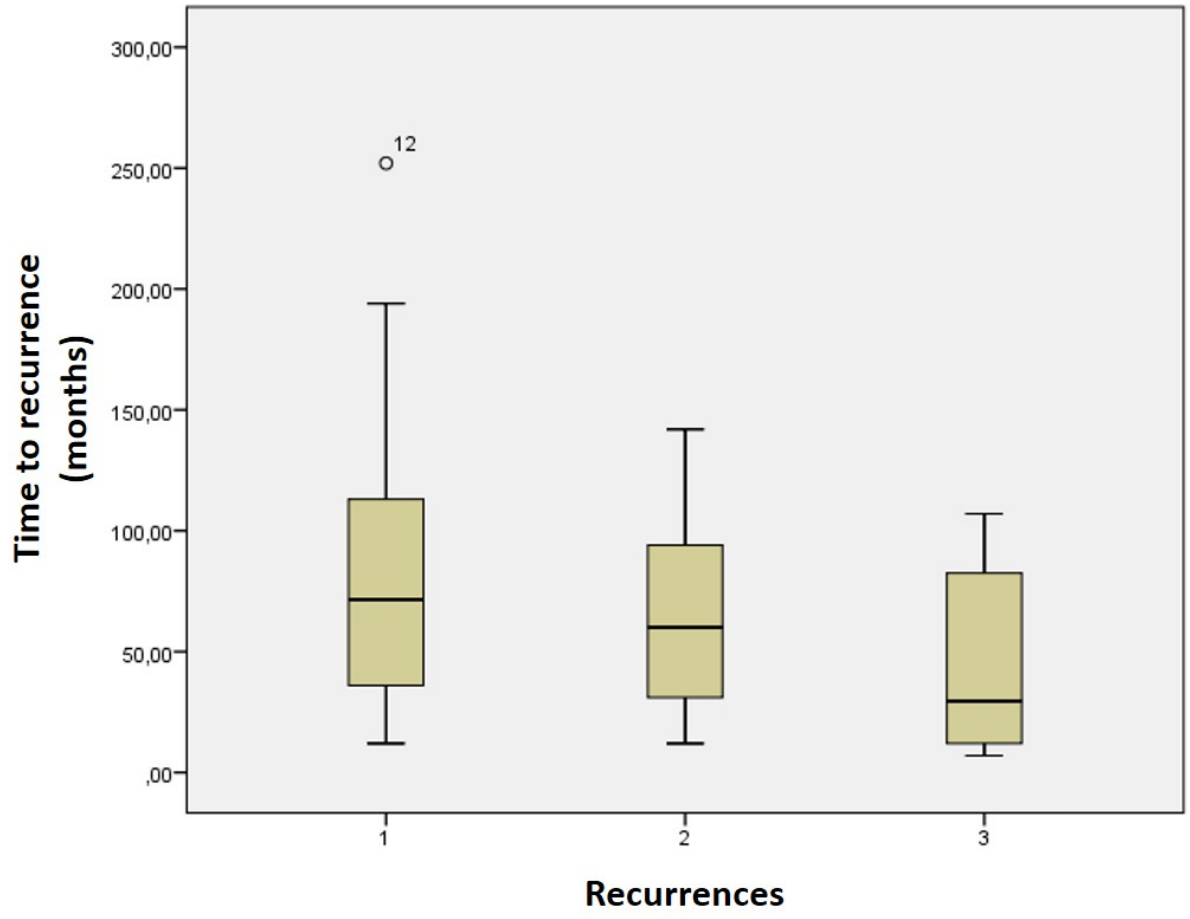

Allergy
Asthma
AERD
Eosinophils at histological exam
Nasal irrigation
Nasal steroids
Recurrence rate
Months
Yes
No
0
20
40
60
80
100
0
100
200
300

Figure 2


Time to recurrence (months)
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150,00
100,00
50,00
,00
12
1
2
3
Recurrences

Figure 3

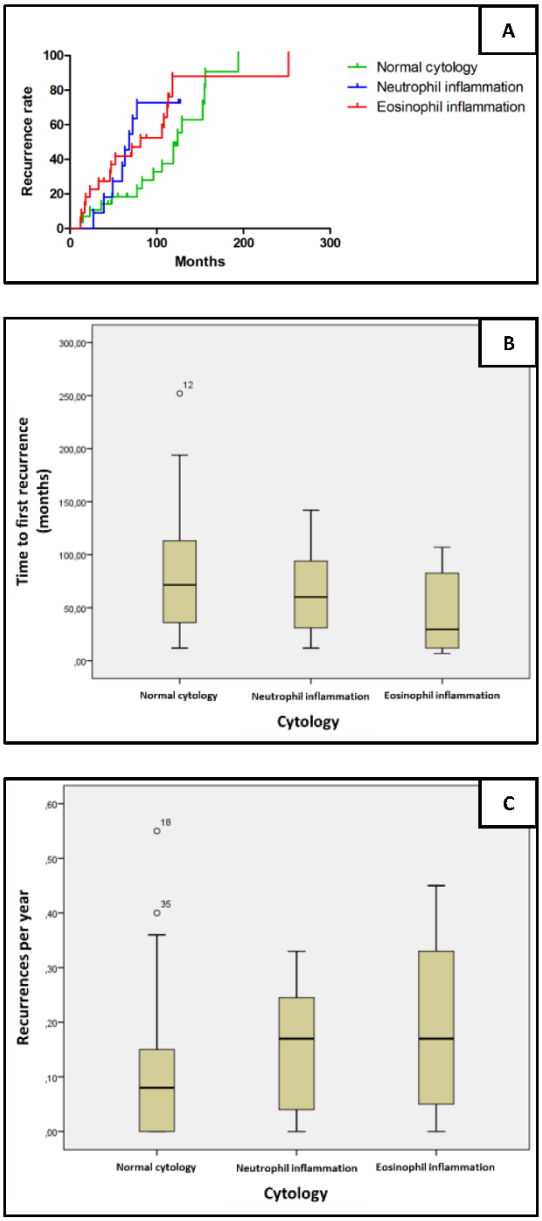
A
Recurrence rate
100
80
60
40
20
0
0
100
200
300
Months
Normal cytology
Neutrophil inflammation
Eosinophil inflammation
B
Time to first recurrence (months)
300,00
250,00
200,00
150,00
100,00
50,00
,00
12
Normal cytology
Neutrophil inflammation
Eosinophil inflammation
Cytology
C
Recurrences per year
,60
,50
,40
,30
,20
,10
,00
18
35
Normal cytology
Neutrophil inflammation
Eosinophil inflammation
Cytology

Figure 4