UNIVERSITEIT GENT

Academic Year 2012 - 2013

Twelve-year follow-up study in patients with nasal polyposis after Functional Endoscopic Sinus Surgery

Cédric BOSTEELS
Sarah DEJONCKHEERE

Promotor: Prof. dr. Ph. Gevaert
Co-promotor: Dr. L. Calus

Dissertation presented in the 2nd Master year
in the programme of

Master of Medicine in Medicine

Date

(signature)

Name (student) (promotor)

DANKWOORD

Alvorens deze masterpoef aan te vatten, wouden we graag nog enkele personen bedanken.

Vooreerst gaat onze oprechte dank uit naar **Prof. dr. Ph. Gevaert**, die ons de mogelijkheid gaf om kennis te maken met en deel te nemen aan wetenschappelijk onderzoek. Uw enthousiasme en gedrevenheid, scherp kritisch oog, wetenschappelijk en klinisch inzicht werkten stimulerend. Wij waarderen de kostbare tijd die u samen met ons nam om onze mails en tussentijdse resultaten te bespreken. Al deze zaken droegen ongetwijfeld bij tot het tot stand komen van deze masterproef. Het was een eer om met u samen te werken.

Evenzeer willen we **dr. L. Calus** graag bedanken voor haar deskundige kennis en hulp. We konden vele malen bij u terecht met vragen en onduidelijkheden. Ook zijn we u dankbaar voor het geschonken vertrouwen, de zelfstandigheid en het groeiproces dat u ons liet doormaken bij het verzamelen van de patiëntendata.

Prof. dr. C. Bachert voor de kritische blik vanuit zijn uitgebreide wetenschappelijke ervaring op de stafvergadering van het Upper Airway Research Laboratorium. Deze bracht ons een heel eind verder.

De medewerkers die het onderzoek van deze follow-up studie voerden in de periodes 1998-2000 en 2006-2007 zijn wij dank verschuldigd. Alsook het Upper Airways Research Laboratorium voor de verwerking van de stalen. Zonder hen was dit werk onmogelijk geweest. De medewerkers van de polikliniek, de artsen en verpleegkundigen van de vakgroep en dienst Neus, Keel en Oor.

Lic. Roos Colman van de Cel Biostatistiek voor het nakijken van de statistische verwerking, het advies en de tips, het overleg en e-mailverkeer. Deze zorgden voor een goede statistische onderbouwing van onze masterproef.

Ook willen we de masterproefcommissie, bestaande uit **Prof. dr. Ph. Gevaert**, **dr. L. Calus** en **dr. M. Dullaers**, bedanken voor het kritisch nalezen en beoordelen van deze masterproef.

Alle patiënten voor hun enthousiaste en belangeloze deelname.

Tenslotte willen we nog heel graag onze familie en vrienden bedanken voor hun niet-aflatende steun.

LIST OF MEDICAL ABBREVIATIONS

AB	Antibiotics
ACT	Asthma Control Test
ARS	Acute rhinosinusitis
AUC	Area under the curve
CCL	C-C Chemokine ligand
CCR	C-C Chemokine receptor
CF	Cystic Fibrosis
CRF	Case Report Form
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyposis
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CT	Computed Tomography
CYSLTR	Cysteinyl leukotriene receptor
DC	Dendritic cell
Dept.	Department
EC	Epithelial cell
ECP	Eosinophil cationic protein
EDTA	Ethylenediaminetetraacetic acid
ENT	Ear Nose and Throat
EPOS	European position paper on rhinosinusitis and nasal polyps
FBC	Full Blood Count
FESS	Functional Endoscopic Sinus Surgery
GINA	Global Initiative for Asthma
GM-CSF	Granulocyte macrophage colony-stimulating factor
GOLD	Global Initiative for Obstructive Lung Disease
GR	Glucocorticoid receptor
GUH	Ghent University Hospital
HSA	Human serum albumin
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin
INCS	Intranasal corticosteroids

IQR	Interquartile range
M2 type	Type 2 macrophage
MCP	Monocyt chemokine protein
MMP	Metalloproteinase
MPO	Myeloperoxidase
mRNA	Messenger ribonucleic acid
NKO	Neus Keel en Oor
NP	Nasal polyp
NPCT	Nasal polyp control test
NSAID	Non-steroidal anti-inflammatory drugs
OCS	Oral corticosteroids
OR	Odds ratio
PG	Prostaglandin
RANTES	Regulated and normal T-cell expressed and secreted
RCT	Randomized clinical trial
ROC	Receiver operating characteristics
SAE	Staphylococcus Aureus Enterotoxin
TGF	Tumor growth factor
Th	Helper T-cell
TIMP	Tissue inhibitor of MMP
TNF	Tumor necrosis factor
URL	Upper airways research laboratory
VCAM	Vascular cell adhesion protein

LIST OF FIGURES

FIG. 1. Medication use over time. ..... - 21 -
FIG. 2. Symptoms over time. ..... - 22 -
FIG. 3. Total symptom score over time. ..... - 23 -
FIG. 4. Total symptom score in 2012 in primary or revision FESS in 2000. ..... - 23 -
FIG. 5. Total symptom score in 2012 in comorbidities. ..... - 24 -
FIG. 6. NP score over time. ..... - 25 -
FIG. 7. NP score in 2012 in comorbidities ..... - 25 -
FIG. 8. NP recurrence during 12 years of follow up in both categories of surgery in 2000.... - 28 -
FIG. 9. NP recurrence during 12 years of follow-up in allergy, asthma and Samter's triad. .. - 28 -
FIG. 10. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up. ..... - 30 -
FIG. 11. Revision FESS during 12 years of follow-up in both categories of surgery in 2000 - 31 -
FIG. 12. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up in both categories of surgery in 2000. ..... - 31 -
FIG. 13. Revision FESS during 12 years of follow-up in allergy, asthma and Samter's triad - 32 -
FIG. 14. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up in comorbidities. ..... - 32 -
FIG. 15. ROC-curve analysis of total symptom score in 2000 to predict revision FESS during 12 years of follow-up ..... - 34 -
FIG. 16. ROC-curve analysis of tissue IL-5 in 2000 to predict revision FESS during 12 years of follow-up ..... - 35 -
FIG. 17. Revision FESS during 12 years of follow-up in patients with or without detectable levels of tissue IL-5 and tissue SAE. ..... - 35 -
FIG. 18. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up. ..... - 36 -
FIG. 19. General therapeutic relief. ..... - 37 -
FIG. 20. Control. ..... - 38 -

LIST OF TABLES

Table 1. Comorbidities over time. .....- 20 -
Table 2. Descriptives in patients with and without NP recurrence. .....- 27 -
Table 3. Descriptives in patients with and without revision FESS .....- 29 -
Table 4. Comparison between NPCT score and EPOS score in 2012. .....- 38 -

LIST OF APPENDICES

Appendix 1: EPOS 2012 control test..... XIV
Appendix 2: CRSwNP management scheme for ENT-specialists. XV
Appendix 3: Treatment evidence and recommendations for adults with CRSWNP..... XVI
Appendix 4: Patient information. XVII
Appendix 5: Flowchart. XIX
Appendix 6: In- and exclusion criteria. XX
Appendix 7: Informed consent. XXI
Appendix 8: Case Report Form. XXII
Appendix 9: Baseline table.....XXXIX
Appendix 10: Biomarkers in 2000. XLI
Appendix 11: Correlation between biomarkers measured in 2000 and the total symptom score at each time of contact. XLIII
Appendix 12: Correlation between biomarkers measured in 2000 and the NP score at each time of contact. XLVI
Appendix 13: Logistic regression between biomarkers measured in 2000 and NP recurrence during the 12-year follow-up period.....XLIX
Appendix 14: Distribution of NP score in patients with and without revision FESS. LI
Appendix 15: Logistic regression between biomarkers measured in 2000 and revision surgery during the 12-year follow-up period..... LII

CONTENTS

DANKWOORD ..... **III**

LIST OF MEDICAL ABBREVIATIONS ..... **IV**

LIST OF FIGURES ..... **VI**

LIST OF TABLES ..... **VII**

LIST OF APPENDICES ..... **VIII**

I. ABSTRACT ..... **- 1 -**

II. INTRODUCTION ..... **- 3 -**

1. Classification and definitions ..... - 3 -
2. Diagnosis ..... - 3 -
   - 2.1. Symptoms ..... - 3 -
   - 2.2. Technical examinations ..... - 3 -
     - 2.2.1. Nasal endoscopy ..... - 3 -
     - 2.2.2. Imaging ..... - 4 -
     - 2.2.3. Nasal cytology, biopsy and bacteriology ..... - 4 -
3. Epidemiology ..... - 4 -
4. Pathophysiology ..... - 4 -
   - 4.1. Histomorphological features ..... - 4 -
   - 4.2. Inflammatory processes ..... - 5 -
     - 4.2.1. Th-2 cytokines and eosinophilic inflammation ..... - 5 -
     - 4.2.2. Th-1 cytokines ..... - 6 -
     - 4.2.3. Local IgE ..... - 6 -
5. Comorbidities ..... - 6 -
   - 5.1. Allergy and atopy ..... - 6 -
   - 5.2. Asthma ..... - 6 -
   - 5.3. Samter’s triad ..... - 7 -
6. CRSwNP treatment ..... - 7 -

6.1. Medical treatment - 7 -
6.1.1. Nasal saline - 7 -
6.1.2. Glucocorticoids - 7 -
6.1.2.1. Topical or intranasal corticosteroids (INCS) - 8 -
6.1.2.2. Systemic or oral corticosteroids (OCS) - 8 -
6.1.3. Antibiotics - 9 -
6.1.4. Anti-IL-5 - 9 -
6.1.5. Anti-IgE - 10 -
6.2. Functional Endoscopic Sinus Surgery (FESS) - 10 -
6.2.1. FESS in general - 10 -
6.2.2. FESS in CRSwNP - 10 -
6.2.3. Outcome of FESS in CRSwNP - 11 -
6.2.3.1. Efficacy - 11 -
6.2.3.2. Recurrence - 11 -
6.2.3.3. Potential influencing factors on outcome of FESS for CRSwNP - 11 -
6.2.3.3.1. Individual factors - 11 -
6.2.3.3.2. Concomitant diseases - 12 -
6.2.3.3.3. Biomarkers - 12 -
6.2.3.3.4. Post-operative medication - 12 -
7. Aims of the study - 13 -
III. MATERIALS AND METHODS - 14 -
1. Patients - 14 -
2. Assessment and procedures - 15 -
2.1. Anamnesis - 15 -
2.2. Clinical examinations - 16 -
2.3. Samples - 17 -
2.3.1. Tissue homogenates - 17 -
2.3.2. Nasal secretions - 17 -

2.3.3. Blood samples - 18 -
3. Statistical analysis - 18 -
4. Literature - 19 -
IV. RESULTS - 20 -
1. Patient characteristics - 20 -
2. Comorbidities - 20 -
3. Medication use - 21 -
4. Symptom score - 22 -
4.1. Symptoms over time - 22 -
4.2. Primary/Revision surgery - 23 -
4.3. Comorbidities - 24 -
4.4. Biomarkers - 24 -
5. NP score - 25 -
5.1. NP score over time - 25 -
5.2. Primary/revision surgery - 25 -
5.3. Comorbidities - 25 -
5.4. Biomarkers - 26 -
6. Recurrence - 27 -
6.1. Descriptives - 27 -
6.2. Statistical analysis - 27 -
6.2.1. Age - 27 -
6.2.2. Sex - 27 -
6.2.3. Primary/revision surgery in 2000 - 28 -
6.2.4. Comorbidities - 28 -
6.2.5. Symptom score - 28 -
6.2.6. NP score - 29 -
6.2.7. Biomarkers - 29 -
7. Revision surgery - 29 -

7.1. Descriptives - 29 -
7.1.1. Kaplan-Meier survival analysis - 30 -
7.2. Statistical analysis - 30 -
7.2.1. Age - 30 -
7.2.1.1. Logistic regression - 30 -
7.2.2. Sex - 30 -
7.2.2.1. Logistic regression - 30 -
7.2.2.2. Kaplan-Meier survival analysis - 30 -
7.2.3. Primary/revision surgery in 2000 - 31 -
7.2.3.1. Logistic regression - 31 -
7.2.3.2. Kaplan-Meier survival analysis - 31 -
7.2.4. Comorbidities - 32 -
7.2.4.1. Logistic regression - 32 -
7.2.4.2. Kaplan-Meier survival analysis - 32 -
7.2.4.2.1. Allergy - 33 -
7.2.4.2.2. Asthma - 33 -
7.2.4.2.3. Samter's triad - 33 -
7.2.5. Symptom score - 33 -
7.2.5.1. Logistic regression - 33 -
7.2.6. NP score - 34 -
7.2.6.1. Logistic regression - 34 -
7.2.7. Biomarkers - 34 -
7.2.7.1. Logistic regression - 34 -
7.2.7.2. Kaplan-Meier survival analysis - 36 -
7.2.7.2.1. Detectable tissue IL-5 - 36 -
7.2.7.2.2. Detectable tissue SAE - 36 -
8. General therapeutic relief - 37 -
9. Assessing control - 38 -

V. DISCUSSION ..... - 39 -

1. Comorbidities and medication use ..... - 39 -
2. Symptoms ..... - 39 -
3. Polyp size ..... - 40 -
4. NP recurrence and revision surgery ..... - 40 -
5. General therapeutic relief ..... - 41 -
6. EPOS 2012 control test as a measure of current disease control ..... - 41 -
7. Limitations of the study ..... - 41 -

VI. REFERENCE LIST ..... - 43 -

APPENDICES XIV

I. ABSTRACT

Introduction:

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a therapeutic challenge for ENT (Ear Nose and Throat)-specialists because of the high recurrence rate. The mucosal inflammatory response is more florid in CRSwNP than in those without nasal polyposis. Next to medical treatment, surgical intervention should be considered in patients who fail to improve after maximal medical treatment. However, no long-term prospective studies are available.

Methods:

In this prospective cohort study, 47 patients with CRSwNP underwent functional endoscopic sinus surgery (FESS) between 1998 and 2000 at the Ghent university hospital, Belgium. Before the initial surgery, all patients were fully characterized and tissue, nasal secretions and serum were examined. Six and 12 years after surgery, patients were invited to a follow-up visit. An ENT examination and questionnaire were performed.

Results:

Twelve years after surgery, 38 out of 47 patients (80.9%) were questioned. In 1998-2000, 50% of these 38 patients underwent primary FESS and 50% underwent revision surgery. Twelve years after surgery there was a significant better symptom score compared to before surgery ($P < 0.001$). The nasal polyp score after 12 years was significantly lower ($P < 0.001$). Further, obstructing nasal polyps (NP score ≥ 3) were only found in 20.0% of the patients compared to 84.2% prior to FESS in 1998-2000. In the 12-year follow-up period 30 out of 38 patients (78.9%) developed recurrent nasal polyps. Patients with allergy and/or Samter's triad had a higher recurrence rate. No significant predictors for recurrence could be identified. Of these 30 patients with recurrent NP, 14 (36.8%) underwent additional revision surgery, from which 7 underwent 1 additional FESS and 7 patients underwent 2 or more revision surgeries. Those 14 patients had a higher amount of allergy (78.6%), asthma (50.0%) and/or Samter's triad (42.9%) compared to those without revision surgery (37.5%, 33.3% and 16.7% respectively). Allergy, total symptom score and tissue Interleukin-5 (IL-5) levels prior to FESS in 1998-2000 were found to be significant predictors for revision surgery.

Conclusion:

This is the first prospective study investigating the outcome of FESS in patients suffering from CRSwNP over 12 years and the first to validate the EPOS 2012 control test. Patients with CRSwNP were subject to recurrent disease and revision surgery more than ten years after surgery. Allergy, asthma and Samter's triad were associated with a negative outcome.

I. ABSTRACT

Introductie:

Chronische rhinosinusitis met nasale polyposis (CRSwNP) is een therapeutische uitdaging voor NKO-specialisten omwille van de grote kans op herval. De mucosale inflammatie is meer uitgesproken in CRSwNP dan in patiënten zonder nasale polyposis. In patiënten die niet verbeteren onder medicamenteuze behandeling, zou een heelkundige interventie overwogen moeten worden. Tot op heden zijn er geen lange termijn prospectieve studies beschikbaar.

Methodologie:

In deze prospectieve cohort studie ondergingen 47 patiënten met CRSwNP tussen 1998 en 2000 FESS in het Universitair Ziekenhuis Gent in België. Voor deze operatie werd een volledig profiel van de patiënten opgesteld. Poliepweefsel, nasale secreties en serum werden onderzocht. Zes en 12 jaar na de operatie werden de patiënten uitgenodigd voor een opvolging. Een NKO onderzoek en een vragenlijst werden uitgevoerd.

Resultaten:

Twaalf jaar na de ingreep werden 38 van de 47 patiënten (80.9%) bevraagd. In 1998-2000 onderging 50% van de 38 patiënten voor de eerste maal FESS en 50% onderging een revisie FESS. Twaalf jaar na FESS waren de symptoom score en nasale poliep score significant beter t.o.v. de preoperatieve periode ($P < 0.001$). Obstructieve neuspoliepen (NP score ≥ 3) waren aanwezig in 20.0% van de patiënten t.o.v. 84.2% voor de operatie in 1998-2000. In deze follow-up van 12 jaar ontwikkelden 30 van de 38 patiënten (78.9%) opnieuw neuspoliepen. In patiënten met allergie en/of Samter's triad was dit recidief hoger. Er konden geen significante predictoren voor CRSwNP recidief weerhouden worden. Van deze 30 patiënten met recidief, ondergingen 14 (36.8%) patiënten een bijkomende operatie, waarvan 7 1 bijkomende FESS ondergingen en 7 patiënten 2 of meer heroperaties. In deze 14 patiënten was er een groter aandeel allergie (78.6%), astma (50.0%) en/of Samter's triad (42.9%) t.o.v. de patiënten zonder heroperatie (37.5%, 33.3% en 16.7% respectievelijk). Allergie, totale symptoom score en IL-5 in weefsel voor FESS in 1998-2000 waren significante predictoren voor het ondergaan van een heroperatie.

Conclusie:

Dit is de eerste prospectieve studie die de ouctome van FESS in patiënten met CRSwNP onderzoekt over een periode van 12 jaar en de eerste die de EPOS 2012 controle test valideert. CRSwNP patiënten hadden vaak recidief en heroperaties tijdens follow-up. Allergie, astma en Samter's triad waren geassocieerd met een negatieve outcome.

II. INTRODUCTION

1. Classification and definitions

The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) (1) defines rhinosinusitis in adults as: inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), and/or facial pain/pressure, and/or reduction or loss of smell. These complaints should be associated with either endoscopic signs of nasal polyps, and/or mucopurulent discharge primarily from middle meatus and/or edema/mucosal obstruction primarily in middle meatus and/or CT (Computed tomography) changes (mucosal changes within the ostiomeatal complex and/or sinuses).

Acute rhinosinusitis (ARS) in adults is defined as the sudden onset of two or more symptoms as listed above, for less than 12 weeks, with symptom free intervals if the problem is recurrent. Chronic rhinosinusitis (CRS) in adults is defined as presence of two or more symptoms as listed above for 12 or more weeks. CRS is currently classified as CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP), clinically based on endoscopic findings (1). Nasal polyps (NP) are grape-like semitransparent extrusions from the sinonasal mucosa, which may, on top of the mucosal inflammation, totally obstruct the nasal cavities and may lead to a total loss of smell (2).

2. Diagnosis

2.1. Symptoms

At the first notification of the problem, the diagnosis of rhinosinusitis is presumed on symptoms alone. The symptoms are mainly the same in ARS, CRSsNP and CRSwNP, but the pattern and intensity may vary. For instance, Litvack et al. (3) reported a significantly increased risk of hyposmia (OR (odds ratio) 2.4) and anosmia (OR 13.2) in nasal polyposis patients compared to CRSsNP. After inquiring the symptoms, anterior rhinoscopy remains the first step in clinical examination, although it is of limited value (1).

2.2. Technical examinations

2.2.1. Nasal endoscopy

Nasal endoscopy involves passing a frequently rigid, or sometimes flexible, endoscope through the nostril to examine the nasal cavity, middle and superior meati, nasopharynx and mucociliary drainage pathways. Nasal endoscopy has a major contribution in the diagnosis of CRS and affords significantly better illumination and visualization of the nasal cavity compared to anterior rhinoscopy (1).

2.2.2. Imaging

The plain sinus x-ray has limited usefulness for the diagnosis of rhinosinusitis and for evaluation of the response to therapy. CT scanning is the modality of choice for the paranasal sinuses due to optimal display of differences between air, bone and soft tissue. As mentioned before, CT scanning is not the primary step in the diagnosis of rhinosinusitis, but has the aim to affirm the symptoms and findings of endoscopic examination after failure of medical therapy. Because of many insignificant abnormalities found in the normal population during scans (4), the diagnosis of CRS based on imaging, in absence of symptoms, is inappropriate (1).

2.2.3. Nasal cytology, biopsy and bacteriology

Generally, cytology has not proven a useful tool in diagnosis of rhinosinusitis. However, lavage with 0.9% saline, microsuction, nasal brushes, nasal tampons, disposable scrapers, etc. are techniques which are largely used for clinical research (1).

3. Epidemiology

There is a deficit of epidemiologic studies exploring the prevalence and incidence of CRSwNP, especially in European countries (1). Although there is still disagreement about the prevalence of nasal polyps, most authors cite a prevalence of 1% to 4%. A population-based nasal endoscopic study in Skovde, Sweden, by Johansson et al. showed a prevalence of nasal polyps of 2.7% of the total population (5). Corresponding to this, autopsy studies found a prevalence of 2% using anterior rhinoscopy (6). However, in Denmark (7) nasal polyps were found in 5 of 19 cadavers, after removing whole nasoethmoidal blocks. From these cadaver studies one may conclude that a significant number of patients with NP does not feel the need to seek medical attention or that the diagnosis of CRSwNP is often missed by physicians. In general, NPs occur in all races, become more common with age (8-12) and are more frequently found in men than in women (13-15). Further, patients who suffer from asthma, cystic fibrosis (CF), Churg-Strauss syndrome, or sarcoidosis, have been shown to suffer from increased rates of nasal polyposis (12, 16, 17), each with their distinct pathophysiological profile.

4. Pathophysiology

4.1. Histomorphological features

At histomorphological level, CRSwNP is typically characterized by the presence of pseudocyst formations consisting of albumin accumulation and tissue edema, and a lack of collagen within the extracellular matrix (18). It has been suggested that low levels of Tumor Growth Factor-β

(TGF-β) contribute to an imbalance between matrix metalloproteinase-9 (MMP-9) and the tissue inhibitor of MMP-1 (TIMP-1), resulting in these remodeling changes (2, 18).

4.2. Inflammatory processes

Regarding the inflammatory processes, CRSsNP is typically a T helper cell-1 (Th-1) driven inflammation, characterized by high levels of Interferon-γ (IFN-γ), Tumor necrosis factor-α (TNF-α) (2) and TGF-β (18) whereas CRSwNP is more heterogeneous. In Caucasian CRSwNP, nasal polyps are characterized by a predominant Th-2 biased eosinophilic inflammation with high levels of local Il-4, Il-5, Il-13 (2), Eosinophil cationic protein (ECP), eotaxin, and Immunoglobulin-E (IgE) (18). Eosinophils appear to be a biomarker for severe, recalcitrant disease (19).

4.2.1. Th-2 cytokines and eosinophilic inflammation

The differentiation of naïve CD4+ cells into a Th-2 cell lineage is vastly influenced by crosstalk between epithelial cell (ECs) and local dendritic cells (DCs) (20). By producing Th-2 cytokines IL-4, IL-5 and IL-13, Th-2 cells are presumably the critical upstream cells driving eosinophilic inflammation in CRSwNP. High levels of these Th2 cytokines have been demonstrated in nasal polyps. IL-5 is highly specific to eosinophil activation and recruitment and plays an essential role in eosinophilic inflammatory processes.

The mechanism of recruitment and activation of eosinophils in CRS involves 3 main processes. First, the nasal ECs secrete eosinophil-attracting chemokines, such as Regulated And Normal T-cell Expressed and Secreted (RANTES), eotaxin -1 (CCL11), -2 (CCL24) and -3 (CCL26), Monocyt Chemokine Protein (MCP) 1-4, all of which work through C-C Chemokine Receptor 3 (CCR3) (21-32). In CRSwNP, these chemokines are elevated (1). The regulation of epithelial chemokine expression is complex, but IL-4 and IL-13 play a key role (33, 34). Secondly, cytokines such as granulocyte macrophage colony-stimulating factor (GM-CSF) and in particular IL-5 have priming and survival promoting effects by inducing increased migration, adhesion and survival of eosinophils in nasal polyp tissue (35-43). IL-5 status is independent of systemic allergy (35, 44-46). Lastly, the endothelium expresses adhesion molecules, especially VCAM-1, which mediates rolling, adhesion and transendothelial migration of eosinophils and is correlated with risk of post-surgical recurrence (47). Once present and activated, eosinophils are believed to damage the mucosa through degranulation and release of cytotoxic mediators, such as eosinophil cationic protein (ECP) (48-51). In addition to direct toxic effects, eosinophils in nasal polyps express C-C Chemokine Ligand 23 (CCL23), which recruits macrophages and monocytes (52). Macrophages convert to the M2 type in the Th-2 milieu (52), and appear to have an impaired ability to phagocytose Staphylococcus aureus (53).

4.2.2. Th-1 cytokines

In contrast to the Th-2 cytokines IL-4, IL-5 and IL-13, the Th-1 cytokine IFN-γ, which has been demonstrated to prevent airway eosinophilia and allergic response, is decreased in Caucasian nasal polyps. Elevated IL-8 levels, another Th-1 cytokine which acts as an neutrophil chemoattractant, in association with an increase of myeloperoxidase-staining cells and myeloperoxidase (MPO) concentrations, illustrate that neutrophils are also involved in the pathogenesis of CRSwNP (54).

4.2.3. Local IgE

IgE is synthesized locally in nasal polyps and is polyclonal. The local elevated IgE levels have been shown to be independent of systemic atopy and serum IgE. Recent studies have demonstrated that the polyclonal IgE in nasal polyps is functional and may cause mast cell degranulation (55). In CRSwNP, mast cells have the potential to induce, augment and maintain eosinophilic inflammation (56, 57). Furthermore, mast cell prostaglandins can activate Th-2 lymphocytes independently of T-cell receptor activation, contributing to the secretion of Th-2 cytokines in nasal polyps (58, 59). The local elevated IgE levels correlate with the presence of IgE to Staphylococcus aureus enterotoxins (SAE-IgE) (44). Exposure to SAE leads to polyclonal T cell activation with a Th-2 cytokine polarization. Higher levels of IL-5, eotaxin and ECP are seen in the presence of SAE-IgE. (60, 61). SAE also have other major impacts on local inflammation in polyp tissue, including an increased tissue remodeling, a reduction of eosinophil apoptosis, the induction of chemokines from epithelial cells (2) and alterations in the eicosanoid pathways.

5. Comorbidities

5.1. Allergy and atopy

The prevalence of allergy in patients with NP has been reported as varying from 10% (62) to 64% (63). Furthermore the risk-ratio of CRS in the allergic rhinitis group in a large cohort was shown to be 4.5 by Walker et al. (64). Contrary to reports that have implicated atopy as being more prevalent in patients with NP, others have failed to show this (17, 63, 65-67). On the other hand, CRS in atopic patients appears to be more severe (1). Recently, Bachert et al. (44) found an association between levels of both total and specific IgE and eosinophilic infiltration in NP, but these findings were unrelated to skin prick test results.

5.2. Asthma

However CRSwNP and asthma are frequently associated in patients, their inter-relationship is poorly understood (68). Wheezing and respiratory discomfort are present in 31% and 42% of

patients with CRSwNP, and asthma is reported by 26% of patients with CRSwNP, compared to 6% of controls (9, 69). Ten percent of the patients suffering from CRSwNP and asthma develop both polyps and asthma simultaneously and the remainder develop polyps first and asthma later (10). The prevalence of CRSwNP has been shown to be higher in patients with non-allergic asthma compared to patients with allergic asthma (70). CRSwNP with comorbid asthma is associated with the presence of local IL-5 and IgE to SAE.

5.3. Samter's triad

A subset of CRSwNP patients has Samter's triad characterized by aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) intolerance, CRSwNP and asthma (1). The unusual severity of the upper airway disease in these patients is reflected by high recurrence of nasal polyps, and frequent need for FESS (71, 72). These patients are usually non-atopic and the prevalence increases over the age of 40 years. Klossek et al. (9) found no difference between sex in 10.033 patients. Zhang et al. (73) found that SAE-IgE can be found in the majority of NP patients who are aspirin sensitive.

6. CRSwNP treatment

CRSwNP is a therapeutic challenge for ENT-specialists. The goal of CRS treatment is to achieve and maintain clinical control. Control is defined by EPOS 2012 guidelines as a disease state in which the patients do not have symptoms or the symptoms are not bothersome, if possible combined with a healthy or almost healthy mucosa and only the need for local medication. EPOS 2012 guidelines propose an assessment of current clinical control in patients with CRS by the use of the table in appendix 1, and indicate the need for further studies, which explore the percentage of patients that can achieve control of disease. There is a need for validation of this table (1).

6.1. Medical treatment

The figure in appendix 2 represents the management of CRSwNP for ENT-specialists as proposed by EPOS 2012. The table in appendix 3 shows the current evidence and recommendations for the treatment of CRSwNP in adults (1).

6.1.1. Nasal saline

A 2007 Cochrane review (74) found that nasal saline is an effective adjuvant treatment for CRS. Irrigation flushes the nasal cavity, facilitating the evacuation of mucus, allergens and irritating substances and reducing the post-nasal drainage (75, 76).

6.1.2. Glucocorticoids

Corticosteroids are found to downregulate epithelial cell cytokine secretion and upregulate the antimicrobials in epithelial cells (77-83). It has been indicated that glucocorticoids can inhibit

eosinophil recruitment, survival and activation in CRS (19, 43, 84-86). In accordance to this, T. Van Zele et al. (87) found reduced IL-5 and ECP levels in nasal secretions and demonstrated the clinical efficacy in the use of oral corticosteroids (OCS).

6.1.2.1.Topical or intranasal corticosteroids (INCS)

When compared to placebo in patients with no prior FESS, pooled data analyses of symptoms, polyp size, polyp recurrence and nasal airflow demonstrated significant benefit in the INCS group, however data analyzed for change in CT scan (88) and quality of life (89) showed no difference from placebo. Patients with prior sinus surgery had a greater response to INCS than patients without sinus surgery, considering polyp size reduction. However, improvement in symptoms and nasal airflow was not statistically different from placebo in the FESS population. Further, regarding the effect of delivery, nasal aerosols and turbohaler were found more effective than nasal spray in symptom control but there was no difference in polyp size reduction and nasal airway patency across various types of topical delivery methods (1). Furthermore, side-effects of topical steroids are rare and the amount of benefit clearly outweighs the risk. Epistaxis and nasal irritation, including itching, sneeze, dry nose and rhinitis are most frequently mentioned and are considered to be drug-related events (1). The bioavailability of INCS varies from <1% to up to 40-50% and influences the risk of systemic adverse effects (90, 91). Potential systemic adverse events related to the administration of INCS, even though infrequent, are effects on growth, ocular effects, effects on bone, and on the hypothalamic-pituitary-adrenal axis (92).

6.1.2.2.Systemic or oral corticosteroids (OCS)

OCS treatment in CRSwNP has demonstrated effects on nasal polyp size, nasal symptom score and nasal expiratory peak flow in several studies (93-95). There is a definite intermediate effect on both symptoms and polyp size, however treatment effects are short lived, given the recommended short period that this therapy is applied (1). The side-effects of oral intake are more prominent than topical application. These adverse effects include bone demineralization, ocular effects such as cataract and glaucoma, negative impact on glucose tolerance, hypertension, pituitary-hypothalamic axis suppression, skin atrophy and subcutaneous bleeding, etc. (1). Clearly, the chance of significant side effects increases with the dose and duration of treatment and therefore measures should be taken to minimize their side effects (1).

EPOS 2012 concludes that there is good evidence that both INCS and OCS are effective for the management of CRSwNP. Due to the chronicity of this condition many treatments will need to be ongoing. Thus the short-lived benefits of OCS therapy need to be balanced with the long-term

potential side-effects. Local therapy appears to be effective but the ability to effectively deliver INCS to the paranasal sinuses may greatly influence the treatment response (1).

6.1.3. Antibiotics

Antibiotics (AB) were introduced in treatment of CRSwNP based on the theory of enterotoxin producing staphylococci as disease modifiers in CRSwNP. Short-term treatment with AB in CRSwNP is defined by EPOS 2012 (1) as treatment less than three weeks with an oral anti-staphylococcal antibiotic such as doxycycline or a quinolone. One randomized clinical trial (RCT) by Van Zele and co-workers (87) showed that doxycycline for 3 weeks reduced pro-inflammatory markers, such as MMP-9, as well as MPO and ECP in nasal secretions and had a small effect on polyp size and post-nasal discharge but no other symptoms compared to placebo. Long-term treatment with AB in CRSwNP is defined as treatment longer than three weeks with a macrolide such as clarithromycine (1). A few studies have shown some effect on polyp size and patient symptoms. The effect seems to be moderate but may be more long lasting than systemic steroids (96-98). The side effects should be taken into account. A first concern is the emergence of resistant bacterial strains, in particular when using a low dose in long-term antibacterial treatment not attaining minimal inhibitory concentrations (99, 100). Secondly, well-known side-effects of AB can occur, including gastrointestinal upset, skin rash and reversible elevation of liver enzymes. In third place, the possible rare side-effects, such as hearing impairment, and interaction between macrolides and drugs can occur (1).

6.1.4. Anti-IL-5

Mepolizumab and reslizumab are humanized anti-IL-5 monoclonal antibodies that reduce the amount of eosinophils in blood and tissues (101, 102). A first study was done by Gevaert et al. in 2006 (103) and included a single intravenous infusion of reslizumab 3mg/kg or 1mg/kg or placebo in CRSwNP patients. There was no significant difference in nasal symptom scores or nasal peak inspiratory flow values and no dose response relation was observed. However, blood eosinophil counts dropped significantly in both active groups, followed by a steep increase above baseline values 8-19 weeks post injection, suggesting a rebound hypereosinophilia. In 2011, a second study was performed also by Gevaert and co-workers (104). In this study CRSwNP patients received 2 single intravenous injections (28 days apart) of 750 mg mepolizumab or placebo and were observed for a period of 48 weeks. The nasal symptom score improved significantly and significantly less sinus opacification in CT scans was observed in the treatment arm. The results of these 2 trials suggest that anti-IL-5 antibodies could play a role in the treatment of selected CRSwNP patients. However it should be noted that a recent reslizumab

study disclosed nasopharyngitis, fatigue, and pharyngolaryngeal pain as common adverse events in asthmatic patients (105).

6.1.5. Anti-IgE

Omalizumab, approved for patients with moderate-to-severe or severe asthma, is a humanized IgG monoclonal antibody that selectively binds to human IgE, and thereby reduces serum and tissue IgE-levels (1). Some ascribe beneficial effects to omalizumab in CRSwNP patients (106-109). A recent randomized, double-blind, placebo-controlled study of allergic and non-allergic patients with nasal polyps and comorbid asthma in 2013 by Gevaert et al. (110) showed a significant decrease in total nasal endoscopic polyp scores after 16 weeks in the omalizumab treated group, which was confirmed by CT. Omalizumab had a beneficial effect on airway symptoms and on quality-of-life scores, irrespective of the presence of allergy. On the other hand, omalizumab may increase the risk of cancer, thrombocytopenia or cardiovascular events and may cause anaphylaxis in approximately 1 patient per 1000 (1).

6.2. Functional Endoscopic Sinus Surgery (FESS)

6.2.1. FESS in general

FESS is defined by the Cochrane review (111) in 2006 as a now well-established strategy, which comprises several techniques, for the treatment of CRS which not responds to medical treatment. FESS is a minimally invasive surgical technique, which allows direct visual examination of the sinuses and involves the clearance of polypoid mucosa and opening of the sinus ostia and the ostiomeatal unit. The term ‘functional’ was originally applied to endoscopic sinus surgery to indicate that it improved mucociliary clearance or ‘functioning’ in the sinus. With regard to side-effects of FESS, a systematic review by Dalziel et al. (112) reported major complications from 0% to 1.5% and minor complications from 1.1% to 20.8% of the cases. Major complications related to FESS may include bleeding, orbital haematoma, damage to intraorbital structures, epiphora, loss of vision, cerebrospinal fluid leak, damage to intracranial structures and death (112-114). Minor complications may include epistaxis, sinus infections, stenosis of the middle antrostomy and intranasal synechiae (111). The reduced risk of complications from FESS correlates with the experience of the operating physician (1).

6.2.2. FESS in CRSwNP

The removal of inflammatory tissue and reduction of the load of antigens, as well as the improvement of sinus ventilation and mucociliary clearance, are the probable mechanisms whereby FESS improves symptoms in nasal polyposis (1). Surgical intervention in the treatment of CRSwNP is considered in patients who fail to improve after a trial of maximal medical treatment. Sinus surgery for CRSwNP patients, should not be thought of as the only treatment

but rather as a modality used to manage patients to remove the disease burden and increase the efficacy of post-operative medical therapy (1).

6.2.3. Outcome of FESS in CRSwNP

6.2.3.1. Efficacy

When considering efficacy in CRSwNP, a number of series have demonstrated that sinus surgery in patients with nasal polyps can result in a prolonged reduction of nasal symptoms and an improvement of quality of life. In 2003 Dalziel et. al (115) performed a systematic review and in three RCTs patients judged their symptoms to be 'improved' or 'greatly improved' in 75 to 95% of cases. In 2005 Alobid et al. (116) compared patients with FESS and INCS in one arm and medical treatment with OCS and INCS in the other arm. At 6 and 12 months there was significant improvement of the nasal symptoms and polyp size in both the two treatment arms in CRSwNP. The beneficial effect of FESS on the polyp size and symptoms was also demonstrated by Bonfils et al. (117) over a 5-year follow-up period. The extent of surgery required to optimize outcomes in CRSwNP patients has not been established, although some reports suggest that outcomes may be improved after more extensive procedures (114, 118).

6.2.3.2. Recurrence

In the retrospective study by Mendelsohn et al. (119) in 2011, disease recurrence rate after 5 years in CRSwNP was 16% and increased to 22% after 10 years. The rate of revision surgery after 5 years was 10% in CRSwNP and increased to 17% after 10 years. In a study by Hopkins et al. was found that revision surgery was indicated in 3.6% of CRSwNP patients at 12 months and 11.8% at 36 months (120). Despite some evidence of an increased rate of revision surgery in CRSwNP (121), patients with polyps may experience more benefit following sinus surgery than CRSsNP patients (122). In literature there is a lack of long-term prospective follow-up studies focusing on the effects of FESS (1).

6.2.3.3. Potential influencing factors on outcome of FESS for CRSwNP

6.2.3.3.1. Individual factors

Reported symptomatology before and after surgery does not differ with age but postoperative objective signs seem to improve more in the elderly (123, 124). However, higher surgical complication rates in elderly were found (125). Comparing the sex, most studies show no statistically significant difference in the improvement of the presenting symptoms (1). No association of NP recurrence with age or sex was observed, however patients presenting with extensive disease suggested by CT scan staging are at higher risk for the development of recurrences after endoscopic surgery for nasal polyps (126).

6.2.3.3.2. Concomitant diseases

For allergy and atopy, studies contradict each other. There are a number of studies indicating a negative influence of atopy on outcome of FESS (121, 127), whereas in recent studies allergy did not seem to be a determinant of NP recurrence (1). Secondly, asthma was shown to be a risk factor of NP recurrence and revision surgery after FESS (119, 128-130), but not in all studies (126, 131). Furthermore, patients with Samter's triad benefit from sinus surgery, but to a lesser extent than patients without Samter's triad (1). They are more prone to disease recurrence and more frequently undergo revision surgery than aspirin tolerant CRSwNP patients (119).

6.2.3.3.3. Biomarkers

There is a lack of studies investigating the effect of biomarkers in tissue, nasal secretions and serum on the prognosis and prediction of response to FESS in patients with CRSwNP. Although one study (132) found an increased number of IL -5 messenger ribonucleic acid (mRNA) in the ethmoid sinus mucosa at the time of FESS in patients that did not respond to surgical intervention.

6.2.3.3.4. Post-operative medication

The long-term efficacy of surgery is almost certainly influenced by the regimen of medical treatment prescribed postoperatively and the subsequent compliance with this regimen (1). This postoperative treatment varies from non-intervention (133), nasal saline irrigation (134), INCS (135), stenting of the middle meatus (136-138) to frequent in-office endoscopic debridement (118) or combinations of these measures in various ways. Prolonged postoperative medical treatment with INCS would appear to improve outcomes post FESS for CRSwNP (1).

7. Aims of the study

1. This is the first prospective cohort follow-up study of twelve years after FESS, as there is a lack of long-term follow-up studies assessing objective and subjective disease status (comorbidities, medication use, symptoms and NP score). This study attempts to investigate the clinical course of CRSwNP over a long follow-up period.
2. Define the rate of NP recurrence and revision surgery twelve years after FESS and time to first revision surgery during follow-up.
3. Define risk factors predicting NP recurrence or revision surgery during twelve years of follow-up after FESS. These potential risk factors present in 2000 include age, sex, primary/revision FESS in 2000, total symptom score, NP score, comorbidities (allergy, asthma and Samter's triad), and inflammatory biomarkers in serum, nasal secretions and nasal tissue.
4. Practice the EPOS 2012 Control Test for the first time in a clinical setting and reflect on its value as a measure of current disease control. Based on the findings, comments en suggestions are given.

III. MATERIALS AND METHODS

1. Patients

The initial patient population of this 12-year prospective cohort study covers 47 patients, who underwent primary or revision FESS for nasal polyposis at the department of Ear, Nose and Throat (dept. ENT) of the Ghent University Hospital (GUH), Belgium, between 03/12/1998 and 11/05/2000. All patients included in the study were of Caucasian origin. CRSwNP was diagnosed based on history, clinical examination, nasal endoscopy and CT scan, following the current guidelines (1). All patients were operated by the same surgeon, Prof. Dr. C. Bachert, except one who was operated by Prof. Dr. I. Dhooge, using identical standard operating procedures. The techniques used for FESS were essentially those described by Messerklinger (139). In our study the same surgical procedure was carried out for all patients by clearing polypoid mucosa, widening of the maxillary ostium, opening of posterior and anterior ethmoid, opening of the sphenoid ostium and finally identification and opening of the nasofrontal duct, using cold instruments. Laser and microdebriders (shaver) were never used in these procedures. A nasal packing was placed and removed 2 days postoperatively and the patient was discharged the same day. Irrigation of the nose with normal saline and vaseline ointment was carried out four times a day. Medical treatment consisting of topical nasal steroid spray was prescribed for three months. Meticulous in-office endoscopic debridement was performed weekly for four weeks. Patients were free to undergo revision surgery during the 12-year follow-up period.

Two control moments were organized, approximately 6 and 12 years after FESS. Initially, each patient was asked by letter (appendix 4), and if no response by telephone, to participate in the follow-up moments at the dept. ENT of the GUH. If patients were unable to come to the GUH, a questionnaire was administered by telephone. The response rate was 57.4% (27/47) after 6 years and 80.9% (38/47) after 12 years of follow-up. A first control moment was organized after 6 years. At that time, 2 of the initial 47 patients were deceased. Between 04/01/2006 and 14/09/2007, data were obtained from 27 patients: 26 patients were examined at the dept. ENT of the GUH and 1 patient preferred to answer the questionnaire by telephone. Nineteen patients did not participate. After 12 years, a final control moment was organized. Between 14/10/2011 and 19/11/2012, data were obtained from 38 patients. A first group of 35 patients was examined at the dept. ENT of the GUH, of whom 23 patients were also examined during the first control moment, 1 patient answered the questionnaire by telephone during the first control moment, and 11 patients did only participate in the control moment in 2012. A second group consisted of 3 patients who preferred to answer the questionnaire by telephone. Further, 6 patients did not

respond to the recall in 2012 and 1 patient was deceased after 2007. This is schematically shown in the flowchart in appendix 5.

At each contact, patients were reckoned to be in good health by questionnaire. Comorbidities, possibly correlated with CRSwNP, such as asthma, allergy, COPD, rhinitis, otitis, aspirin intolerance and/or atopic dermatitis were no reason for exclusion. The specific in- and exclusion criteria are shown in appendix 6 and are valid for the time of inclusion and the two follow-up moments. At each contact, a written informed consent was obtained from all subjects (appendix 7). The study was approved by the ethical committee (EC/2011/818) of the GUH and insured by the No Fault Insurance GUH.

2. Assessment and procedures

2.1. Anamnesis

A complete Case Report Form (CRF) of 2000, 2006 and 2012 can be found in appendix 8. At each contact, the medical history of the patient was assessed. The diagnosis of asthma and COPD was performed by a lung physician and classified according to the prevailing guidelines by use of spirometry (respectively GINA (140) and GOLD (141) guidelines (CRF in appendix 8)). The atopic status was evaluated in 2000 by skin prick test to common inhalant allergens and was further inquired during follow-up (142). The diagnosis of NSAID intolerance was primarily based on the clinical picture, namely the presence of asthma, nausea, erythema or other complaints shortly after ingestion of ASA. Samter's triad was assumed in patients with CRSwNP, concomitant asthma and an earlier experience with intolerance to NSAIDs. Recent complaints associated with rhinitis and/or otitis and/or a history of atopic dermatitis were explored. The patients were asked if they had undergone ENT-related surgery prior and posterior to the FESS in 1998-2000 and other surgical procedures ever. These data were used to identify revision surgery. Family history (allergy, aspirin intolerance, CRSwNP, etc.), former and current profession and occupations, environmental exposure, medication use, the consumption of tobacco, alcohol and/or illicit drugs are aspects further dealt in the questionnaire. Asthma medication was defined as the use of inhalation corticosteroids (ICS) and/or bronchodilatating inhalation drugs. ENT-related and general anamnestic information was carefully noted each time. Symptoms related with CRSwNP (nasal obstruction, rhinorrhea, sternutation, hyposmia, headache and eye symptoms) were quantified during each contact by the patient from 0 to 3 (0 = no complaints, 1 = mild, 2 = moderate, 3 = severe) for his/her best period posterior to the FESS in 1998-2000, and for his/her current state. The total symptom score ranging from 0 to 18, is the sum of the 6 aforementioned symptoms. Duration of the post-operatively best period was also

asked. The general therapeutic response is defined as the extent of improvement of symptoms compared to pre-FESS baseline in 1998-2000 and is scored from 1 to 5 (1 = complete relief, 2 = marked relief, 3 = moderate relief, 4 = slight relief, 5 = no relief). The patients were asked if they would do the FESS of 1998-2000 back then again with the knowledge that they have now. A non-validated nasal polyposis control test (NPCT), designed by analogy with the validated asthma control test (ACT) (143), was performed only in 2012, based on 5 questions scored from 0-5 (0 = maximal complaints, 5 = no complaints) with a total score ranging from 0-25. The ACT was also performed in all patients seen in 2012. NPCT and ACT were both classified as very poorly controlled (<15), not well-controlled (15-19) and well-controlled (20-25). The specific questions of the NPCT and ACT can be found in the CRF in appendix 8. The patients with comorbidities (allergy, asthma, COPD and Samter's triad) were asked at each visit in what extent they have noticed an evolution in their symptoms due to the comorbidity, posterior to the FESS in 1998-2000 based on a 5-point scale (-2 = clearly worse, -1 = moderately worse, 0 = no change, +1 = moderately better, +2 = clearly better). Changes in medication use for sinonasal complaints in the last 3 weeks (oral/nasal/inhalation corticosteroids, antihistamines, asthma medication, antibiotics, physiological nasal lavage and/or others) and throughout follow-up were assessed. An assessment of current control of each patient with CRSwNP was done as proposed by the EPOS guidelines 2012 by the use of the table in appendix 1.

Quality control of the data in the CRF has been done by a third person that was not involved in the completion of the CRFs by comparing the source data with the CRF.

2.2. Clinical examinations

A rhinoscopia anterior and nasal endoscopy was performed in each nostril at each contact during the course of the study. Both techniques explore the nasal cavity for CRS, infection and/or synechiae. The size of nasal polyps was scored by endoscopy from 0-3 on each side using the original Davos scoring system (0=no polyps, 1=polyps posterior to the middle nasal turbinate, 2=polyps inferior to the middle nasal turbinate, 3=massive polyposis) (1). The nasal polyp score is the sum of the right and left Davos score, ranging from 0 to 6. Recurrence was defined as a nasal polyp score greater than 0 and/or a revision surgery during follow-up. The oropharynx was examined with the aid of a throat spatula and a light source. The outer ear canal and tympanic membrane of the ear were examined with an otoscope. Shortly before the FESS in 1998-2000, each patient was subjected to a CT-scan of the sinuses, which was scored using the Lund-Mackay score based on points given for degree of opacification (0=normal, 1=partial opacification, 2=total opacification) in the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus and ostiomeatal complex on each side (1). In context of the study, no new

CT scan was scheduled in the period postoperatively. But patients who had a recent CT scan, were asked to bring it with them at the follow-up moments.

2.3. Samples

Just before the FESS in 1998-2000 and at follow-up in 2012, blood samples and nasal secretions were collected for each patient. Furthermore nasal polyp tissue was obtained during FESS in 2000. All samples were immediately processed, separated and stored at their specific optimal temperature until analysis. Samples collected in 1998-2000 have been assayed by the Upper Airways Research Laboratory (URL), Ghent University, Belgium. Analysis of the samples collected in 2012 has not yet been done, but can be performed in the future.

2.3.1. Tissue homogenates

Freshly obtained tissue specimens were weighed, and 1 ml of 0.9% NaCl solution was added per every 0.1 g tissue. The tissue was then homogenized with a mechanical homogenizer (B. Braun Melsungen, Germany) at 1000 rpm for 5 minutes on ice. After homogenization, the suspension was centrifuged at 3500 rpm for 10 minutes at 4°C and the supernatans separated and stored at -80°C until analysis. All samples were assayed for IL-5 (pg/ml, ELISA, Innogenetics), IL-5Rα (pg/ml, ELISA, R&D Systems, Minneapolis, MN, USA), TGF-β1 (pg/ml, ELISA, R&D Systems, Minneapolis, MN, USA), MPO (ng/ml, ELISA, Oxis Research, Immunosource, Zoersel, Belgium), IL-18 (pg/ml, ELISA, MBL, Naka-ku, Nagoya, Japan), ECP (µg/l) and albumin (g/l, UniCAP system, Pharmacia Diagnostics, Uppsala, Sweden). All supernatants were assayed for total IgE (kUA/l) and specific IgE antibodies by the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden) namely: SAE A, B, C, D, E, TSST (kUA/l), grass mix 1 (kUA/l), house dust mite mix 2 (kUA/l), mold mix 2 (kUA/l), tree mix 9 (kUA/l). ImmunoCap coated with human serum albumine (HSA) or glycine were used to evaluate any non-specific binding of IgE.

2.3.2. Nasal secretions

Nasal secretions were collected by placing sinus packs (IVALON 4000 plus 3.5x0.9x1.2cm surgical product M-Pact, Eudora, Kan) in both nasal cavities for exactly 5 minutes. The quantity of secretions collected was determined by comparing the weight of the sinus pack before and after insertion. In order to mobilize the nasal secretions out of the sinus pack, 3 milliliters of 0.9% NaCl solution were added to the tube which was stored at 4°C for 2 hours. The sinuspack was then placed into the shaft of a syringe (placed into another tube) and centrifuged at 1500 g for 15 minutes at 4°C to recover all fluids. Supernatants were separated and stored in aliquots at -20°C until analysis. All supernatants were assayed for IL-5 (pg/ml), IL-5Rα (pg/ml), ECP (µg/l), IgE (µg/l) and sIgE (SEA,C,TSST) (µg/l) using the corresponding techniques as described previously.

2.3.3. Blood samples

Peripheral blood was collected in each patient by performing a standard venipuncture using two Becton Dickinson 3 ml EDTA tubes and two Becton Dickinson 10 ml serum tubes. EDTA blood was carefully mixed, divided into Eppendorf 1.5 ml safelock aliquots, and stored at -80°C until a full blood count (FBC) was performed. Serum blood samples were allowed to clot at room temperature for 20-30 minutes, centrifuged at 1500 g for 10 minutes at 4°C, and sera was separated. The supernatants were divided into aliquots, and stored at -20°C. All supernatants were assayed for IL-5Rα (pg/ml), albumin (g/l), ECP (µg/l), IgE (kUA/l), grass mix 1 (kUA/l), house dust mite mix 2 (kUA/l), SAE A, B, C, D, E, TSST (kUA/l), mold mix 2 (kUA/l), tree mix 9 (kUA/l) using the corresponding techniques as described previously. ImmunoCap coated with human serum albumine (HSA) or glycine were used to evaluate any non-specific binding of IgE.

3. Statistical analysis

Statistical analysis was performed with the SPSS 21.0 software. Data are expressed as absolute numbers and percentages, as median and interquartile range (IQR), in bar graphs, Box and whisker plots and Kaplan-Meier curves. Statistical significance was assessed using two-tailed tests and was defined as $P < 0.05$. After Bonferroni correction for comparison of three groups, P-values less than 0.016 were considered statistically significant.

When comparing two categorical variables, the McNemar test, the Bowker's test for symmetry, the Chi square test or the Fisher's exact test was used. The two sample McNemar test was used to compare two paired variables with each two categories. When there were more than two categories for both of the paired variables, the Bowker's test for symmetry was used. The Chi square test was applied when comparing two unpaired variables. If however the expected value in any of the cells of a contingency table was below five, the Fisher's exact test was used instead of the Chi square test.

Because the results did not follow a normal distribution, the continuous variables were analysed using non-parametric tests, including the Wilcoxon matched-pairs signed-ranks test, the Mann-Whitney U test, the Kruskal-Wallis test or the Spearman rank correlation coefficient (r_s). Differences between the paired data were calculated by using the two sample Wilcoxon matched-pairs signed-ranks test. For unpaired data, comparisons were made by using the two sample Mann-Whitney U test, or the Kruskal-Wallis test if comparing more than two samples.

Spearman rank correlation coefficient was used to assess the relationships between two continuous variables.

To identify possible predictors of recurrence and revision surgery after FESS, logistic regression was performed. For continuous predictors, the Hosmer-Lemeshow test was done, to determine if the logistic regression analysis could be performed. To determine the best predictors, a Receiver Operating Characteristic (ROC) curve analysis was generated for all significant continuous predictors. In a ROC curve the true positive rate (sensitivity) is plotted against the false positive rate (100-specificity) for the different possible cut-off values of a variable. For significant predictors, a cut-off value corresponding with the highest accuracy (minimal false negative and false positive results) was determined. For each ROC curve, the area under the curve (AUC) was calculated, measuring the accuracy of the logistic regression analysis.

Surgery-free survival following FESS in 2000 was investigated with Kaplan-Meier analysis. The Mantel-Cox Log Rank Test was used to compare the surgery-free survival curves in categorical variables.

4. Literature

First, the topic of CRSwNP was explored and studied using the doctoral theses of Prof. Dr. Ph. Gevaert (144) and Dr. Th. Van Zele (145). Further, PubMed and Web of Science were searched using combinations and synonyms of following keywords: chronic rhinosinusitis, nasal polyps, diagnosis, imaging, epidemiology, pathophysiology, inflammation, remodelling, immunology, T-cell cytokines, interleukin-5, Staphylococcus Aureus, superantigens, IgE, asthma, allergy, Samter's triad, treatment, nasal irrigations, corticosteroids, antibiotics, FESS and guidelines. Articles and reviews were assessed based on the abstract. EPOS 2012 (1) was withheld as the major fundamental guideline to achieve this thesis. Relevant references of EPOS 2012 were further investigated. The articles used in this thesis can be found in the reference list.

IV. RESULTS

The baseline table found in appendix 9 depicts demographics, medication, comorbidities and disease severity information in the total CRSwNP patient group seen at each given time point, i.e. 47 patients prior to FESS in 2000, 27 (57.4%) patients in 2006 and 38 (80.9%) patients in 2012. The table in appendix 10 presents biomarkers, measured just before FESS in 2000 in the 47 patients. Further results are based on the cohort of 38 CRSwNP patients seen 12 years after FESS in 2000. Twenty-five out of these 38 patients were intermediately seen 6 years after FESS in 2000.

1. Patient characteristics

The cohort of 38 CRSwNP patients followed up for 12 years after FESS in 2000 consisted of 25 (65.8%) men and 13 (34.2%) women and had a median age of 47 years. The ratio of the sex was approximately the same in the 25 patients who were also seen at follow-up in 2006. The median age increased over time because the population was followed up for 12 years. In the cohort, 19 (50%) patients underwent FESS for the first time in 2000. For the other 19 (50%) patients, FESS in 2000 was a revision surgery. In these latter 19 patients, 10 patients had 1 FESS and 9 patients had 2 or more FESS prior to inclusion in 2000 (appendix 9).

2. Comorbidities

Table 1. Comorbidities over time.

	2000 (N=38)	**2006** (N=25)	**2012** (N=38)
Allergy	20 (52.6)	14 (56.0)	20 (52.6)
Asthma	15 (39.5)	10 (40.0)	15 (39.5)
Samter's triad	10 (26.3)	5 (20.0)	10 (26.3)

Data are expressed as N (%).

Table 1 represents the frequency of comorbidities at each contact. Allergy (52.6%), asthma (39.5%) and aspirin intolerance (26.3%) were highly prevalent in the CRSwNP study group. According to the current GINA-classification, 12 (80.0%) patients were considered to have intermittent asthma and 3 (20.0%) to have moderate persistent asthma in 2012. In 2000, 5 patients with asthma did not have aspirin sensitivity whereas 10 patients accord the Samter's triad. The number of patients suffering from a comorbidity decreased nor increased during follow-up. When inquiring the 20 allergy patients, 13 (65.0%) reported no difference, whereas 1

(5.0%) and 6 (30.0%) patients reported a moderate respectively clear improvement of the allergy related symptoms at their postoperatively best moment. The distribution of this symptomatic evolution is maintained in 2012, although one patient shifted from a clear to a moderate improvement. Of the 15 asthmatic patients, 11 (73.3%) regarded their asthma related symptoms to be unaltered, 2 (13.3%) as moderately better and 2 (13.3%) as clearly better at their postoperatively best moment. In 2012 however, one patient (6.7%) considered his postoperatively asthma related symptoms to be much worsened, whereas 7 (46.7%), 4 (26.7%) and 3 (20.0%) patients reported no, a moderate or a respectively clear improvement of these symptoms. In patients with Samter's triad, the evolution of aspirin intolerance could not be judged because these patients avoided intake of NSAIDs since diagnosed.

3. Medication use

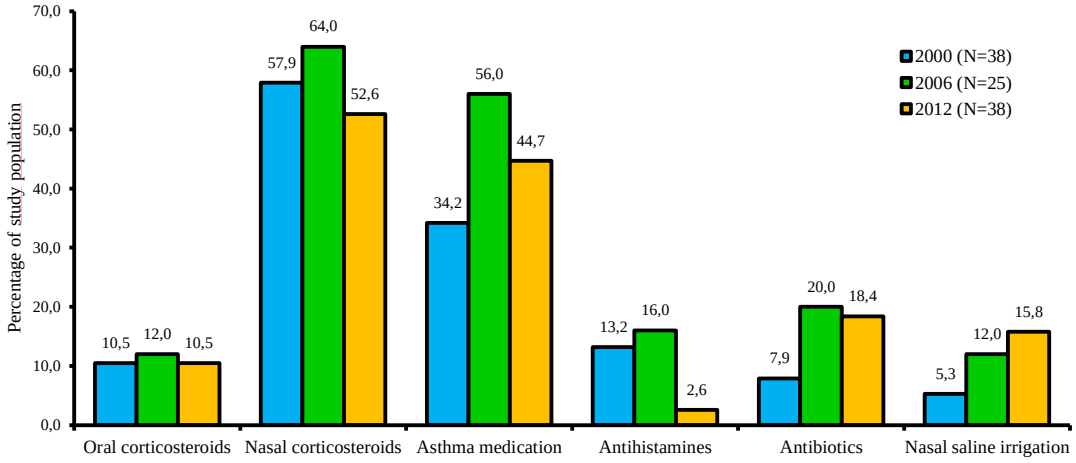


FIG. 1. Medication use over time.

As shown in figure 1, the use of medication did not significantly differ between the 3 moments of contact, although asthma medication use and in particular inhalation corticosteroids tended to be higher during follow-up. Ten (66.7%) out of the 15 asthmatic patients used asthma medication pre-operatively. At the contact moments during follow-up, all asthmatic patients mentioned current treatment with asthma medication. Asthma medication use was also picked up by questionnaire in other obstructive pulmonary diseases. Over time, 14 (64.0%) patients in 2006 and 20 (52.6%) patients in 2012 used INCS as an ongoing treatment, compared to 22 (57.9%) pre-operatively. Prior to surgery in 2000, 4 (10.5%) patients took OCS in the last 3 weeks. At follow-up, 3 (12.0%) patients in 2006 and 4 (10.5%) patients in 2012 used OCS. The antihistamine use changed from 5 (13.2%) patients pre-operatively to 4 (16.0%) in 2006 and 1 (2.6%) in 2012. Prior to FESS in 2000, 3 (60.0%) of the antihistamine users were allergic, whereas during follow-up all users were allergic. The use of AB tended to be higher during

follow-up with an increase from 3 (7.9 %) patients in 2000 to 5 (20.0%) out of 25 patients in 2006 and 7 (18.4%) patients in 2012. In 2006 and 2012, 3 (12.0%) respectively 6 (15.8%) patients applied nasal saline irrigation compared to 2 (5.3%) patients in the period prior to FESS in 2000.

4. Symptom score

4.1. Symptoms over time

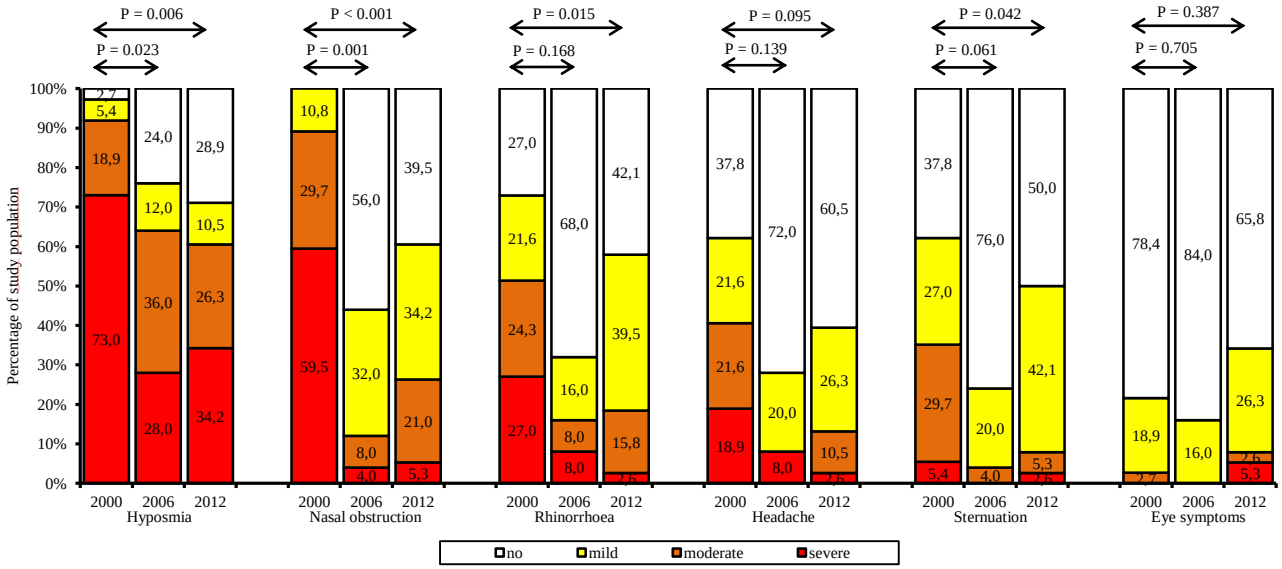


FIG. 2. Symptoms over time.

Figure 2 shows the distribution in percentages of severity of the inquired symptoms at each time of contact. Hyposmia and nasal obstruction were the most predominant symptoms preoperatively, bothersome, i. e. moderate to severe (score $\geq$ 2), in 35 (91.9%) and 34 (89.2%) patients respectively. Patients reported an improvement of their hyposmia in 2006 (P = 0.023), and in 2012 (P = 0.006), compared to hyposmia pre-operatively, although not significantly in 2006 after Bonferroni correction. Nasal obstruction was significantly improved after 6 (P = 0.001) and 12 years (P < 0.001). The 2 other symptoms mentioned in the EPOS 2012 definition of CRS, rhinorrhoea and headache, were bothersome in 19 (51.3%) and 15 (40.5%) patients respectively prior to FESS in 2000. Six years after surgery, these symptoms appeared to decrease, but no significant improvement could be found. Over 12 years only rhinorrhoea was significantly improved (P = 0.015). Headache was not significantly improved in 2012 (P = 0.095). Compared to the aforementioned symptoms, patients were less troubled by sternutation and eye symptoms pre-operatively and during follow-up. Fewer patients mentioned bothersome sternutation after 12 years, although not significantly after Bonferroni corection (P = 0.042).

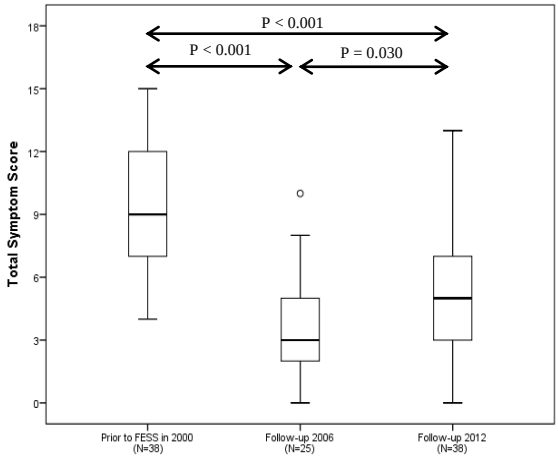


FIG. 3. Total symptom score over time.

The total symptom score, with a median of 9 in 2000, 3 in 2006 and 5 in 2012, differed significantly ($P < 0.001$) between the three moments of contact (Figure 3). The total symptom score was significantly lower 6 ($P < 0.001$) and 12 ($P < 0.001$) years after FESS in 2000. Between 2006 and 2012, the total symptom score seemed to increase, although not significantly after Bonferroni correction ($P = 0.030$). A positive correlation between the total symptom score in 2000 and 2012 was found ($r_s = 0.423$ ($P = 0.009$)), indicating that a patient with a high (low) total symptom score in 2000 tended to obtain a high (low) total symptom score in 2012. No significant correlation could be found between the total symptom score in 2000 and 2006 ($r_s = 0.160$ ($P = 0.445$)).

4.2.Primary/Revision surgery

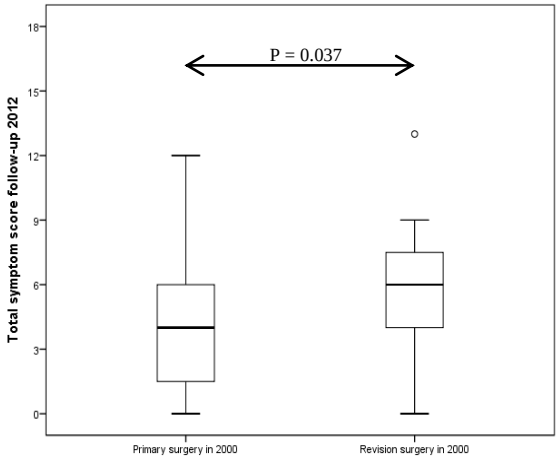


FIG. 4. Total symptom score in 2012 in primary or revision FESS in 2000.

The medians of the total symptom score in 2012 were 4 and 6 with corresponding IQR = 1-6 and 4-8 in respectively the primary and revision FESS group in 2000 (Figure 4). The total symptom score in 2012 was significantly higher ($P = 0.037$) in the patients who underwent revision surgery compared to those who underwent FESS for the first time in 2000. Note however that the

total symptom score prior to FESS in 2000 and at follow-up in 2006 did not significantly differ between the primary and revision surgery groups (P = 0.317 and P = 0.501 respectively).

4.3.Comorbidities

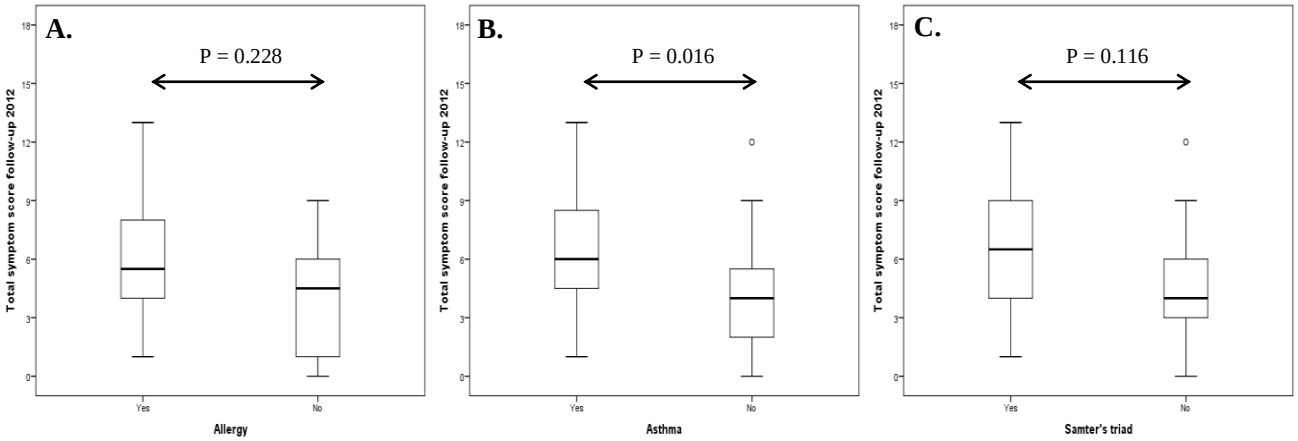


FIG. 5. Total symptom score in 2012 in comorbidities. A. Allergy. **B.** Asthma. **C.** Samter's triad.

Figure 5 shows the distribution of the total symptom score in 2012 in patients with allergy, asthma and Samter's triad. Preoperatively in 2000 and at follow-up in 2006 and 2012, no significant difference could be found in the total symptom score between patients with or without allergy (P = 0.098, P = 0.051 and P = 0.228). Although, patients with allergy tended to have a higher total symptom score at each time of contact. In 2012, the total symptom score was significantly higher in patients with asthma (P = 0.016). The same trend was observed when questioning the symptom score in asthmatic patients in 2000 and 2006, although not significant (P = 0.244, respectively P = 0.261). Patients with Samter's triad reported a higher total symptom score pre-operatively in 2000 and at follow-up in 2006 and 2012, however this difference could not be proven to be significant at any time (P = 0.324, P = 0.192 and P = 0.116 respectively).

4.4.Biomarkers

The table in appendix 11 summarizes the correlation between biomarkers measured in 2000 and the total symptom score at each time of contact. The total symptom score in 2012 showed a significant positive correlation with tissue IL-5Rα (r_s = 0.344, P = 0.034), tissue ECP (r_s = 0.390, P = 0.017), tissue SAE A (r_s = 0.378, P = 0.021), IL-5 in nasal secretions (r_s = 0.408, P = 0.013), serum eosinophils percentage (r_s = 0.400, P = 0.039) and serum tree mix 9 (r_s = 0.500, P = 0.021).

5. NP score

5.1. NP score over time

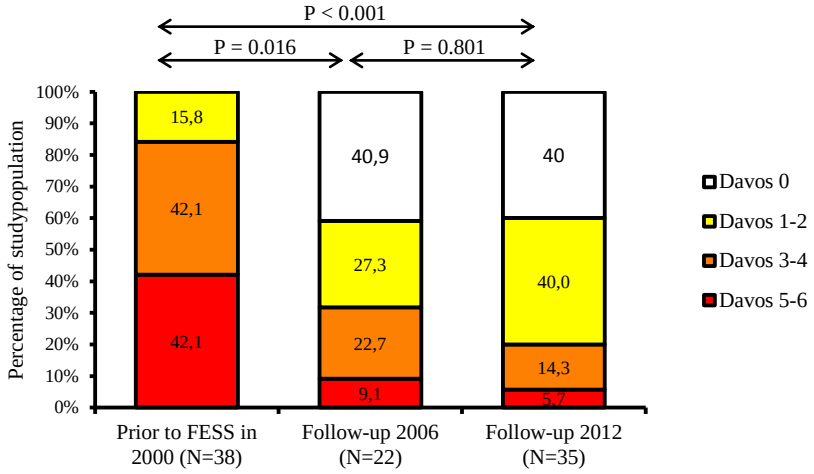


FIG. 6. NP score over time.

Figure 6 shows the distribution in percentages of NP score in 4 categories at each time of contact. Prior to FESS in 2000, all patients had nasal polyps. Six years after FESS in 2000, endoscopic examination of the nasal cavity in 22 patients showed absent polyps in 9 patients (40.9%). Six patients (27.3%) were scored as 1 or 2, 5 (22.7%) as 3 or 4 and 2 (9.1%) as 5 or 6. In 2012, 14 (40.0%) out of 35 endoscopic examined patients were polyp-free, 14 (40.0%) had a polyp score of 1 or 2, 5 (14.3) had a score of 3 or 4 and 2 (5.7%) had a score of 5 or 6. Compared to the NP score prior to FESS in 2000, the NP score was significantly decreased in 2006 (P = 0.016) and in 2012 (P < 0.001).

5.2. Primary/revision surgery

At the three times of contact, no significant difference in NP score was found between patients who underwent primary or revision FESS in 2000 (P = 1.000 in 2000, P = 0.856 in 2006 and P = 0.618 in 2012).

5.3. Comorbidities

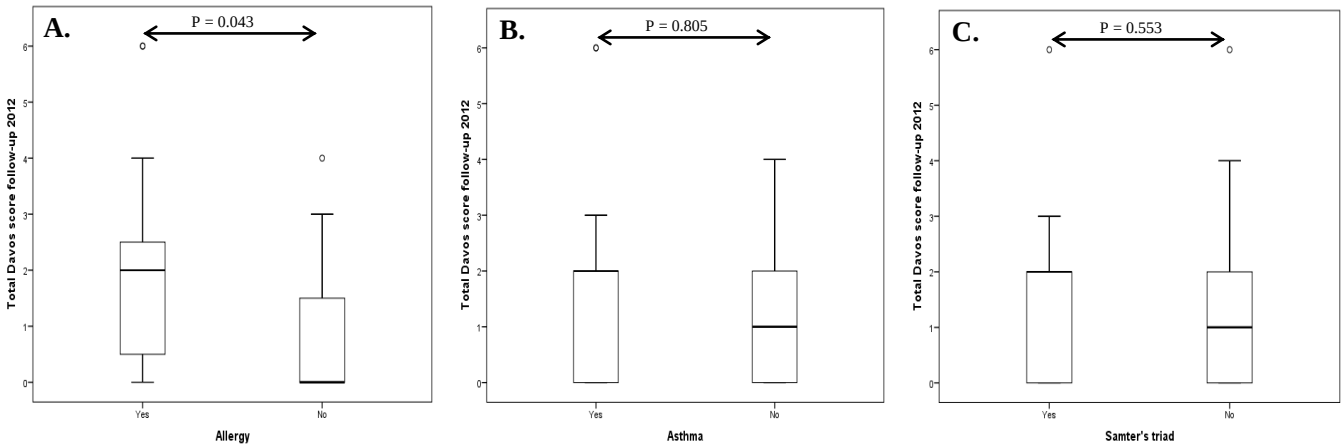


FIG. 7. NP score in 2012 in comorbidities. A. Allergy. **B.** Asthma. **C.** Samter's triad.

Figure 7 illustrates that the NP score at follow-up in 2012 was significantly higher in patients with allergy (P = 0.043) compared to those without allergy. In 2000 and 2006, no significant difference could be found in the NP score between patients with or without allergy (P = 0.063, respectively P = 0.123), although allergy patients tended to have a higher NP score at each time of contact. Pre-operatively in 2000 and at follow-up in 2006 and 2012, a higher median NP score was observed in patients with asthma, however this difference could not be proven to be significant at any time of contact (P = 0.329, P = 0.680 and P = 0.805 respectively). The same trend was observed when investigating the NP score in patients with Samter's triad, but no significant difference was shown (P = 0.101 in 2000, P = 0.356 and P= 0.553 in 2012).

5.4.Biomarkers

The table in appendix 12 summarizes the correlations between biomarkers measured in 2000 and the NP score at each time of contact. The NP score in 2000 showed a significant positive correlation with tissue grass mix 1 (r_s = 0.431, P = 0.008), tissue SAE C (r_s = 0.364, P = 0.027) and serum albumin (r_s = 0.589, P = 0.010). In 2006, a significant positive correlation was found between the NP score and tissue IgE (r_s = 0.492, P = 0.024), tissue grass mix 1 (r_s = 0.575, P = 0.005), tissue SAE A (r_s = 0.556, P = 0.007), tissue SAE C (r_s = 0.472, P = 0.026), tissue SAE D (r_s = 0. 474, P = 0.026), tissue mold mix 2 (r_s = 0.478, P = 0.038) and ratio tissue IgE/albumin (r_s = 0.561, P = 0.010). The NP score in 2012 showed a significant positive correlation with tissue mold mix 2 (r_s = 0.380, P = 0.042) and IL-5 in nasal secretions (r_s = 0.377, P = 0.031).

In 2006, the NP score was significantly higher in patients with detectable SAE in tissue (P = 0.014 in 2006), but only borderline significantly higher in 2000 and 2012 (P = 0.063 in 2000 and P = 0.051 in 2012).

6. Recurrence

6.1. Descriptives

Table 2. Descriptives in patients with and without NP recurrence.

	Recurrence (N=30)	No recurrence (N=8)	P value
Sex (M/F)	18/12 (60.0/40.0)	7/1 (87.5/12.5)	0.222
Age (years) in 2012	60 (48-66)	61 (53-80)	0.350
Total symptom score in 2000	9 (7-12)	9 (8-11)	0.928
NP score in 2000	4 (4-6)	5 (3-5)	0.765
Primary/revision FESS in 2000	14/16 (46.7/53.3)	5/3 (62.5/37.5)	0.693
Allergy	18 (60.0)	2 (25.0)	0.117
Asthma	12 (40.0)	3 (37.5)	1.000
Samter's triad	9 (30.0)	1 (12.5)	0.653
Detectable tissue IL-5	22 (73.3)	4 (50.0)	0.200
Tissue IL-5 (pg/ml)	185.75 (43.00-444.68)	64.51 (43.00-234.23)	0.160
Tissue ECP (µg/l)	10764.67 (4331.32-16899.80)	2883.01 (631.43-16696.24)	0.137
Tissue IgE (kUA/l)	398.46 (205.39-1213.63)	600.98 (121.64-1150.09)	0.808

Data are expressed as median (IQR) or as N (%)

Thirty (78.9%) out of 38 patients developed recurrence during 12 years of follow-up. Table 2 expresses demographics, comorbidities, disease severity information, tissue IL-5, ECP and IgE in the 30 patients with and the 8 patients without NP recurrence. No significant differences between both groups were found.

6.2. Statistical analysis

6.2.1. Age

In the younger patients NP tended to recur more during follow-up, although age was not significantly predictive for NP recurrence over 12 years (OR 0.96, 95% CI 0.91 to 1.0, P = 0.212).

6.2.2. Sex

Sex did not significantly influence the risk of NP recurrence, although women tended to develop more frequently NP recurrence during follow-up than men (OR 4.7, 95% CI 0.51 to 43, P = 0.174).

6.2.3. Primary/revision surgery in 2000

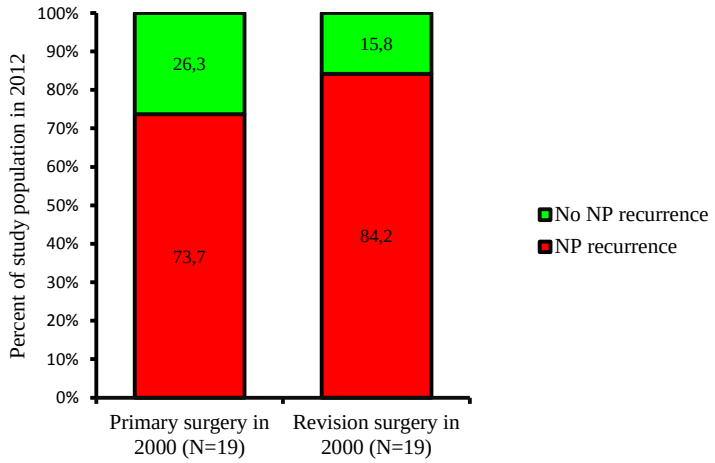


FIG. 8. NP recurrence during 12 years of follow up in both categories of surgery in 2000.

Figure 8 compares the NP recurrence rate over 12 years between the 19 patients who underwent FESS for the first time in 2000 and the 19 patients who underwent a revision surgery in 2000. Although the revision surgery group from 2000 tended to have a higher risk for recurrent nasal polyps, this did not reach the significance level (OR 1.9, 95% CI 0.38 to 9.4, P = 0.430).

6.2.4. Comorbidities

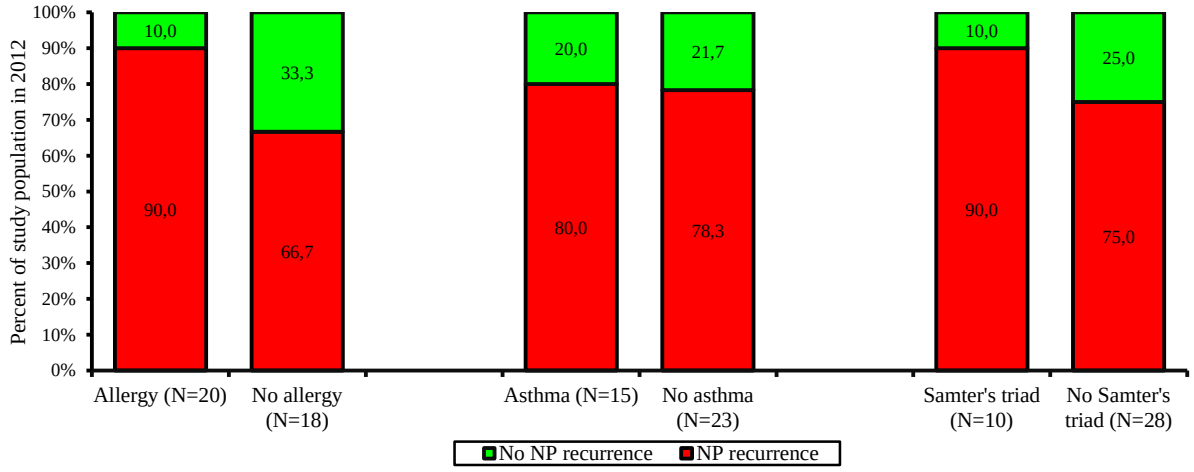


FIG. 9. NP recurrence during 12 years of follow-up in allergy, asthma and Samter's triad.

When investigating the possible contribution of allergy, asthma and Samter's triad to the risk of NP recurrence during follow-up (figure 9), none of these comorbidities could be identified as a significant predictor for NP recurrence (OR 4.5, 95% CI 0.78 to 26.1, P = 0.094 in allergy, OR 1.1, 95% CI 0.22 to 5.5, P= 0.898 in asthma and OR 3.0, 95% CI 0.32 to 28, P = 0.336 in Samter's triad).

6.2.5. Symptom score

The total symptom score pre-operatively in 2000 could not be considered as a significant predictive risk factor for NP recurrence (OR 1.0, 95% CI 0.75 to 1.3, P = 0.984).

6.2.6. NP score

Increasing NP score tended to be associated with a higher risk of NP recurrence during follow-up, although NP score could not be proven to be a significant predictor (OR 1.1, 95% CI 0.6 to 2, P = 0.660).

6.2.7. Biomarkers

As summarized in the table in appendix 13, none of the biomarkers measured in 2000 could be identified as a significant predictor for NP recurrence over the 12-year follow-up period. When considering tissue IL-5 and tissue SAE to be detectable or non-detectable, the presence of IL-5 in tissue and SAE in tissue could not be withheld as significant predictors for NP recurrence during follow-up (OR 1.4, 95% CI 0.27 to 6.8, P = 0.712, OR 0.12, 95% CI 0.1 to 1.7, P = 0.118 and OR 2.7, 95% CI 0.55 to 14, P = 0.217 respectively).

7. Revision surgery

7.1. Descriptives

Table 3. Descriptives in patients with and without revision FESS.

	Revision FESS (N=14)	**No revision FESS** (N= 24)	**P value**
Sex (M/F)	9/5 (64.3/35.7)	16/8 (66.7/33.3)	1.000
Age (years) in 2012	50 (46-63)	63 (53-67)	0.10
Total symptom score in 2000	10 (8-13)	8 (7-9)	0.015
NP score in 2000	4 (4-6)	4 (3-5)	0.273
Primary/revision FESS in 2000	5/9 (35.7/64.3)	14/10 (58.3/41.7)	0.179
Allergy	11 (78.6)	9 (37.5)	0.014
Asthma	7 (50.0)	8 (33.3)	0.311
COPD	0 (0.0)	3 (12.5)	0.283
Samter's triad	6 (42.9)	4 (16.7)	0.127
Detectable tissue IL-5	11 (78.6)	15 (62.5)	0.472
Tissue IL-5 (pg/ml)	360.84 (103.92-521.84)	112.94 (43.00-228.88)	0.029
Tissue ECP (µg/l)	12375.00 (5239.77-19360.00)	8340.56 (1391.55-15885.27)	0,387
Tissue IgE (kUA/l)	763.60 (365.20-1361.30)	318.30 (141.33-1073.75)	0,159

Data are expressed as median (IQR) or as N (%)

Fourteen (36.8%) out of 38 patients had a need for revision surgery in the 12 years of follow-up, from which 7 patients underwent 1 revision FESS and 7 patients underwent 2 or more revision surgeries after 2000. Table 3 expresses demographics, comorbidities, disease severity information, tissue IL-5, ECP and IgE in the 14 patients with and the 24 patients without revision surgery. Patients with revision surgery after FESS in 2000 had a higher total symptom score in 2000 (P = 0.015). The proportion of patients with allergy (78.6%) was significantly higher in the

group with revision surgery after 2000 (P = 0.014). Tissue IL-5 levels (pg/ml) in 2000 were significantly higher in patients who later would undergo revision surgery.

7.1.1. Kaplan-Meier survival analysis

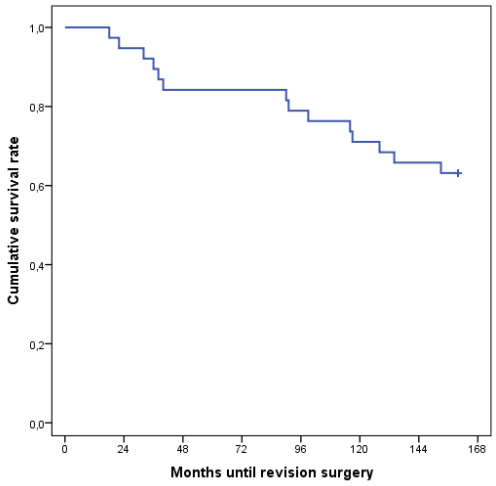


FIG. 10. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up.

Figure 10 illustrates Kaplan-Meier survival analysis for the time period between the FESS in 2000 and first revision surgery within the timeframe of follow-up. The overall surgery-free rate at 6 years was 84.2% (32/38). By the 12-year follow-up period this number had dropped to a surgery-free rate of 63.2% (24/38) in the total study population. The time to revision FESS ranged from 18 to 153 months, with a median of 91 months.

7.2. Statistical analysis

7.2.1. Age

7.2.1.1. Logistic regression

Patients who underwent revision surgery were relatively younger, although age was not significantly predictive for revision surgery over 12 years (OR 0.96, 95% CI 0.91 to 1.0, P = 0.108).

7.2.2. Sex

7.2.2.1. Logistic regression

When sex was taken into account, the female sex could not be considered as a significant risk factor for revision surgery during the 12-year follow-up period (OR 1.11, 95% CI 0.28 to 4.4, P = 0.881).

7.2.2.2. Kaplan-Meier survival analysis

The surgery-free survival rate for revision FESS after 2000 during the 12 years of follow-up did not significantly differ in both sexes using the Mantel-Cox Log Rank Test (P = 0.954). After 6 years, the surgery-free survival rate was 92.3% (12/13) in women, and 80.0% (20/25) in men. This surgery-free rate continued to decline to 61.5% (8/13) in women and 64.0% (16/25) in men

at the end of the 12-year follow-up period. In the patients who underwent revision surgery during follow-up, the time to revision surgery ranged from 18 to 153 months with a median of 99 months in women. In men, the time to revision surgery ranged from 22 to 134 months with a median of 40 months.

7.2.3. Primary/revision surgery in 2000

7.2.3.1. Logistic regression

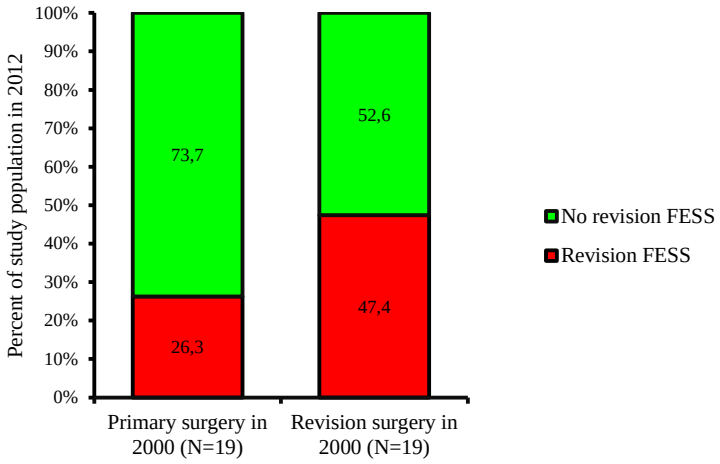


FIG. 11. Revision FESS during 12 years of follow-up in both categories of surgery in 2000.

Revision surgery in 2000 was not a significant predictor for revision FESS over the 12 years of follow-up (OR 2.52, 95% CI 0.6 to 9.8, P = 0.193).

7.2.3.2. Kaplan-Meier survival analysis

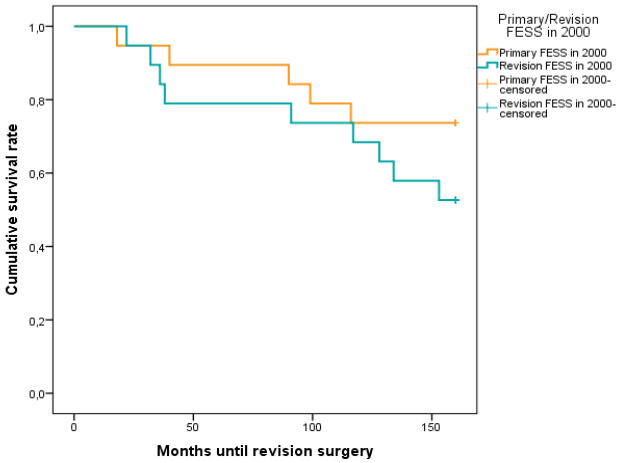


FIG. 12. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up in both categories of surgery in 2000.

Figure 12 compares the course of the surgery-free survival rate during the 12-year follow-up period in patients with primary FESS in 2000 to the patients with revision FESS in 2000. As one can see in the Kaplan-Meier survival graph (figure 12), the surgery-free survival rate was higher in the patients who underwent primary FESS in 2000, although this did not reach the level of significance (P = 0.220). In the 19 patients with primary FESS in 2000, 17 (89.5%) patients were

surgery-free after 6 years. This surgery-free survival rate further declined to 73.7% (14/19) after 12 years of follow-up. The time to first revision surgery in the 5 patients with primary FESS in 2000 ranged from 18 to 116 months with a median of 90 months. When considering the 19 patients with revision surgery in 2000, 15 (78.9%) patients did not undergo revision in the first 6 years of follow-up. By the 12-year follow-up period this number had dropped to 10 (52.6%) out of the 19 patients. The time to first revision surgery in the 9 patients with revision FESS in 2000 ranged from 22 to 153 months with a median of 91 months.

7.2.4. Comorbidities

7.2.4.1. Logistic regression

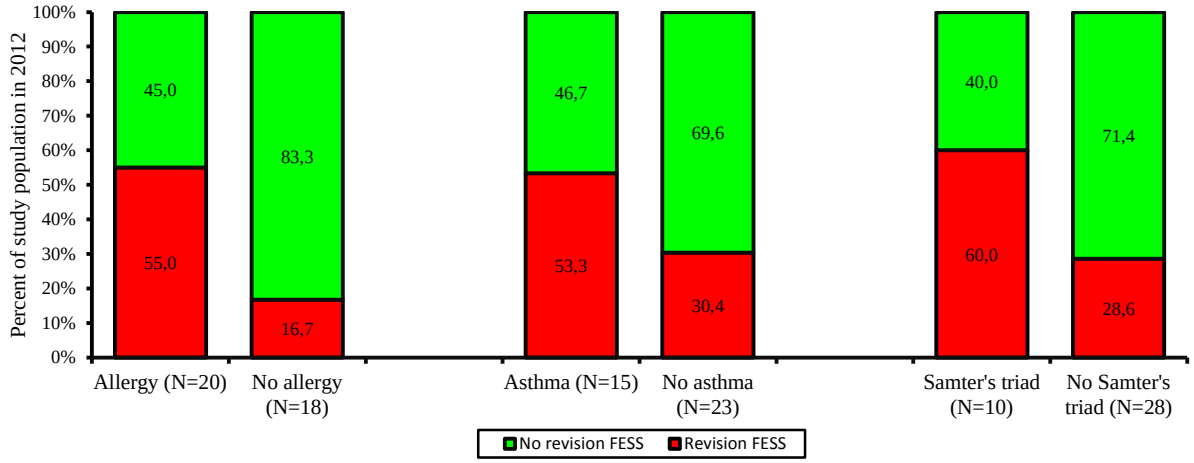


FIG. 13. Revision FESS during 12 years of follow-up in allergy, asthma and Samter's triad.

When investigating the possible contribution of allergy, asthma and Samter's triad to the risk of revision surgery during the 12-year follow-up period, only allergy could be identified as a significant predictor for FESS revision during follow-up (OR 6.1, 95% CI 1.3 to 28, P = 0.020 in allergy, OR 2.0, 95% CI 0.52 to 7.7, P = 0.314 in asthma and OR 3.8, 95% CI 0.83 to 17, P = 0.086 in Samter's triad).

7.2.4.2. Kaplan-Meier survival analysis

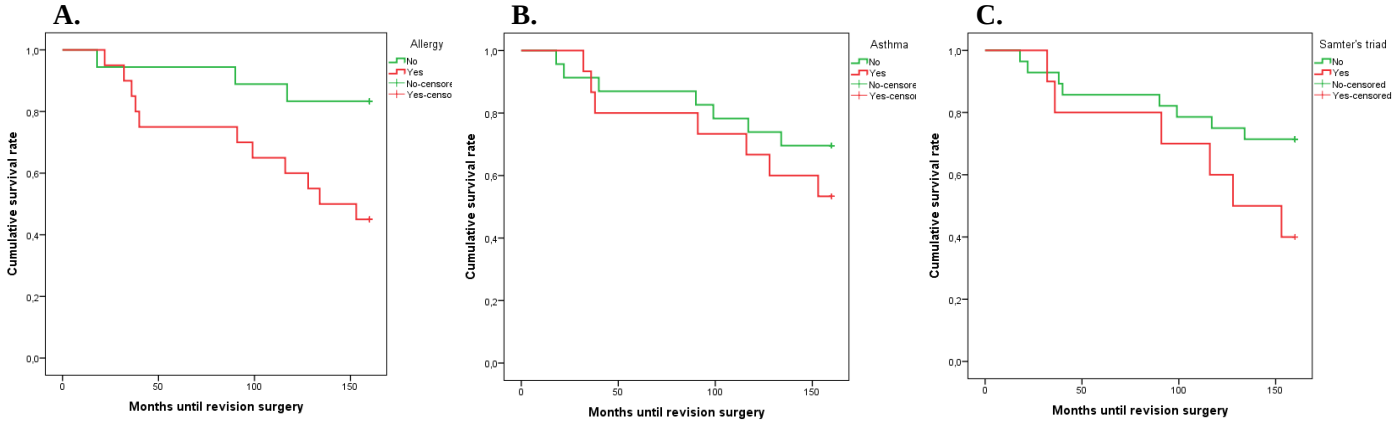


FIG. 14. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up in comorbidities.
A. Allergy. **B.** Asthma. **C.** Samter's triad.

7.2.4.2.1. Allergy

Figure 14.A. illustrates Kaplan-Meier survival analysis in allergic and non-allergic patients over the 12-year follow-up period. The survival curve was significantly higher in non-allergic patients (P = 0.020). After 6 years, the surgery-free survival rate was 75.0% (15/20) in the 20 allergic patients and 94.4% (17/18) in the 18 non-allergic patients. By the 12-year follow-up period these numbers dropped to a surgery-free rate of 45.0% (9/20) and 83.3% (15/18) for patients with, and patients without allergy respectively. In patients with allergy, the time to first revision surgery during follow-up ranged from 22 to 152 months with a median of 91 months. In patients without allergy, the time to first revision surgery during follow-up ranged from 18 to 117 months with a median of 90 months.

7.2.4.2.2. Asthma

The surgery-free survival rate for revision FESS after 2000 during the 12 years of follow-up did not significantly differ in patients with or without asthma (P = 0.350) (figure 14.B.). After 6 years, the surgery-free survival rate was 80.0% (12/15) and 87.5% (20/23) in patients with and without asthma respectively. Another 6 years later, this was only 53.3% (8/15) and 69.6% (16/23). The time to first revision surgery in the 15 asthmatic patients ranged from 32 to 153 months with a median of 91 months, compared to 18 to 134 months with a median of 90 months in the 23 patients without asthma.

7.2.4.2.3. Samter's triad

Figure 14.C. displays the surgery-free survival rate in patients with and without Samter's triad. However the surgery-free survival rate tended to be higher in patients without Samter's triad, no significant difference in the surgery-free survival distributions between patients with and patients without Samter's triad could be found (P = 0.098). After 6 years, the surgery-free survival rate was 80% (8/10) in the 10 patients with Samter's triad and 85.7% (24/28) in the 28 patients without Samter's triad. By the 12-year follow-up period these numbers further declined to a surgery-free rate of 40.0% (4/10) and 71.4% (20/28) for patients with, and patients without allergy respectively. In patients with Samter's triad, the time to first revision surgery during follow-up ranged from 32 to 153 months with a median of 104 months. In patients without Samter's triad, the time to first revision surgery during follow-up ranged from 18 to 134 months with a median of 65 months.

7.2.5. Symptom score

7.2.5.1. Logistic regression

The total symptom score pre-operatively in 2000 was proven to be a significant predictive risk factor for revision surgery during follow-up over 12 years (OR 1.43, 95% CI 1.1 to 1.9, P =

0.020), implicating that the higher the total symptom score preoperatively the higher the risk for a revision surgery. The OR suggests that for each increase of 1 point on the total symptom score preoperatively, the odds of revision surgery in the subsequent 12 years of follow-up increases by 43%.

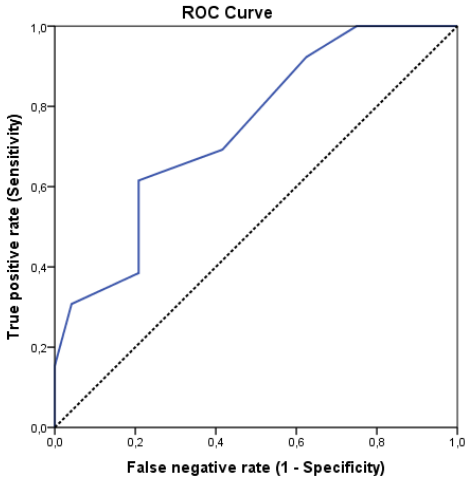


FIG. 15. ROC-curve analysis of total symptom score in 2000 to predict revision FESS during 12 years of follow-up (diagonal segments are produced by ties)

A cut-off value of 10 (sensitivity 61.5% and specificity 79.2%) was determined using a ROC-curve analysis (figure 15). The AUC was 74.2% (95% CI 57.9% to 90.5%, P = 0.016), indicating that the accuracy of the logistic regression test was fair.

7.2.6. NP score

7.2.6.1. Logistic regression

NP score could not be included in logistic regression processing because of a significant Hosmer-Lemeshow test (P = 0.035). The distribution of NP score in patients with and without revision FESS is shown in a histogram in appendix 14.

7.2.7. Biomarkers

7.2.7.1. Logistic regression

Of the biomarkers measured in 2000, only tissue IL-5 (pg/ml) could be identified as a significant predictor for NP revision surgery over the 12-year follow-up period (OR 1.004, 95% CI 1.001 to 1.008, P = 0.021), implicating that the higher the IL-5 levels preoperatively the higher the risk for a revision surgery. The OR suggests that for each increase of 1 pg in tissue IL-5 preoperatively, the odds of revision surgery in the subsequent 12 years of follow-up increases by 0.4%. The table in appendix 15 provides an overview of logistic regression performed in all biomarkers measured in 2000 as predictor for revision FESS during follow-up.

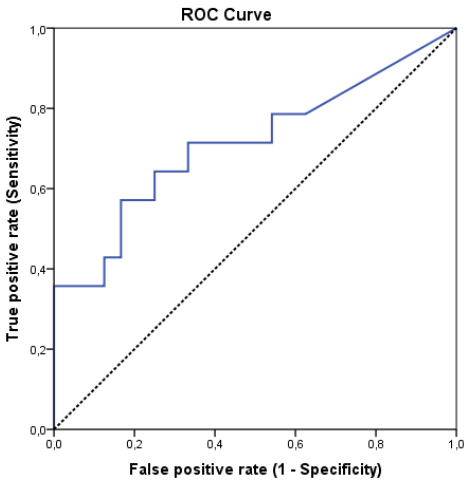


FIG. 16. ROC-curve analysis of tissue IL-5 in 2000 to predict revision FESS during 12 years of follow-up (diagonal segments are produced by ties)

A cut-off value of 177.5 pg/ml (sensitivity 71.4% and specificity 66.7%) was determined using a ROC-curve analysis (figure 16). The AUC was 71.3% (95% CI 52.9% to 89.7%, P = 0.016), indicating that the accuracy of the logistic regression test was fair.

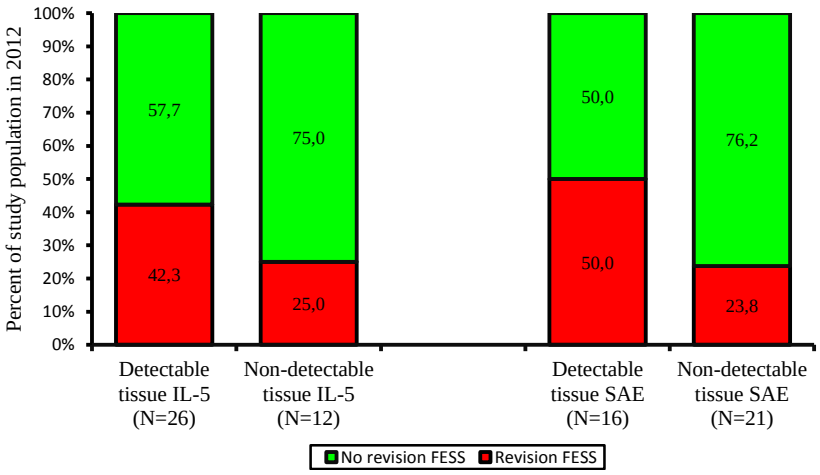


FIG. 17. Revision FESS during 12 years of follow-up in patients with or without detectable levels of tissue IL-5 and tissue SAE.

When considering IL-5 to be detectable or non-detectable in tissue, patients with a detectable IL-5 in tissue tended to have a higher risk for FESS revision, although this could not be proven to be significant (OR 2.2, 95% CI 0.48 to 10, P = 0.310). Analogously, detectable SAE in tissue could not be identified as a significant risk factor for revision FESS (OR 3.2, 95% CI 0.79 to 13, P = 0.104).

7.2.7.2.Kaplan-Meier survival analysis

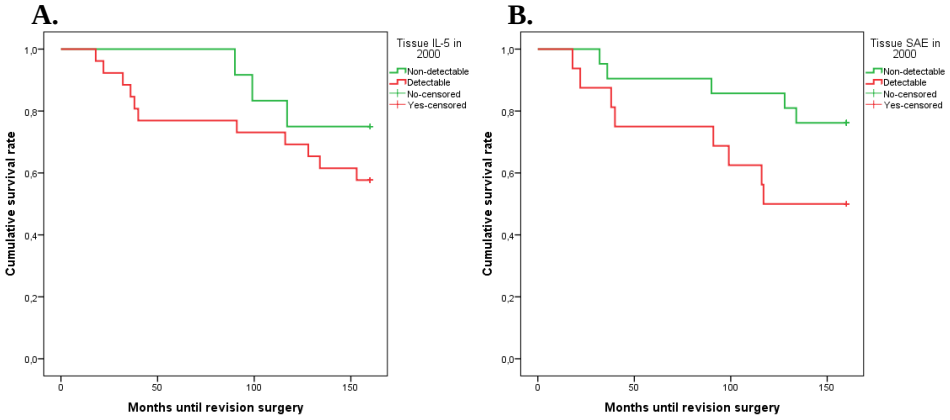


FIG. 18. Kaplan-Meier surgery-free survival analysis during 12 years of follow-up. A. Tissue IL-5. B. Tissue SAE.

7.2.7.2.1. Detectable tissue IL-5

Figure 18.A. illustrates Kaplan-Meier survival analysis over the 12-year follow-up period in patients with and without detectable IL-5 in tissue prior to FESS in 2000. The survival curve tended to be higher in patients without detectable IL-5 in tissue, although not significantly (P = 0.294). After 6 years, the surgery-free survival rate was 76.9% (20/26) in the 26 patients with detectable tissue IL-5 and 100.0% (12/12) in the 12 patients without detectable tissue IL-5. By the 12-year follow-up period these numbers dropped to a surgery-free rate of 57.6 % (15/26) and 75.0% (9/12) respectively. In patients with detectable tissue IL-5 in 2000, the time to first revision surgery during follow-up ranged from 18 to 153 months with a median of 40 months. In patients without allergy, the time to first revision surgery during follow-up ranged from 90 to 117 months with a median of 99 months.

7.2.7.2.2. Detectable tissue SAE

The surgery-free survival rate for revision FESS after 2000 during the 12 years of follow-up did not significantly differ in patients with and without detectable tissue SAE in 2000 (P = 0.083), although it seemed to be higher in patients without detectable tissue SAE. (figure 18.B.). After 6 years, the surgery-free survival rate was 75.0% (12/16) and 90.4% (19/21) in patients with and without detectable tissue SAE respectively. Another 6 years later, this rate further declined to 50.0% (8/16) and 76.2% (16/21). The time to first revision surgery in the 16 patients with detectable SAE in tissue ranged from 18 to 117 months with a median of 65.5 months, compared to 32 to 134 months with a median of 90 months in the 21 patients without detectable SAE in tissue.

8. General therapeutic relief

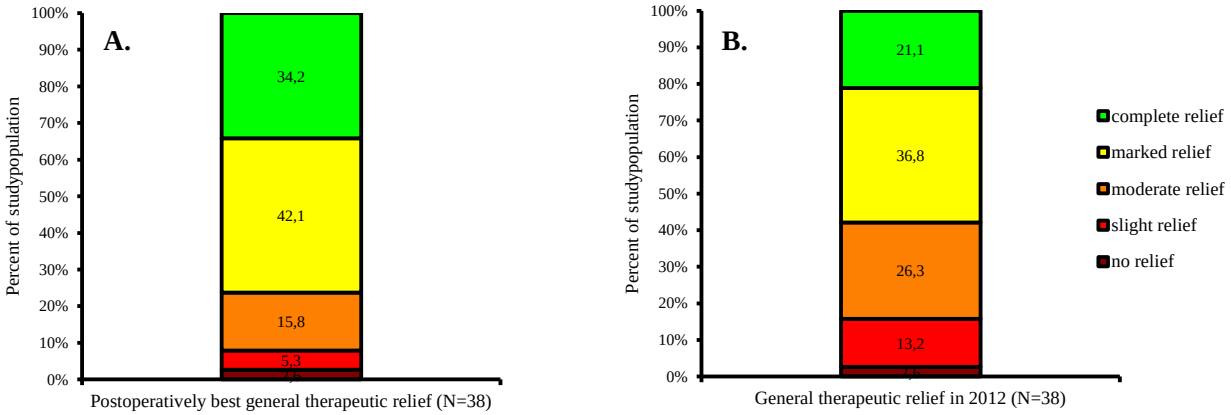


FIG. 19. General therapeutic relief.
A. Postoperatively best general therapeutic relief due to FESS in 2000.
B. General therapeutic relief in 2012.

When inquiring the best general therapeutic relief due to the FESS in 2000 over the twelve-year period (figure 19.A.), 13 (34.2%) out of the 38 patients reported a complete, 16 (42.1%) a marked, 6 (15.8%) a moderate and 2 (5.3%) a slight relief. One (2.6%) patient experienced no relief due to the surgery in 2000 and underwent a revision surgery during follow-up. When inquiring the current general therapeutic relief in 2012 (figure 19.B.), 8 (21.1%) out of the 38 patients reported a complete, 14 (36.8%) a marked, 10 (26.3%) a moderate and 5 (13.2%) a slight relief. At the contact moment in 2012, one (2.6%) patient experienced no relief in 2012, despite 2 revision surgeries during follow-up.

When patients were asked in 2012 if they would do the FESS again 12 years ago with the knowledge they had in 2012, 36 (94.7%) out of the 38 patients answered ‘Yes’. Two patients (5.3%) answered ‘No’. One patient reported a severe bleeding after FESS in 2000 as the cause of her regret of the FESS in 2000. The other patient reported that she did not experience a marked improvement after FESS in 2000 and the two revision surgeries she had afterwards.

9. Assessing control

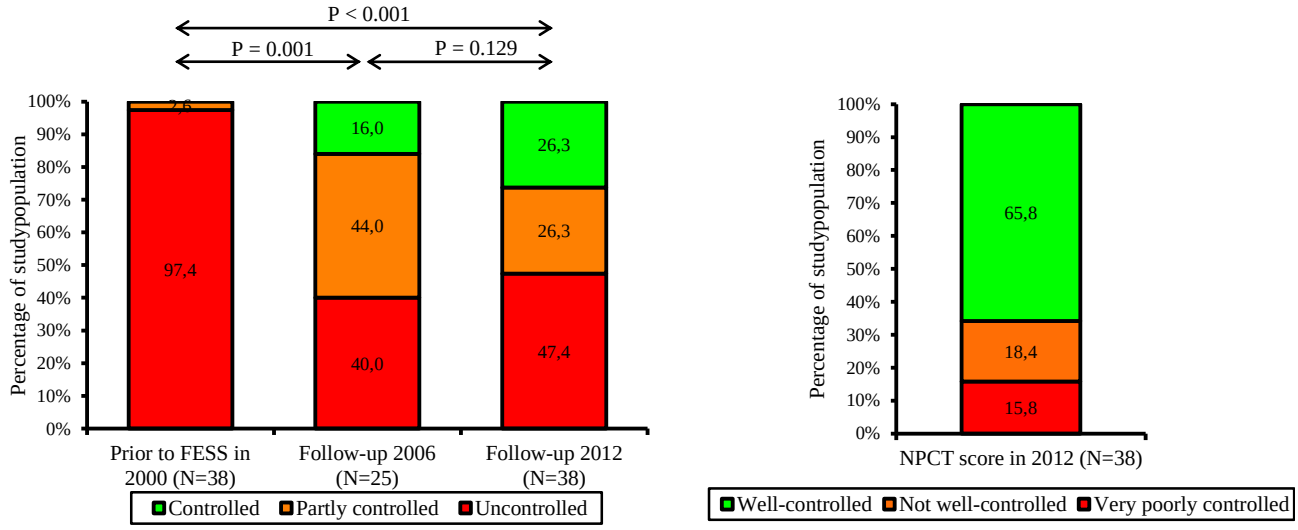


FIG. 20. Control.
A. EPOS score over time. **B.** NPCT score at follow-up in 2012.

Figure 20.A. shows the distribution in percentages of the EPOS score categories at each time of contact. Compared to the EPOS score prior to FESS in 2000, the EPOS score significantly improved in 2006 (P = 0.001) and in 2012 (P < 0.001). Figure 20.B. shows the distribution in percentages of the NPCT score categories at follow-up in 2012.

Table 4. Comparison between NPCT score and EPOS score in 2012.

		NPCT score at follow-up in 2012			Total
		Well-controlled	Not well-controlled	Very poorly controlled	
EPOS score follow-up 2012	Controlled	9	1	0	10
	Partly Controlled	9	1	0	10
	Uncontrolled	7	5	6	18
Total		25	7	6	38

When comparing the EPOS score categories in 2012 with the NPCT score categories in 2012, a significant difference in distribution was found (P < 0.001) (Table 4). Seven patients, uncontrolled according the EPOS score in 2012, were well-controlled according the NPCT score in 2012. Five of these 7 patients were automatically classified as uncontrolled according the EPOS guidelines based on a recent need for systemic AB and/or OCS. The other 2 patients were classified as uncontrolled based on 3 or more clinical and/or endoscopic findings. The 6 patients, very poorly controlled according the NPCT score in 2012, were also uncontrolled according the EPOS score in 2012.

V. DISCUSSION

This is the first prospective cohort follow-up study of 12 years after FESS. The use of the same surgical technique in all patients is one of the strengths of this study. Other studies have shorter follow-up, have a retrospective nature or use different surgical techniques, and thereby their results are difficult to compare to the results of the current study. As CRSwNP is a frequently recurrent disease, the outcome after surgery will depend on the length of follow-up. A longer follow-up period can provide a more realistic representation of the results that could be expected in a similar patient group over time. This is confirmed by the review of Dalziel et al. (115) which found that studies with longer follow-up periods, reported a higher NP recurrence rate. The prospective study with the longest follow-up period, found in literature, was performed by Bonfils et al. (117) over a 5-year period. The study by Mendelsohn et al. (119) was retrospective over a 10 year-period. The study by Vento et. al (72) in 2000 was a prospective study over a 20-year period, but the performed surgical techniques were different from the current study.

1. Comorbidities and medication use

Twenty-five up to 50% of the patients with allergy and/or asthma experienced an improvement of their allergy and/or asthma related complaints, suggesting the hypothesis that FESS could have a beneficial effect on both diseases, which was already demonstrated for asthma by Proimos et al. (146). Besides FESS, the improvement of asthma in these patients could be partly explained by the higher use of asthma medication in asthmatic patients in 2012.

At each time of contact approximately 60% of the patients were adherent to INCS, suggesting that INCS help to suppress the revival of the disease. Thereby EPOS 2012 (1) highly recommends prolonged postoperative treatment with INCS in all patients with NP. The increase of AB use can be explained as a recent approach to treat CRSwNP, illustrated by the study by Van Zele et al. (87).

2. Symptoms

Nasal obstruction and hyposmia can be considered as the most abundant symptoms in CRSwNP patients, and are, just like the lesser pronounced symptoms rhinorrhoea, sternutation and headache, susceptible for amelioration trough FESS measurable up to 12 years. This manifests itself in a notable decrease of the total symptom score during follow-up, demonstrating that FESS may contribute to the alleviation of the subjective symptomatic burden of CRSwNP in the long term, which is in line with the findings in the short term (115). This observed improvement of the symptoms can possibly be explained by the removal of the inflammatory polypoid mucosa

and enhancement of the nasal patency. The results of this study suggest that patients with a high total symptom score in 2000, revision surgery in 2000, asthma and/or elevated markers of a more florid local eosinophilic inflammation in 2000 (tissue IL-5Rα, tissue ECP and/or IL-5 in nasal secretions) were more likely to have a worse symptomatic outcome in 2012 compared to patients who had not. The higher total symptom score in 2012 in patients with higher levels of SAE A in tissue in 2000, points to a possible role of bacterial SAE as disease modifiers (44).

3. Polyp size

FESS had a beneficial effect on the polyp size during long-term follow-up, which is in accordance with the conclusions of Alobid et al. (116) after 12 months and Bonfils et al. (117) after 5 years of follow-up. Patients who had a high NP score in 2000, allergy and/or high levels of certain biomarkers in 2000 (tissue specific mold mix IgE, IL-5 in nasal secretions) were more likely to have a high NP score in 2012 compared to patients who had not. The polyp size was consistent in patients over time, meaning that a higher NP score in 2000 led to a higher NP score in 2012. The high NP size in 2012 in patients with high IL-5 levels in nasal secretions in 2000 can indicate that IL-5 fosters polyp formation and can determine the final polyp size (48).

4. NP recurrence and revision surgery

At 12 years, a NP recurrence rate of 78.9% and a FESS revision rate of 36.8% were found in the study population. It is therefore remarkable that not all patients with NP recurrence felt the need to undergo a revision surgery during the 12-year follow-up period, suggesting that not every NP recurrence has to be followed by a FESS reintervention and that surgery is not always indispensable to obtain subjective wellbeing in CRSwNP. None of the investigated factors could be identified as a significant predictive factor for NP recurrence during follow-up. This is in line with the findings of Akhtar et al. (126) for age, sex, asthma and Samter's triad, and Young et al. (131) for allergy, asthma and Samter's triad. Although some studies identified asthma and Samter's triad as prognostic factors for an increased NP recurrence rate (119, 128, 130).

Allergy, total symptom score in 2000 and tissue IL-5 were found to be significant predictors for revision surgery during follow-up. Moreover, allergic patients underwent a revision surgery sooner than non-allergic patients. Patients who underwent revision surgery during follow up, had a higher total symptom score prior to FESS in 2000 and at follow-up in 2012. This suggests that these patients reflect a more severe disease phenotype. As IL-5 is a key inflammatory mediator in the pathophysiology of nasal polyps (2) by recruiting, activating and prolonging the survival of eosinophils, this could be an explanation of the positive predictive value of IL-5 levels for

revision FESS during follow-up. In literature, only asthma and Samter's triad could be withheld as determinants for revision surgery (119, 129). In this study however, these comorbidities showed only a non-significant trend as predictors for revision.

5. General therapeutic relief

Despite the chronicity, the high recurrence rate and the frequent need for revision surgery in patients with CRSwNP, the vast majority of the patients experienced a moderate to complete relief of their disease and considered the FESS in 2000 as an essential contributing factor.

6. EPOS 2012 control test as a measure of current disease control

This study attempted to validate current clinical control by the EPOS 2012 control test (appendix 1). The results suggest that the EPOS 2012 control test overrates the amount of uncontrolled patients, notwithstanding that a marked proportion of these patients considered themselves to be well-controlled by NPCT. An explanation can be found in the fact that OCS and/or AB use is included in the assessment of the EPOS 2012 control test. Further it is unclear why other systemic medication such as anti-IgE and anti-IL-5 are not included. Thereby the EPOS 2012 control test attempts to assess the current clinical control in the last month, but inquires the use of OCS and/or AB in the last 3 months. But eventually, one can also wonder if the criteria of systemic medication use belong in a test assessing the current control.

7. Limitations of the study

This study has some limitations, such as the small sample size of 47 patients and the relatively high dropout rate at follow-up in 2012 (9/47): 3 patients deceased, 4 patients could not be tracked and 2 patients were not prepared to participate. In particular, this loss of follow-up led to an attrition bias, because only patients who completed the follow-up were taken into account. Of the patients contacted by telephone, only the questionnaire was inquired, but no clinical examination, endoscopy and collection of samples could be performed. Further, a dual selection bias can be remarked. First, the study population consisted of patients who were in treatment in the tertiary care centre of GUH. Secondly, patients participating in this study were CRSwNP patients in such a condition that required a FESS. At time of inclusion, there was a balanced distribution between patients needing primary and revision surgery. Because the patients of this study were also included in the anti-IL-5 trial of 2006 (103), none of the patients underwent revision surgery between 2003 and 2005.

CRSwNP is a chronic, recalcitrant condition, especially in patients with allergy, asthma and/or Samter's triad, which needs ongoing treatment and requires an accurate medical follow-up. This is the first long-term prospective study investigating the outcome in patients suffering from CRSwNP 12 years after FESS and the first to validate the EPOS 2012 control test. This study concludes that patients with CRSwNP regard FESS as a beneficial procedure to improve their general wellbeing, despite the relapsing character of the disease and the high proportion of patients with a need for revision surgery. Up to 12 years after surgery, FESS led to a significant improvement of CRSwNP related symptoms and polyp size. The clinical amelioration was due to a better control of NP after FESS, and not to an increase of steroid treatment. Of the patients with CRSwNP 78.9% were subject to recurrent disease, whereas only 36.8% needed revision surgery, implicating that NP recurrence does not necessarily has to lead to revision surgery. Nevertheless, a marked part of the patients did not feel the need to seek medical attention despite the presence of nasal polyps, meaning that nasal polyps do not always have to compromise the subjective wellbeing. No significant predictors for NP recurrence after FESS could be identified, although a high total symptom score, allergy and/or high IL-5 levels in tissue were associated with a higher risk for revision FESS. Patients should be informed about the marked likelihood of recurrence and/or revision surgery. In citing the risk for recurrence and/or revision surgery to a patient, rates should be stratified according to preoperative comorbidities and other predictors. Further investigations of the possible role of these and other predictors are recommended.

VI. REFERENCE LIST

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1-12.
2. Calus L, Van Zele T, Derycke L, Krysko O, Dutre T, Tomassen P, et al. Local inflammation in chronic upper airway disease. Current pharmaceutical design. 2012;18(16):2336-46.
3. Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. The Laryngoscope. 2008 Dec;118(12):2225-30.
4. Fokkens W, Lund V, Mullol J, European Position Paper on R, Nasal Polyps g. European position paper on rhinosinusitis and nasal polyps 2007. Rhinology Supplement. 2007 (20):1-136.
5. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. The Annals of otology, rhinology, and laryngology. 2003 Jul;112(7):625-9.
6. Larsen PL, Tos M. Origin of nasal polyps. The Laryngoscope. 1991 Mar;101(3):305-12.
7. Larsen PL, Tos M. Site of origin of nasal polyps. Transcranially removed naso-ethmoidal blocks as a screening method for nasal polyps in autopsy material. Rhinology. 1995 Dec;33(4):185-8.
8. Collins MM, Pang YT, Loughran S, Wilson JA. Environmental risk factors and gender in nasal polyposis. Clinical otolaryngology and allied sciences. 2002 Oct;27(5):314-7.
9. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. Allergy. 2005 Feb;60(2):233-7.
10. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 1996 Sep-Oct;17(5):243-9.
11. Larsen K, Tos M. A long-term follow-up study of nasal polyp patients after simple polypectomies. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies. 1997;254 Suppl 1:S85-8.
12. Rugina M, Serrano E, Klossek JM, Crampette L, Stoll D, Bebear JP, et al. Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience. Rhinology. 2002 Jun;40(2):75-9.
13. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. International journal of epidemiology. 1999 Aug;28(4):717-22.
14. Hosemann W, Gode U, Wagner W. Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. American journal of otolaryngology. 1994 Mar-Apr;15(2):85-98.
15. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. Acta oto-laryngologica. 2002 Mar;122(2):179-82.
16. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clinical otolaryngology and allied sciences. 2000 Feb;25(1):19-22.
17. Settipane GA. Epidemiology of nasal polyps. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 1996 Sep-Oct;17(5):231-6.
18. Van Bruaene N, Bachert C. Tissue remodeling in chronic rhinosinusitis. Current opinion in allergy and clinical immunology. 2011 Feb;11(1):8-11.
19. Schleimer R, Kato A, Kern RC. Eosinophils in CRS. In: Lee JJ, Rosenberg HF, editors. Eosinophils in Health and Disease. 1 ed. San Diego, USA: Academic Press; 2013. p. 508-19.
20. Hammad H, Lambrecht BN. Dendritic cells and airway epithelial cells at the interface between innate and adaptive immune responses. Allergy. 2011 May;66(5):579-87.
21. Allen JS, Eisma R, LaFreniere D, Leonard G, Kreutzer D. Characterization of the eosinophil chemokine RANTES in nasal polyps. The Annals of otology, rhinology, and laryngology. 1998 May;107(5 Pt 1):416-20.
22. Bartels J, Maune S, Meyer JE, Kulke R, Schluter C, Rowert J, et al. Increased eotaxin-mRNA expression in non-atopic and atopic nasal polyps: comparison to RANTES and MCP-3 expression. Rhinology. 1997 Dec;35(4):171-4.
23. Beck LA, Stellato C, Beall LD, Schall TJ, Leopold D, Bickel CA, et al. Detection of the chemokine RANTES and endothelial adhesion molecules in nasal polyps. The Journal of allergy and clinical immunology. 1996 Oct;98(4):766-80.
24. Combadiere C, Ahuja SK, Tiffany HL, Murphy PM. Cloning and functional expression of CC CKR5, a human monocyte CC chemokine receptor selective for MIP-1(alpha), MIP-1(beta), and RANTES. Journal of leukocyte biology. 1996 Jul;60(1):147-52.
25. Daugherty BL, Siciliano SJ, DeMartino JA, Malkowitz L, Sirotina A, Springer MS. Cloning, expression, and characterization of the human eosinophil eotaxin receptor. The Journal of experimental medicine. 1996 May 1;183(5):2349-54.
26. Jahnsen FL, Haye R, Gran E, Brandtzaeg P, Johansen FE. Glucocorticosteroids inhibit mRNA expression for eotaxin, eotaxin-2, and monocyte-chemotactic protein-4 in human airway inflammation with eosinophilia. Journal of immunology. 1999 Aug 1;163(3):1545-51.

27. Meyer JE, Bartels J, Gorogh T, Sticherling M, Rudack C, Ross DA, et al. The role of RANTES in nasal polyposis. American journal of rhinology. 2005 Jan-Feb;19(1):15-20.
28. Molinaro RJ, Bernstein JM, Koury ST. Localization and quantitation of eotaxin mRNA in human nasal polyps. Immunological investigations. 2003 Aug;32(3):143-54.
29. Mullol J, Roca-Ferrer J, Alobid I, Pujols L, Valero A, Xaubet A, et al. Effect of desloratadine on epithelial cell granulocyte-macrophage colony-stimulating factor secretion and eosinophil survival. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2006 Jan;36(1):52-8.
30. Olze H, Forster U, Zuberbier T, Morawietz L, Luger EO. Eosinophilic nasal polyps are a rich source of eotaxin, eotaxin-2 and eotaxin-3. Rhinology. 2006 Jun;44(2):145-50.
31. Shin SH, Park JY, Jeon CH, Choi JK, Lee SH. Quantitative analysis of eotaxin and RANTES messenger RNA in nasal polyps: association of tissue and nasal eosinophils. The Laryngoscope. 2000 Aug;110(8):1353-7.
32. Yao T, Kojima Y, Koyanagi A, Yokoi H, Saito T, Kawano K, et al. Eotaxin-1, -2, and -3 immunoreactivity and protein concentration in the nasal polyps of eosinophilic chronic rhinosinusitis patients. The Laryngoscope. 2009 Jun;119(6):1053-9.
33. Kuperman DA, Schleimer RP. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. Current molecular medicine. 2008 Aug;8(5):384-92.
34. Matsukura S, Stellato C, Plitt JR, Bickel C, Miura K, Georas SN, et al. Activation of eotaxin gene transcription by NF-kappa B and STAT6 in human airway epithelial cells. Journal of immunology. 1999 Dec 15;163(12):6876-83.
35. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. The Journal of allergy and clinical immunology. 1997 Jun;99(6 Pt 1):837-42.
36. Denburg JA, Otsuka H, Ohnisi M, Ruhno J, Bienenstock J, Dolovich J. Contribution of basophil/mast cell and eosinophil growth and differentiation to the allergic tissue inflammatory response. International archives of allergy and applied immunology. 1987;82(3-4):321-6.
37. Gauldie J, Cox G, Jordana M, Ohno I, Kirpalani H. Growth and colony-stimulating factors mediate eosinophil fibroblast interactions in chronic airway inflammation. Annals of the New York Academy of Sciences. 1994 May 28;725:83-90.
38. Hamilos DL, Leung DY, Huston DP, Kamil A, Wood R, Hamid Q. GM-CSF, IL-5 and RANTES immunoreactivity and mRNA expression in chronic hyperplastic sinusitis with nasal polyposis (NP). Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1998 Sep;28(9):1145-52.
39. Lamblin C, Bolard F, Gosset P, Tsicopoulos A, Perez T, Darras J, et al. Bronchial interleukin-5 and eotaxin expression in nasal polyposis. Relationship with (a)symptomatic bronchial hyperresponsiveness. American journal of respiratory and critical care medicine. 2001 Apr;163(5):1226-32.
40. Ohnishi M, Ruhno J, Bienenstock J, Milner R, Dolovich J, Denburg JA. Human nasal polyp epithelial basophil/mast cell and eosinophil colony-stimulating activity. The effect is T-cell-dependent. The American review of respiratory disease. 1988 Sep;138(3):560-4.
41. Park HS, Jung KS, Shute J, Roberts K, Holgate ST, Djukanovic R. Allergen-induced release of GM-CSF and IL-8 in vitro by nasal polyp tissue from atopic subjects prolongs eosinophil survival. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1997 Jul;10(7):1476-82.
42. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. Journal of immunology. 1997 Apr 15;158(8):3902-8.
43. Xaubet A, Mullol J, Lopez E, Roca-Ferrer J, Rozman M, Carrion T, et al. Comparison of the role of nasal polyp and normal nasal mucosal epithelial cells on in vitro eosinophil survival. Mediation by GM-CSF and inhibition by dexamethasone. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1994 Apr;24(4):307-17.
44. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. The Journal of allergy and clinical immunology. 2001 Apr;107(4):607-14.
45. Bachert C, Wagenmann M, Rudack C, Hopken K, Hillebrandt M, Wang D, et al. The role of cytokines in infectious sinusitis and nasal polyposis. Allergy. 1998 Jan;53(1):2-13.
46. Wagenmann M, Gartner-Akerboom M, Helmig P. Increased production of type-2 and type-1 cytokines in nasal polyps. J Allergy Clin Immun. 2000 Jan;105(1):S210-S.
47. Eweiss A, Dogheim Y, Hassab M, Tayel H, Hammad Z. VCAM-1 and eosinophilia in diffuse sino-nasal polyps. Eur Arch Oto-Rhino-L. 2009 Mar;266(3):377-83.
48. Bachert C, Gevaert P, Holtappels G, Cuvelier C, van Cauwenberge P. Nasal polyposis: from cytokines to growth. American journal of rhinology. 2000 Sep-Oct;14(5):279-90.
49. Bernardes JF, Shan J, Tewfik M, Hamid Q, Frenkiel S, Eidelman DH. Protein nitration in chronic sinusitis and nasal polyposis: role of eosinophils. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 Nov;131(5):696-703.

50. Harlin SL, Ansel DG, Lane SR, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. The Journal of allergy and clinical immunology. 1988 May;81(5 Pt 1):867-75.
51. Venge P, Bystrom J, Carlson M, Hakansson L, Karawacjzyk M, Peterson C, et al. Eosinophil cationic protein (ECP): molecular and biological properties and the use of ECP as a marker of eosinophil activation in disease. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1999 Sep;29(9):1172-86.
52. Poposki JA, Uzzaman A, Nagarkar DR, Chustz RT, Peters AT, Suh LA, et al. Increased expression of the chemokine CCL23 in eosinophilic chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2011 Jul;128(1):73-81 e4.
53. Krysko O, Holtappels G, Zhang N, Kubica M, Deswarte K, Derycke L, et al. Alternatively activated macrophages and impaired phagocytosis of S. aureus in chronic rhinosinusitis. Allergy. 2011 Mar;66(3):396-403.
54. Tomassen P, Van Zele T, Zhang N, Perez-Novo C, Van Bruaene N, Gevaert P, et al. Pathophysiology of chronic rhinosinusitis. Proceedings of the American Thoracic Society. 2011 Mar;8(1):115-20.
55. Zhang Y, Endam LM, Filali-Mouhim A, Bosse Y, Castano R, Desrosiers M. Polymorphisms in the nitric oxide synthase 1 gene are associated with severe chronic rhinosinusitis. American journal of rhinology & allergy. 2011 Mar-Apr;25(2):e49-54.
56. Balzar S, Strand M, Rhodes D, Wenzel SE. IgE expression pattern in lung: relation to systemic IgE and asthma phenotypes. The Journal of allergy and clinical immunology. 2007 Apr;119(4):855-62.
57. Pawankar R, Lee KH, Nonaka M, Takizawa R. Role of mast cells and basophils in chronic rhinosinusitis. Clinical allergy and immunology. 2007;20:93-101.
58. Perez Novo CA, Jedrzejczak-Czechowicz M, Lewandowska-Polak A, Claeys C, Holtappels G, Van Cauwenberge P, et al. T cell inflammatory response, Foxp3 and TNFRS18-L regulation of peripheral blood mononuclear cells from patients with nasal polyps-asthma after staphylococcal superantigen stimulation. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2010 Sep;40(9):1323-32.
59. Xue L, Gyles SL, Wettey FR, Gazi L, Townsend E, Hunter MG, et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemoattractant receptor-like molecule expressed on Th2 cells. Journal of immunology. 2005 Nov 15;175(10):6531-6.
60. Langier S, Landsberg R, Sade K, Kivity S. Anti-IL-5 immunomodulates the effect of Staphylococcus aureus enterotoxin on T cell response in nasal polyps. Rhinology. 2011 Dec;49(5):570-6.
61. Patou J, Gevaert P, Van Zele T, Holtappels G, van Cauwenberge P, Bachert C. Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps. The Journal of allergy and clinical immunology. 2008 Jan;121(1):110-5.
62. Blumstein GI, Tuft L. Allergy treatment in recurrent nasal polyposis: its importance and value. The American journal of the medical sciences. 1957 Sep;234(3):269-80.
63. Drake-Lee AB. Histamine and its release from nasal polyps: preliminary communication. Journal of the Royal Society of Medicine. 1984 Feb;77(2):120-4.
64. Walker C, Williams H, Phelan J. Allergic rhinitis history as a predictor of other future disqualifying otorhinolaryngological defects. Aviation, space, and environmental medicine. 1998 Oct;69(10):952-6.
65. Bunnag C, Pacharee P, Vipulakom P, Siriyananda C. A study of allergic factor in nasal polyp patients. Annals of allergy. 1983 Feb;50(2):126-32.
66. Pepys J, Duveen GW. Negative skin tests in allergic rhinitis and nasal polyposis. International archives of allergy and applied immunology. 1951;2(2):147-60.
67. Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Annals of allergy. 1994 Jan;72(1):19-24.
68. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. The Journal of allergy and clinical immunology. 2001 Nov;108(5 Suppl):S147-334.
69. Downing E, S. Braman, and G.A. Settipane. Bronchial reactivity in patients with nasal polyposis before and after polypectomy. The Journal of allergy and clinical immunology. 1962;69(1):102.
70. Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D, Group EC. Allergic vs nonallergic asthma: what makes the difference? Allergy. 2002 Jul;57(7):607-13.
71. Kowalski ML. Aspirin-sensitive rhinosinusitis and asthma. Clinical allergy and immunology. 2007;19:147-75.
72. Vento SI, Ertama LO, Hytonen ML, Wolff CH, Malmberg CH. Nasal polyposis: clinical course during 20 years. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2000 Sep;85(3):209-14.
73. Zhang N, Gevaert P, van Zele T, Perez-Novo C, Patou J, Holtappels G, et al. An update on the impact of Staphylococcus aureus enterotoxins in chronic sinusitis with nasal polyposis. Rhinology. 2005 Sep;43(3):162-8.
74. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane database of systematic reviews. 2007 (3):CD006394.

75. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Congdon DJ, Adolphson CR, et al. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2005 Aug;116(2):362-9.
76. Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Nov;137(5):815-21.
77. Bobic S, van Drunen CM, Callebaut I, Hox V, Jorissen M, Fokkens WJ, et al. Dexamethasone-induced apoptosis of freshly isolated human nasal epithelial cells concomitant with abrogation of IL-8 production. Rhinology. 2010 Dec;48(4):401-7.
78. Schleimer RP. Glucocorticoids suppress inflammation but spare innate immune responses in airway epithelium. Proceedings of the American Thoracic Society. 2004;1(3):222-30.
79. Watanabe K, Shirasaki H, Kanaizumi E, Himi T. Effects of glucocorticoids on infiltrating cells and epithelial cells of nasal polyps. The Annals of otology, rhinology, and laryngology. 2004 Jun;113(6):465-73.
80. Mullol J, Roca-Ferrer J, Xaubet A, Raserra J, Picado C. Inhibition of GM-CSF secretion by topical corticosteroids and nedocromil sodium. A comparison study using nasal polyp epithelial cells. Respiratory medicine. 2000 May;94(5):428-31.
81. Mullol J, Xaubet A, Gaya A, Roca-Ferrer J, Lopez E, Fernandez JC, et al. Cytokine gene expression and release from epithelial cells. A comparison study between healthy nasal mucosa and nasal polyps. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1995 Jul;25(7):607-15.
82. Roca-Ferrer J, Mullol J, Lopez E, Xaubet A, Pujols L, Fernandez JC, et al. Effect of topical anti-inflammatory drugs on epithelial cell-induced eosinophil survival and GM-CSF secretion. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1997 Jul;10(7):1489-95.
83. Xaubet A, Mullol J, Roca-Ferrer J, Pujols L, Fuentes M, Perez M, et al. Effect of budesonide and nedocromil sodium on IL-6 and IL-8 release from human nasal mucosa and polyp epithelial cells. Respiratory medicine. 2001 May;95(5):408-14.
84. Mullol J, Lopez E, Roca-Ferrer J, Xaubet A, Pujols L, Fernandez-Morata JC, et al. Effects of topical anti-inflammatory drugs on eosinophil survival primed by epithelial cells. Additive effect of glucocorticoids and nedocromil sodium. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1997 Dec;27(12):1432-41.
85. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Carrion T, Rosello-Catafau J, et al. [Eosinophil activation by epithelial cells of the respiratory mucosa. Comparative study of normal mucosa and inflammatory mucosa]. Medicina clinica. 1997 May 31;109(1):6-11.
86. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Picado C. Comparative study of the effects of different glucocorticosteroids on eosinophil survival primed by cultured epithelial cell supernatants obtained from nasal mucosa and nasal polyps. Thorax. 1995 Mar;50(3):270-4.
87. Van Zele T, Gevaert P, Holtappels G, Beule A, Wormald PJ, Mayr S, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. The Journal of allergy and clinical immunology. 2010 May;125(5):1069-76 e4.
88. Aukema AA, Mulder PG, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. The Journal of allergy and clinical immunology. 2005 May;115(5):1017-23.
89. Olsson P, Ehnhage A, Nordin S, Stjarne P, Group NSS. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. Rhinology. 2010 Sep;48(3):325-30.
90. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy. 2008 Oct;63(10):1292-300.
91. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. Drug safety : an international journal of medical toxicology and drug experience. 2003;26(12):863-93.
92. Bielory L, Blaiss M, Fineman SM, Ledford DK, Lieberman P, Simons FE, et al. Concerns about intranasal corticosteroids for over-the-counter use: position statement of the Joint Task Force for the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2006 Apr;96(4):514-25.
93. Benitez P, Alobid I, de Haro J, Berenguer J, Bernal-Sprekelsen M, Pujols L, et al. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. The Laryngoscope. 2006 May;116(5):770-5.
94. Lildholdt T, Fogstrup J, Gammelgaard N, Kortholm B, Ulsoe C. Surgical versus medical treatment of nasal polyps. Acta oto-laryngologica. 1988 Jan-Feb;105(1-2):140-3.
95. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Archives of otolaryngology--head & neck surgery. 1997 Jun;123(6):595-600.

96. Ichimura K, Shimazaki Y, Ishibashi T, Higo R. Effect of new macrolide roxithromycin upon nasal polyps associated with chronic sinusitis. Auris, nasus, larynx. 1996;23:48-56.
97. Suzuki H, Shimomura A, Ikeda K, Oshima T, Takasaka T. Effects of long-term low-dose macrolide administration on neutrophil recruitment and IL-8 in the nasal discharge of chronic sinusitis patients. The Tohoku journal of experimental medicine. 1997 Jun;182(2):115-24.
98. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. American journal of rhinology. 2000 May-Jun;14(3):143-8.
99. Maruyama S, Yoshioka H, Fujita K, Takimoto M, Satake Y. Sensitivity of group A streptococci to antibiotics. Prevalence of resistance to erythromycin in Japan. American journal of diseases of children. 1979 Nov;133(11):1143-5.
100. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. The New England journal of medicine. 1997 Aug 14;337(7):441-6.
101. Mepolizumab: 240563, anti-IL-5 monoclonal antibody - GlaxoSmithKline, anti-interleukin-5 monoclonal antibody - GlaxoSmithKline, SB 240563. Drugs in R&D. 2008;9(2):125-30.
102. Walsh GM. Reslizumab, a humanized anti-IL-5 mAb for the treatment of eosinophil-mediated inflammatory conditions. Current opinion in molecular therapeutics. 2009 Jun;11(3):329-36.
103. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. The Journal of allergy and clinical immunology. 2006 Nov;118(5):1133-41.
104. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. The Journal of allergy and clinical immunology. 2011 Nov;128(5):989-95 e1-8.
105. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. American journal of respiratory and critical care medicine. 2011 Nov 15;184(10):1125-32.
106. Grundmann SA, Hemfort PB, Luger TA, Brehler R. Anti-IgE (omalizumab): a new therapeutic approach for chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2008 Jan;121(1):257-8.
107. Guglielmo M, Gulotta C, Mancini F, Sacchi M, Tarantini F. Recalcitrant nasal polyposis: achievement of total remission following treatment with omalizumab. Journal of investigational allergology & clinical immunology : official organ of the International Association of Asthmology. 2009;19(2):158-9.
108. Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. American journal of rhinology. 2007 Jul-Aug;21(4):428-32.
109. Vennera MD, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. Thorax. 2011 Sep;66(9):824-5.
110. 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. The Journal of allergy and clinical immunology. 2013 Jan;131(1):110-6 e1.
111. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. Cochrane database of systematic reviews. 2006 (3):CD004458.
112. Dalziel K, Stein K, Round A, Garside R, Royle P. Endoscopic sinus surgery for the excision of nasal polyps: A systematic review of safety and effectiveness. American journal of rhinology. 2006 Sep-Oct;20(5):506-19.
113. Stankiewicz JA. Complications of endoscopic sinus surgery. Otolaryngologic clinics of North America. 1989 Aug;22(4):749-58.
114. Stankiewicz JA. Cerebrospinal fluid fistula and endoscopic sinus surgery. The Laryngoscope. 1991 Mar;101(3):250-6.
115. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Health technology assessment. 2003;7(17):iii, 1-159.
116. Alobid I, Benitez P, Bernal-Sprekelsen M, Roca J, Alonso J, Picado C, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy. 2005 Apr;60(4):452-8.
117. Bonfils P. Evaluation of the combined medical and surgical treatment in nasal polyposis. I: functional results. Acta oto-laryngologica. 2007 Apr;127(4):436-46.
118. Selivanova O, Kuehnemund M, Mann WJ, Amedee RG. Comparison of conventional instruments and mechanical debriders for surgery of patients with chronic sinusitis. American journal of rhinology. 2003 Jul-Aug;17(4):197-202.
119. Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. The Annals of otology, rhinology, and laryngology. 2011 Mar;120(3):162-6.
120. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. The Laryngoscope. 2009 Dec;119(12):2459-65.

121. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. The Laryngoscope. 2004 May;114(5):811-3.
122. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2006 Oct;31(5):390-8.
123. Lee JY, Lee SW. Influence of age on the surgical outcome after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. The Laryngoscope. 2007 Jun;117(6):1084-9.
124. Sil A, Mackay I, Rowe-Jones J. Assessment of predictive prognostic factors for functional endoscopic sinus surgery in a 5-year prospective outcome study. American journal of rhinology. 2007 May-Jun;21(3):289-96.
125. Ramadan HH, VanMetre R. Endoscopic sinus surgery in geriatric population. American journal of rhinology. 2004 Mar-Apr;18(2):125-7.
126. Akhtar S, Ikram M, Azam I, Dahri T. Factors associated with recurrent nasal polyps: a tertiary care experience. JPMA The Journal of the Pakistan Medical Association. 2010 Feb;60(2):102-4.
127. Georgalas C, Hansen F, Videler WJ, Fokkens WJ. Long terms results of Draf type III (modified endoscopic Lothrop) frontal sinus drainage procedure in 122 patients: a single centre experience. Rhinology. 2011 Jun;49(2):195-201.
128. Matsuwaki Y, Ookushi T, Asaka D, Mori E, Nakajima T, Yoshida T, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. International archives of allergy and immunology. 2008;146 Suppl 1:77-81.
129. Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. Ear, nose, & throat journal. 2007 Jul;86(7):409-11.
130. Zhang Z, Linkin DR, Finkelman BS, O'Malley BW, Jr., Thaler ER, Doghramji L, et al. Asthma and biofilm-forming bacteria are independently associated with revision sinus surgeries for chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2011 Jul;128(1):221-3 e1.
131. Young J, Frenkiel S, Tewfik MA, Mouadeb DA. Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. American journal of rhinology. 2007 Nov-Dec;21(6):743-7.
132. Lavigne F, Nguyen CT, Cameron L, Hamid Q, Renzi PM. Prognosis and prediction of response to surgery in allergic patients with chronic sinusitis. The Journal of allergy and clinical immunology. 2000 Apr;105(4):746-51.
133. Fernandes SV. Postoperative care in functional endoscopic sinus surgery? The Laryngoscope. 1999 Jun;109(6):945-8.
134. Bugten V, Nordgard S, Steinsvag S. The effects of debridement after endoscopic sinus surgery. The Laryngoscope. 2006 Nov;116(11):2037-43.
135. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology. 2005 Mar;43(1):2-10.
136. Bugten V, Nordgard S, Skogvoll E, Steinsvag S. Effects of nonabsorbable packing in middle meatus after sinus surgery. The Laryngoscope. 2006 Jan;116(1):83-8.
137. Catalano PJ, Roffman EJ. Evaluation of middle meatal stenting after minimally invasive sinus techniques (MIST). Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2003 Jun;128(6):875-81.
138. Miller RS, Steward DL, Tami TA, Sillars MJ, Seiden AM, Shete M, et al. The clinical effects of hyaluronic acid ester nasal dressing (Merogel) on intranasal wound healing after functional endoscopic sinus surgery. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2003 Jun;128(6):862-9.
139. Stammberger H, Hawke M. Essentials of endoscopic sinus surgery. St. Louis: Mosby; 1993. xv, 212 p. p.
140. Global Strategy for Asthma Management and Prevention [Internet]. 2012 [updated 2012 Dec; Cited 2013 Mar]. Available from: www.ginasthma.org.
141. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Internet]. 2013 [updated 2013 Feb; cited 2013 Mar]. Available from: www.goldcopd.org.
142. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy. 2009 Oct;64(10):1498-506.
143. Asthma Control Test [Internet]. 2012 [updated 2012 Jan; cited 2013 Mar]. Available from: www.asthmacontroltest.com.
144. Gevaert P. Eosinophilic inflammation in nasal polyposis: regulation of interleukin-5 and interleukin-5 receptor alpha isoforms [Doctoral thesis]. Belgium: Ghent University; 2004.
145. Van Zele T. Nasal polyposis: differentiation of chronic sinus disease and impact of Staphylococcus aureus enterotoxins [Doctoral thesis]. Belgium: Ghent University; 2008.
146. Proimos E, Papadakis CE, Chimona TS, Kiagiadaki D, Ferekidis E, Yiotakis J. The effect of functional endoscopic sinus surgery on patients with asthma and CRS with nasal polyps. Rhinology. 2010 Sep;48(3):331-8.

APPENDICES

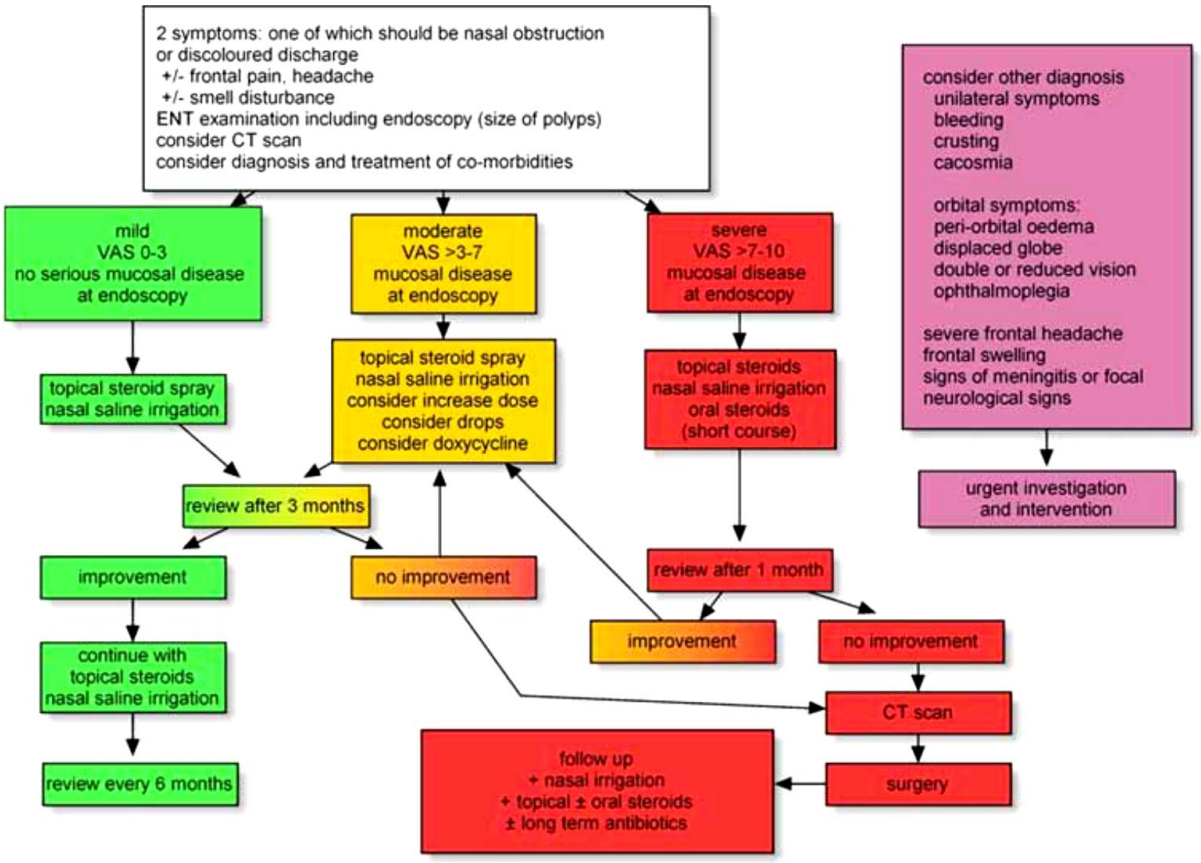
Appendix 1: EPOS 2012 control test.

Retrieved from (1).

Assessment of current clinical control of CRS (in the last month)			
Characteristic	**Controlled (all of the following)**	**Partly Controlled (at least one present)**	**Uncontrolled**
Nasal blockage	Not present or not bothersome	Present on most days of the week	Three or more features of partly controlled CRS
Rhinorrhea/ Postnasal drip	Little and mucous	Mucopurulent on most days of the week	
Facial pain/headachec	Not present or not bothersome	Present	
Smell	Normal or only slightly impaired	Impaired	
Sleep disturbance or fatigue	Not impaired	Impaired	
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa (nasal polyps, mucopurulent secretions, inflamed mucosa)	
Systemic medication needed to control disease	Not needed	Need of a course of antibiotics or systemic corticosteroids **in the last three months**	Need of long term antibiotics or systemic corticosteroids **in the last month**

Appendix 2: CRSwNP management scheme for ENT-specialists.

Retrieved from (1)



Appendix 3: Treatment evidence and recommendations for adults with CRSWNP.

Adapted from (1)

Therapy	Level	Grade of recommendation	Relevance
Nasal saline irrigation	Ib, no data in single use	D	Yes for symptomatic relief
INCS	Ia	A	Yes
OCS	Ia	A	Yes
Oral AB short term <4 weeks	Ib and Ib(-)[*]	C[#]	Yes, small effect
Oral AB long term ≥12 weeks	III	C	Yes, especially if IgE is not elevated, small effect
Anti-leukotrienes	Ib(-)	A(-)[%]	No
Anti-IL-5	no data	D	Unclear
Anti-IgE	Ib(-)	A(-)	No

[*] Ib(-): Ib sudy with a negative outcome.

[#] Short term AB show one positive and one negative study. Therefore recommendation C.

[%] A(-): Grade A recommendation **not** to use.

Appendix 4: Patient information.

Patiënteninformatie

Follow up van het natuurlijk verloop en resultaat 10 jaar na neuschirurgie.

Onderzoekers: Prof. Dr. P. Gevaert
Prof. Dr. C. Bachert
Dr. Lien Calus

Inleiding
U werd geopereerd aan de neus op de afdeling neus-, keel-, oorheelkunde UZ-Gent tussen 1999 en 2000. U wordt nu gevraagd om deel te nemen aan een wetenschappelijke onderzoeksstudie ter evaluatie van het resultaat ongeveer tien jaar na deze ingreep. Hiervoor dient u eenmalig terug te komen voor het invullen van een vragenlijst en een neusonderzoek. Wij vragen u om de volgende informatie aandachtig te lezen.

Doel van de studie
1) Het bepalen van het natuurlijk verloop en resultaat na een neusingreep
2) Effect van de ingreep op de ontstekingsparameters in bloed en neusvocht.

Procedures
Uw dokter zal vragen stellen omtrent de evolutie van uw neus en sinusklachten en de geneesmiddelen die u neemt. Gegevens omtrent de evolutie van de scores van uw symptomen sinds uw ingreep en de wijzigingen in medicatie zullen nagevraagd worden. Er zullen enkele onderzoeken uitgevoerd worden: algemeen lichamelijk onderzoek, bloedonderzoek (ongeveer 5 ml bloed is vereist) en een rhinoscopie (een onderzoek van de binnenzijde van de neus). Er zal een sponsje in de neus geplaatst worden om neussecreties te verzamelen. Er wordt geen beeldvorming uitgevoerd maar indien u beschikt over beeldvorming (bv. CT-scan) van het neus-, keel- en oorgebied, gelieve deze dan mee te nemen op het bezoek aan onze dienst. Ook in zake medicatie wordt u gevraagd om de verpakkingen mee te brengen naar het studiebezoek.

Laboratiumonderzoeken op bloed en neussecretie:
Uw bloed en neussecreties worden in het laboratorium onderzocht op de aanwezigheid van ontstekingsmerkers (IgE, ECP, IL-5, Sol- IL-5Ralph en TGFbeta).

Mogelijke voordelen
Deelname aan deze studie zal geen direct therapeutisch voordeel met zich meebrengen. U krijgt een gratis controle NKO-onderzoek, met een herevaluatie van uw neus- en sinusklachten. Dit onderzoek zal ongeveer 1 uur in beslag nemen.
Bovendien kan deze studie waardevolle informatie verschaffen over het natuurlijk verloop van neuspoliepen en de evolutie na chirurgie, wat nuttig kan zijn voor andere patiënten in de toekomst.

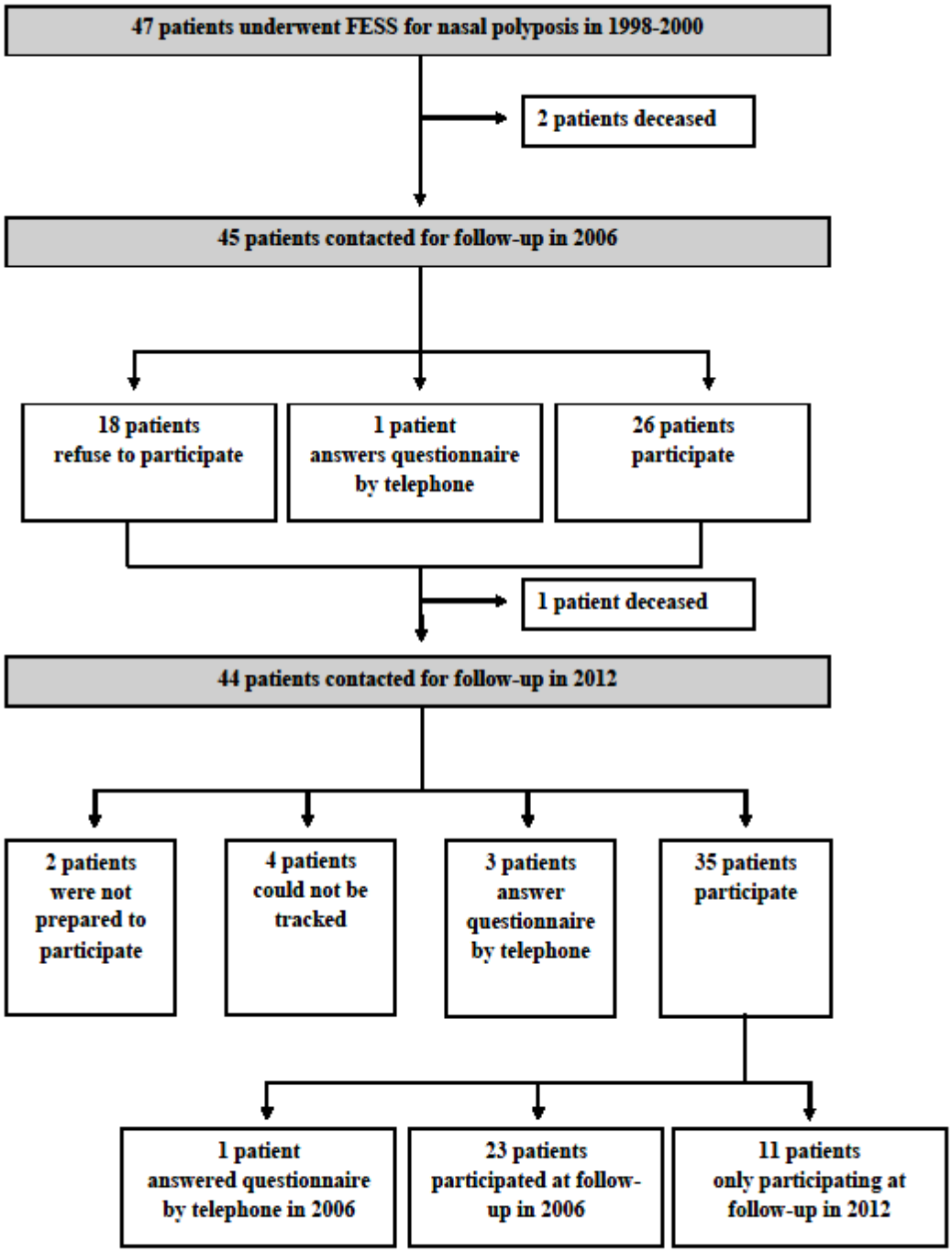
Compensatie voor deelname
Het onderzoek is volledig gratis en u krijgt een billijke vergoeding van 25 euro.

Vrijwillige deelname
Uw deelname aan de studie is volledig vrijwillig. U kan weigeren om deel te nemen aan de studie en u kunt zich op elk ogenblik terugtrekken uit de studie zonder dat u hiervoor een reden moet opgeven en zonder dat dit invloed zal hebben op de relatie tussen u en uw onderzoekende of behandelende arts. Als u deelneemt, wordt u gevraagd het toestemmingsformulier te tekenen.

Vertrouwelijkheid
Alle persoonlijke informatie, die tijdens het onderzoek wordt verkregen zal strikt vertrouwelijk worden behandeld en U zal niet persoonlijk worden genoemd in eender welk eindrapport. Alle inlichtingen, die verzameld worden gedurende deze studie, zullen op computer gezet worden. In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal u persoonlijke levenssfeer worden gerespecteerd en kunt U inzage krijgen in deze gegevens. In geval van foutieve gegevens kan U uw behandelende arts vragen om deze fouten te verbeteren.
Vertegenwoordigers van de opdrachtgever, auditoren, de Commissie voor Medische Ethiek en de bevoegde overheden hebben rechtstreeks toegang tot Uw medische dossiers om de procedures van de studie en/of de gegevens te controleren, zonder de vertrouwelijkheid te schenden. Dit kan enkel binnen de grenzen die door de betreffende wetten zijn toegestaan. Door het toestemmingsformulier, na voorafgaande uitleg, te ondertekenen stemt U in met deze toegang.
Als u akkoord gaat om aan deze studie deel te nemen, zullen uw persoonlijke en klinische gegevens tijdens deze studie worden verzameld en gecodeerd (hierbij kan men uw gegevens nog terug koppelen naar uw persoonlijk dossier). Elke informatie die u rechtstreeks als persoon identificeert, zal door uw arts op een vertrouwelijke manier bewaard worden in uw medisch dossier, volgens de huidige Belgische wet op de bescherming van gegevens. Voor deze studie werd een verzekering afgesloten conform de Belgische wet van 7 mei 2004.
Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan dit ziekenhuis en wordt uitgevoerd volgens de richtlijnen van ICH/GCP opgesteld in de verklaring van Helsinki opgesteld ter bescherming van individuen deelnemend aan klinische studies. In geen geval dient u de goedkeuring door de Commissie voor Medische Ethiek te beschouwen als een aanzet tot deelname aan deze studie.

Contactpersoon
Uw onderzoekende arts zal de huisarts op de hoogte brengen van uw deelname aan deze studie, tenzij u dit weigert.
Indien u vragen heeft betreffende deze studie aarzel dan niet om het onderzoeksteam in het ziekenhuis te contacteren. U kan steeds contact op nemen met Dr. Lien Calus op het telefoonnummer 09/3325181 of Prof Philippe Gevaert 09/3322332.

Appendix 5: Flowchart.



Appendix 6: In- and exclusion criteria.

Inclusie criteria

a. Patiënten zijn minstens 18 jaar oud, ongeacht geslacht en etniciteit.
b. Patiënten ondergingen sinuschirurgie omwille van neuspoliepen tussen 1998 en 2000 en werden toen geïncludeerd in de studie.
c. Patiënten verkeren in goede gezondheid en hebben geen klinisch significante ziekte die zou interfereren met de studieplanning of –procedures en geen veiligheidsrisico inhoudt.
d. Patiënten zijn bereid tot het geven van een informed consent, zich te houden aan de geplande bezoeken en zich te houden aan de richtlijnen met betrekking tot medicatie.
e. Vrouwelijke patiënten in de vruchtbare periode dienen zich te houden aan een medisch aanvaarde, adequate vorm van anticonceptie gedurende het verloop van de studie.
f. Mannelijke patiënten zijn akkoord om een adequate vorm van anticonceptie te gebruiken gedurende het verloop van de studie.

Exclusie criteria

a. Vrouwelijke patiënten zijn niet zwanger, geven geen borstvoeding of zijn niet premenarcheaal.
b. Patiënten ontvingen geen stootkuur corticosteroïden 4 weken voor aanvang van het studiebezoek.
c. Patiënten hebben geen systemische fungoïde infecties, ernstige hypertensie (bloeddruk hoger dan 15/9.5 mmHg of neemt meer dan 2 antihypertensieve medicaties), diabetes type 1 en 2, tuberculose, zona oftalmica.
d. Patiënten hebben geen mucoviscidose, primaire ciliaire dysfunctie of het syndroom van Kartagener in de medische voorgeschiedenis.
e. Patiënten zijn niet gediagnosticeerd met een parasitaire infectie.
f. Patiënten zijn niet gekend als zijnde positief voor HIV, noch voor hepatitis B surface-antigenen of C antilichamen. Er zullen geen testen uitgevoerd worden op het studiebezoek.
g. Patiënten hebben de 4 weken voorafgaand aan het studiebezoek geen acute astmatische aanval die een hospitaalopname noodzaakte (met uitzondering van spoedraadpleging, dewelke resulteerde in onmiddellijk ontslag en zonder hospitalisatie)
h. Patiënten hebben 3 maand voorafgaand aan het studiebezoek geen immunotherapie gekregen.

Appendix 7: Informed consent.

Toestemmingsformulier ter deelname aan studie
Follow up van het natuurlijk verloop en resultaat 10 jaar na neuschirurgie.

Ik, ondergetekende ……..geboren op……... verklaar mij akkoord, na voorgaande informatie te hebben gelezen en besproken met de arts, om deel te nemen aan deze studie.
Ik werd ingelicht dat persoonlijke gegevens door de onderzoekende artsen van het Universitair Ziekenhuis Gent ingezien kunnen worden en alleen in een geanonimiseerde vorm voor onderzoek en publicaties gebruikt worden.
Men heeft mij ingelicht over het bestaan van een verzekeringspolis in geval er letsel zou ontstaan dat aan de studieprocedures is toe te schrijven.

Ik begrijp dat ik mijn toestemming tot deelname op gelijk welk ogenblik kan intrekken, zonder dat ik daarvoor een reden moet opgeven.

Ik heb voldoende tijd gehad om een beslissing te nemen en verklaar hierbij dat ik vrijwillig deelneem aan deze studie.
Ik weet dat mijn deelname vrijwillig is. Dit zal geen invloed hebben op mijn huidige of toekomstige behandeling. Ik heb een kopie van dit toestemmingsformulier ontvangen.

Getekend _____ Datum _____
Naam + handtekening (Patiënt)

Ik, ……... (naam arts in drukletters) bevestig hierbij dat bovengenoemde patiënt de informatie en het toestemmingsformulier gelezen en begrepen heeft, dat alle vragen een bevredigend antwoord hebben gekregen en dat de patiënt vrijwillig zijn toestemming tot deelname aan de studie heeft gegeven.

Getekend _____ Datum _____
Naam + handtekening (Onderzoeker of medewerker)

Appendix 8: Case Report Form.

1. 2000

Studie nasale polypose

Naam: **Voornaam:** **Geslacht: M / V**
Adres:

Geb.dat:
Nr:

Huidige Anamnese: **Datum:**

Symptomen

neusobstructie	geen / weinig / matig / ernstig
neusloop	geen / weinig / matig / ernstig
niezen	geen / weinig / matig / ernstig
reukstoornis	geen / weinig / matig / ernstig
hoofdpijn	geen / weinig / matig / ernstig
oogsymptomen	geen / weinig / matig / ernstig

Historische Anamnese:

Ontstaan Poliepen?
Beroep?
Familiaal?

Chirurgische ingrepen:

Naam:	Voornaam:	Datum:	Nr:

Allergie ja / nee specifieer:.....

Asthma ja / nee specifieer:.....

Aspirine overgevoeligheid ja / nee asthma
huidreactie

Andere: Diabetes
Hypertensie
.....

Allergietesten:

Medicatie(vnl. laatste 4 weken):

Steroiden ja / nee lokaal / algemeen
specifieer:.....

Antbiotica ja / nee specifieer:.....

Andere ja / nee specifieer:.....

Usus: Roken ja / nee

Naam:	Voornaam:	Datum:	Nr:

Onderzoeken:

Endoscopisch (Davos Scale):

Davos 0: geen poliepen ; Davos 1: poliepen achter de middenste neusschelp ;
Davos 2: poliepen onder de middenste neusschelp; Davos 3: massieve poliepen.

Nasale polypose:

Rechts:	Davos 0	Davos 1	Davos 2	Davos 3
Links:	Davos 0	Davos 1	Davos 2	Davos 3

Opmerkingen:

CT-scan (Lund V.):

0: geen opaciteit ; 1: enige opaciteit ; 2: totale opaciteit

	Rechts	Links
Maxillaire sinus (0,1,2)		
Anterior Ethmoid (0,1,2)		
Posterior Ethmoid (0,1,2)		
Sphenoid (0,1,2)		
Frontale sinus (0,1,2)		
Osteomeataal Complex (0,2)		
Totaal		

Opmerkingen:

Patient behoort tot de volgende groep:

- ☐ patiënt met nasale polyposis
- ☐ patiënt met nasale polyposis, geen respons op 4 w locale steroïden
- ☐ patiënt met recidief nasale polyposis na chirurgie
- ☐ patiënt met seizoensgebonden en perenniale rhinitis
- ☐ patiënt met aspirine overgevoeligheid
- ☐ controle

Datum: **Onderzoeker:**

2. 2006

Opvolgstudie nasale polypose

Naam: Geslacht: m/v

Adres: Geb.dat:

IWTnr:

Tel:

Huidige datum:
Datum ingreep:

Type ingreep: FESS / conchotomie / septoplastie
Diagnose bij ingreep: 1 Controle
2 Controle + allergie
3 CRS
4 NP
5 NP + asthma
6 NP + Asthma + aspirine intolerance

Evolutie van symptomen na neuschirurgie en huidige symptomen
0 = geen klachten
1 = weinig
2 = matig
3 = ernstig

Symptomen	**Pre-op**	**Post-op (beste)**	**Hoelang post-op (maanden)**	**Nu**
Neusobstructie				
Neusloop				
Niezen				
Reukstoornis				
Hoofdpijn				
Oogsymptomen				

Algemeen Therapeutisch antwoord post-op (beste) periode:…….

1	Complete Relief	Virtually no symptoms are present.
2	Marked Relief	Symptoms are greatly improved and although present are scarcely troublesome.
3	Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4	Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5	No Relief	No relief, symptoms are unchanged, or worse than pre-treatment baseline

Algemeen Therapeutisch antwoord huidige

1	Complete Relief	Virtually no symptoms are present.
2	Marked Relief	Symptoms are greatly improved and although present are scarcely troublesome.
3	Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4	Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5	No Relief	No relief, symptoms are unchanged, or worse than pre-treatment baseline

Medicatie voor sinonasale klachten

Type	Medicatie post-op	Stop medicatie	Medicatie -vrije periode	Huidig
Orale GCS				
Nasale GCS				
Antihistaminica				
Antibiotica				
Asthma medicatie				
Inhalatie GCS				
Andere…				

Onderzoeken:
Endoscopisch (Davos scale)
Davos 0: geen poliepen
Davos 1: poliepen achter de middenste neusschelp
Davos 2: poliepen onder de middenste neusschelp
Davos 3: massieve poliepen

Pre-op	Pre-op	Post-op				Huidig	
Re	Li	Rec NP	CRS	infectie	synech	Re	Li

Opmerkingen:

Comorbiditeit
+2 = duidelijke verbetering
+1 = milde verbetering
0 = geen verandering
-1 = milde verergering
-2 = ernstige verergering

	Pre-op Ja-nee	Post-op (beste)	Hoelang post-op (maanden)	Nu
Allergie				
Asthma				
COPD				
Aspirine intol				

Andere medische antecedenten:

Opmerkingen:

CT-scan (Lund V.) in post op periode
0: geen opaciteit 1: enige opaciteit 2: totale opaciteit

Sinus (0 – 1 – 2)	**Rechts**	**Links**
Frontale sinus		
Maxillaire sinus		
Anterieur ethmoid		
Posterieur ethmoid		
Sphenoidale sinus		
Osteomeataal complex (0 of 2)		
Totaal		

Opmerking:

Bloed
Neussecretie merocel:

3. 2012

Opvolgstudie nasale polypose

IWTnr:

Informed Consent: ☐ OK

Inclusie- en Exclusiecriteria

Inclusie Criteria	**J**	**N**
a. Patiënten zijn minstens 18 jaar oud, ongeacht geslacht en etniciteit.		
b. Patiënten ondergingen sinuschirurgie omwille van neuspoliepen tussen 1998 en 2000 en werden toen geïncludeerd in de studie.		
c. Patiënten verkeren in goede gezondheid en hebben geen klinisch significante ziekte die zou interfereren met de studieplanning of –procedures en geen veiligheidsrisico inhoudt.		
d. Patiënten zijn bereid tot het geven van een informed consent, zich te houden aan de geplande bezoeken en zich te houden aan de richtlijnen met betrekking tot medicatie.		
e. Vrouwelijke patiënten in de vruchtbare periode dienen zich te houden aan een medisch aanvaarde, adequate vorm van anticonceptie gedurende het verloop van de studie.		
f. Mannelijke patiënten zijn akkoord om een adequate vorm van anticonceptie te gebruiken gedurende het verloop van de studie.		

Exclusie Criteria	**J**	**N**
a. Vrouwelijke patiënten zijn niet zwanger, geven geen borstvoeding of zijn niet premenarcheaal.		
b. Patiënten ontvingen geen stootkuur corticosteroïden 4 weken voor aanvang van het studiebezoek.		
c. Patiënten hebben geen systemische fungoïde infecties, ernstige hypertensie (bloeddruk hoger dan 15/9.5 mmHg of neemt meer dan 2 antihypertensieve medicaties), diabeter type 1 en 2, tuberculose, zona oftalmica.		
d. Patiënten hebben geen mucoviscidose, primaire ciliaire dysfunctie of het syndroom van Kartagener in de medische voorgeschiedenis.		
e. Patiënten zijn niet gediagnosticeerd met een parasitaire infectie.		
f. Patiënten zijn niet gekend als zijnde positief voor HIV, noch voor hepatitis B surface-antigenen of C antilichamen. Er zullen geen testen uitgevoerd worden op het studiebezoek.		
g. Patiënten hebben de 4 weken voorafgegaand aan het studiebezoek geen acute astmatische aanval die een hospitaalopname noodzaakte (met uitzondering van spoedraadpleging, dewelke resulteerde in onmiddellijk ontslag en zonder hospitalisatie)		
h. Patiënten hebben 3 maand voorafgaand aan het studiebezoek geen immunotherapie gekregen.		

Data
Datum ingreep:
Datum inclusie IWT1:
Datum inclusie IWT2:
Huidige datum:

Ingreep
Type ingreep: FESS / conchotomie / septoplastie

Diagnose bij ingreep: 1 Controle
2 Controle + allergie
3 CRS
4 NP
5 recidief NP

Geassocieerde aandoeningen

Allergie: ☐ JA ☐ NEE
Aan: ……

Rhinitis: ☐ JA ☐ NEE

Asthma: ☐ JA ☐ NEE

- Duur: ……
- Aantal exacerbaties in het afgelopen jaar:…….
- Aantal hospitalisatieperiodes: …….
- GINA-classificatie: …….

GINA Classification of Asthma Severity

	Symptoms/Day	**Symptoms/Night**	**PEF or FEV1**	**PEF variability**
STEP 1 Intermittent	< 1 time a week Asymptomatic and normal PEF between attacks	≤ 2 times a month	≥ 80%	< 20%
STEP 2 Mild Persistent	> 1 time a week but < 1 time a day Attacks may affect activity	> 2 times a month	≥ 80%	20-30%
STEP 3 Moderate Persistent	Daily Attacks affect activity	> 1 time a week	60%-80%	> 30%

STEP 4 Severe Persistent	Continuous Limited physical activity	Frequent	≤ 60%	> 30%

- PEF, Peak Expiratory Flow (als % t.o.v. verwachte waarde); FEV1, Forced Expiratory Volume in the first second.
- PEF variability: $((PEF_{evening} - PEF_{morning})x100)/(0,5x(PEF_{evening} + PEF_{morning}))$
- • The presence of one of the features of severity is sufficient to place a patient in that category.
- • Patients at any level of severity-even intermittent asthma-can have severe attacks.

COPD: ☐ JA ☐ NEE

- Duur: ……
- Aantal exacerbaties in het afgelopen jaar:…….
- Aantal hospitalisatieperiodes: …….
- GOLD-classificatie: …….

GOLD Staging System for COPD Severity

Stage	**Description**	**Findings (based on postbronchodilator FEV1)**
0	At risk	Risk factors and chronic symptoms but normal spirometry
I	Mild	$FEV_1/FVC < 0,70$ $FEV_1 \geq 80\%$ predicted value May have symptoms
II	Moderate	$FEV_1/FVC < 0,70$ $50\% \leq FEV_1 \leq 80\%$ predicted value May have chronic symptoms
III	Severe	$FEV_1/FVC < 0,70$ $30\% \leq FEV_1 \leq 50\%$ predicted value May have chronic symptoms
IV	Very severe	$FEV_1/FVC < 0,70$ $FEV_1 \leq 80\%$ predicted or $FEV_1 < 50\%$ predicted value AND severe chronic respiratory symptoms

GOLD = Global Initiative for Chronic Obstructive Lung Disease; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity.

Otitis: ☐ JA ☐ NEE

Aspirine overgevoeligheid: ☐ JA ☐ NEE

Atopische dermatitis: ☐ JA ☐ NEE

Antecedenten

Nko-gerelateerde chirurgie:

……

……

Bijkomende chirurgie nko na ingreep:

……

……

Overige chirurgie/antecedenten:

……

……

Huidige anamnese:

……

……

……

……

Systeemanamnese:

(Oogproblemen, Endocrinologie, Dermatologie, Longziekten, Cardiovasculair; Gastro-intestinaal, Musculoskeletaal, Neurologie, Genito-urinair, Hematologisch, Immunologisch, Psychiatrisch)

……

……

……

……

Familiale voorgeschiedenis:

……

……

Beroep (+blootstelling):

……

……

Medicatie:

……

……

……

……

Usus:

Tabak: ☐ JA ☐ NEE

……

……

Alcohol: ☐ JA ☐ NEE

……

……

Drugs: ☐ JA ☐ NEE

……

……

Evolutie van symptomen en medicatiegebruik na neuschirurgie en huidige situatie

0 = geen klachten
1 = weinig
2 = matig
3 = ernstig

Symptomen	**Pre-op**	**Post-op (beste)**	**Hoelang post-op (maanden)**	**Nu**
Neusobstructie				
Neusloop				
Niezen				
Reukstoornis				
Hoofdpijn				
Oogsymptomen				

Algemeen Therapeutisch antwoord post-op (beste) tov initiele chirurgie periode:…….

1	Complete Relief	Virtually no symptoms are present.
2	Marked Relief	Symptoms are greatly improved and although present are scarcely troublesome.
3	Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4	Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5	No Relief	No relief, symptoms are unchanged, or worse than pre-treatment baseline

Algemeen Therapeutisch antwoord huidige: .....

1	Complete Relief	Virtually no symptoms are present.
2	Marked Relief	Symptoms are greatly improved and although present are scarcely troublesome.
3	Moderate Relief	Symptoms are present and may be troublesome but are noticeably improved.
4	Slight Relief	Symptoms are present and only minimal improvement has been obtained.
5	No Relief	No relief, symptoms are unchanged, or worse than pre-treatment baseline

Zou u met de huidige kennis de toenmalige ingreep laten uitvoeren hebben:

☐ JA ☐ NEE

Nasale Polypose Controle Test

1. Hoe vaak heeft u door astma op het werk, op school of thuis minder kunnen doen dan normaal gedurende de afgelopen 4 weken ?

De hele tijd	1	Meestal	2	Soms	3	Zelden	4	Nooit	5

2. Hoe vaak bent u kortademig geweest gedurende de afgelopen 4 weken?

Vaker dan 1 keer per dag	1	1 keer per dag	2	3 tot 6 keer per week	3	1 of 2 keer per week	4	Helemaal niet	5

3. Hoe vaak bent u 's nachts of 's morgens vroeger dan normaal wakker geworden door uw astmaklachten (piepen, hoesten, kortademigheid, een drukkend gevoel of pijn op de borst) gedurende de afgelopen 4 weken?

4 of meer nachten per week	1	2 tot 3 nachten per week	2	1 keer per week	3	1 of 2 keer	4	Helemaal niet	5

4. Hoe vaak heeft u uw inhalator (pufjes) met snelwerkende medicatie (zoals Ventolin ®) gebruikt om een astma-aanval te stoppen gedurende de afgelopen 4 weken ?

3 keer of vaker per dag	1	1 of 2 keer per dag	2	2 of 3 keer per week	3	1 keer per week of minder	4	Helemaal niet	5

5. Hoe beoordeelt u de mate waarin u uw astma onder controle had gedurende de afgelopen 4 weken ?

Helemaal niet onder controle	1	Slecht onder controle	2	Enigszins onder controle	3	Goed onder controle	4	Volledig onder controle	5

6. Hoe vaak bent u uw reukzin verloren de afgelopen 4 weken?

4 of meer dagen per week	1	2 tot 3 dagen per week	2	1 keer per week	3	1 of 2 keer	4	Helemaal niet	5

7. Hoe vaak heeft u korsten in de neus en/of geel/groene slijmen opgesnoten de afgelopen 4 weken?

Dagelijks	1	4 keer per week	2	2 tot 3 keer per week	3	1 of 2 keer	4	Helemaal niet	5

8. Hoe vaak bent u 's nachts of 's morgens vroeger dan normaal wakker geworden door uw neuspoliepen (neusverstopping, drukkend gevoel, …) gedurende de afgelopen 4 weken?

4 of meer nachten per week	1	2 tot 3 nachten per week	2	1 keer per week	3	1 of 2 keer	4	Helemaal niet	5

9. Hoe vaak heeft u door uw neuspoliepen op het werk, op school of thuis minder kunnen doen dan normaal gedurende de afgelopen 4 weken ?

De hele tijd	1	Meestal	2	Soms	3	Zelden	4	Nooit	5

10. Hoe beoordeelt u de mate waarin u uw neuspoliepen onder controle had gedurende de afgelopen 4 weken ?

Helemaal niet onder controle	1	Slecht onder controle	2	Enigszins onder controle	3	Goed onder controle	4	Volledig onder controle	5

Totaalscore:

Medicatie voor sinonasale klachten

Type	Medicatie post-op	Stop medicatie	Medicatievrije periode	Huidig
Orale GCS				
Nasale GCS				
Antihistaminica				
Antibiotica				
Asthma medicatie				
Inhalatie GCS				
Fysiologische neusspoelingen				
Andere…				

Onderzoeken:

- Rhinoscopia anterior:

……

……..

- Endoscopisch (Davos scale):

Davos 0: geen poliepen
Davos 1: poliepen achter de middenste neusschelp
Davos 2: poliepen onder de middenste neusschelp
Davos 3: massieve poliepen

Pre-op (IWT1)		**Post-op**	**Huidig**				
Re	Li	Rec NP	CRS	infectie	synech	Re	Li
		Na hoeveel maand?					

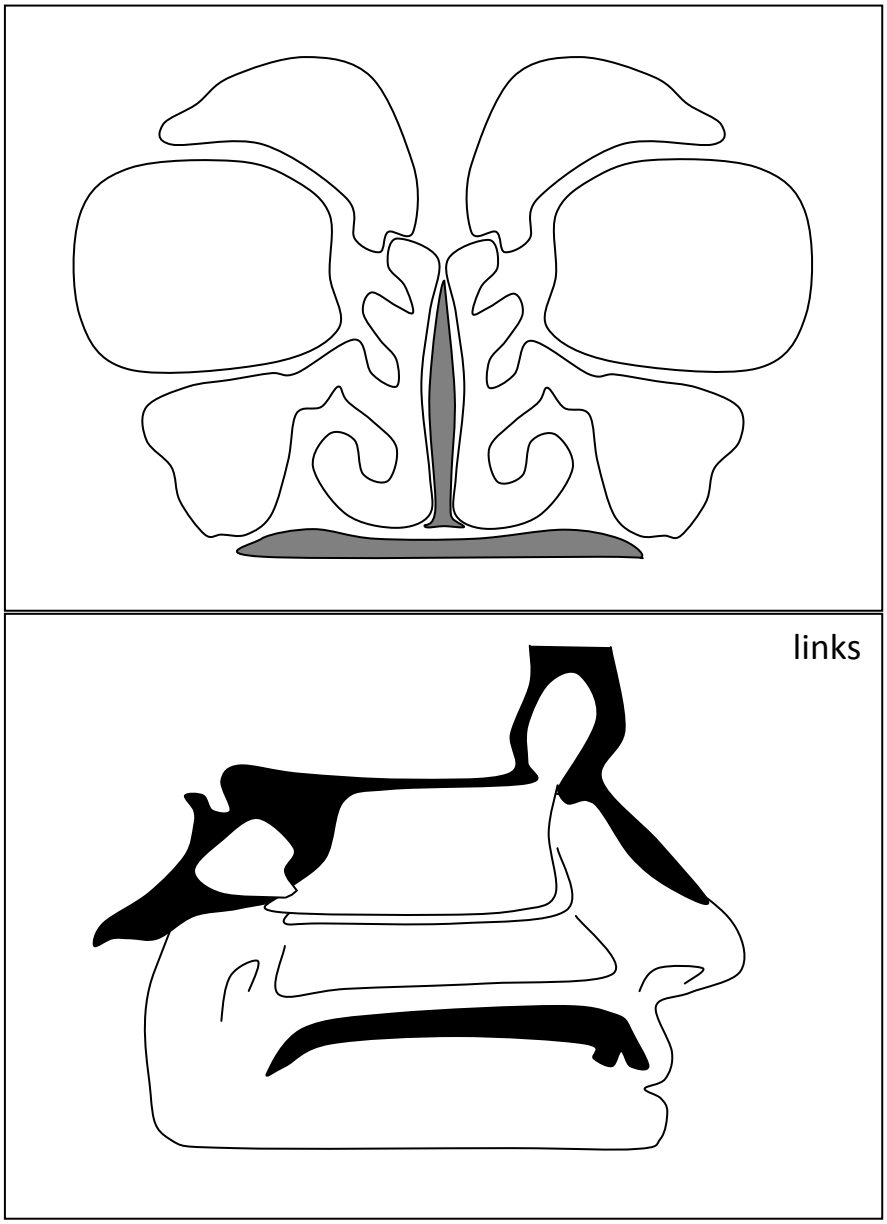
Nasale endoscopie:

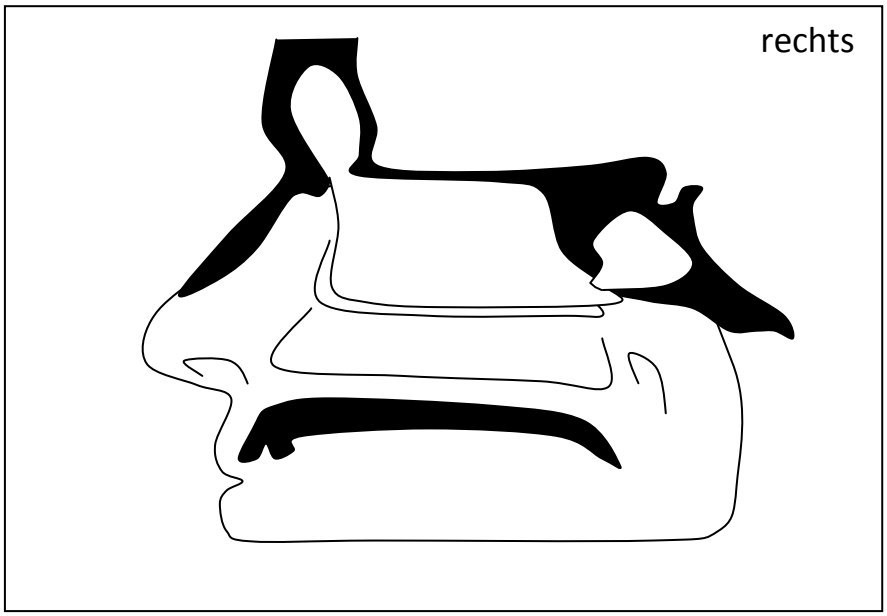
.....

.....

.....

.....


links



- Keelinspectie:

……

……

……

……

- Otoscopie:

……

……

……

……

Comorbiditeit

+2 = duidelijke verbetering
+1 = milde verbetering
0 = geen verandering
-1 = milde verergering
-2 = ernstige verergering

	Pre-op Ja-nee	Post-op (beste)	Hoelang post-op (maanden)	Nu
Allergie				
Asthma				
COPD				

Aspirine intol				

Opmerkingen:

……

……..

CT-scan (Lund Mackay score) in post op periode

Datum:

0: geen opaciteit 1: enige opaciteit 2: totale opaciteit

Sinus (0 – 1 – 2)	**Rechts**	**Links**
Frontale sinus		
Maxillaire sinus		
Anterieur ethmoid		
Posterieur ethmoid		
Sphenoidale sinus		
Osteomeataal complex (0 of 2)		
Totaal		

Opmerking:

……

……..

Stalen

Bloedafname: EDTA ☐

Serum ☐

Neussecretie merocel: ☐

Pre gewicht: …….. Post gewicht: ……..

Handtekening onderzoek Datum

Appendix 9: Baseline table.

Baseline table			
	2000 (N=47)	**2006** (N=27)	**2012** (N=38)
Sex (*M/F*)	33/14 (70.2/29.8)	17/10 (63.0/37.0)	25/13 (65.8/34.2)
Age (years)	49 (37-58)	57 (45-61)	60 (49-67)
Primary/revision FESS in 2000	22/25 (46.8/53.2)	16/11 (59.3/40.7)	19/19 (50.0/50.0)
Comorbidity			
Allergy	24 (51.1)	16 (59.3)	20 (52.6)
Asthma	18 (38.3)	11 (40.7)	15 (39.5)
Samter's triad	11 (23.4)	5 (18.5)	10 (26.3)
Medication			
Oral corticosteroids	8 (17.0)	3 (11.1)	4 (10.5)
Nasal corticosteroids	27 (57.4)	17 (63.0)	20 (52.6)
Antihistamines	6 (12.8)	5 (18.5)	1 (2.6)
Antibiotics	5 (10.6)	5 (18.5)	7 (18.4)
Asthma medication	14 (29.8)	15 (55.6)	17 (44.7)
Inhalation corticosteroids	10 (21,3)	14 (51.9)	15 (39.5)
Nasal saline irrigation	4 (8.5)	3 (11.1)	6 (15.8)
Symptom Score			
Nasal Obstruction	3 (2-3)	0 (0-1)	1 (0-2)
Rhinorrhoea	2 (0-3)	0 (0-1)	1 (0-1)
Sternutation	1 (0-2)	0 (0-0)	0.5 (0-1)
Smell disturbance	3 (2-3)	2 (1-3)	2 (0-3)
Headache	1 (0-2)	0 (0-1)	0 (0-1)
Eye symptoms	0 (0-0)	0 (0-0)	0 (0-1)
Total Symptom Score	8 (7-11)	3 (2-5)	5 (3-7)
NP score			
Davos 0	0 (0)	11 (45.8)	14 (40.0)
Davos 1-2	8 (17.0)	6 (25.0)	14 (40.0)
Davos 3-4	20 (42.6)	5 (20.8)	5 (14.3)
Davos 5-6	19 (40.4)	2 (8.3)	2 (5.7)
Total NP score	4 (3-6)	1 (0-4)	1 (0-2)
EPOS Score			
Controlled	0 (0,0)	5 (18.5)	10 (26.3)
Partly Controlled	2 (4.3)	12 (44.4)	10 (26.3)

Uncontrolled	45 (95.7)	10 (37.1)	18 (47.4)

Data are expressed as N (%) or as median (IQR).

Appendix 10: Biomarkers in 2000.

Biomarkers in 2000 (N=47)	
Tissue	
IL-5 (pg/ml)	133.24 (43.00-338.58)
Detectable IL-5	31 (66.0%)
IL-5Ra (pg/ml)	5003.01 (1765.61-21069.23)
Ratio IL-5Ra/IL-5	31.05 (13.02-115.31)
TGF-B1 (pg/ml)	9534.22 (7457.03-20760.85)
MPO (ng/ml)	6878.56 (2805.72-14874.40)
IL-18 (pg/ml)	15373.60 (6738.21-22019.14)
ECP (µg/l)	7460.43 (1837.00-14870.74)
Albumin (g/l)	21,12 (18.01-25.69)
IgE (kUA/l)	432.30 (146.30-1155.90)
Staphylococcus Aureus enterotoxine A (kUA/l)	/ *
Staphylococcus Aureus enterotoxine B (kUA/l)	/ *
Staphylococcus Aureus enterotoxine C (kUA/l)	/ *
Staphylococcus Aureus enterotoxine D (kUA/l)	/ *
Staphylococcus Aureus enterotoxine E (kUA/l)	/ *
Staphylococcus Aureus enterotoxine TSST (kUA/l)	0.00 (0.00-4.07)
Detectable Staphylococcus Aureus enterotoxine (N=46)	18 (39.1)
Grass mix 1 (kUA/l)	3.88 (0.00-5.78)
House dust mite mix 2 (kUA/l)	4.08 (0.00-8.03)
Mold mix 2 (kUA/l)	5.75 (0.00-9.60)
Tree mix 9 (kUA/l)	4.30 (0.00-8.03)
Ratio Tissue IgE/albumin	20.71 (7.90-57.60)
Nasal secretions	
IL-5 (pg/ml)	30.00 (30.00-131.21)
IL-5Ra (pg/ml)	1135.84 (497.57-5357.62)
Ratio IL-5Ra/IL-5	26.43 (9.83-48.63)
ECP (µg/l)	527.95 (254.60-1157.03)
IgE (µg/l)	283.44 (109.38-440.85)
*sIgE(SEA,C,TSST)*factor (µg/l)*	/ *
Serum	
IL-5Ra (pg/ml)	414.90 (297.00-744.70)
Eosinophils (#/µl)	435 (225-658)
Eosinophils (%)	6.6 (3.5-10.4)

Albumin (g/l)	43.9 (40.9-54.9)
ECP (µg/l)	26.10 (21.00-40.00)
IgE (kUA/l)	157.0 (48.5-278.0)
Staphylococcus Aureus enterotoxine A (kUA/l)	/ *
Staphylococcus Aureus enterotoxine B (kUA/l)	/ *
Staphylococcus Aureus enterotoxine C (kUA/l)	/ *
Staphylococcus Aureus enterotoxine D (kUA/l)	/ *
Staphylococcus Aureus enterotoxine E (kUA/l)	/ *
Staphylococcus Aureus enterotoxine TSST (kUA/l)	/ *
Grass mix 1 (kUA/l)	0.00 (0.00-0.54)
House dust mite mix 2 (kUA/l)	0.00 (0.00-1.72)
Mold mix 2 (kUA/l)	/ *
Tree mix 9 (kUA/l)	/ *
Ratio IgE/Albumin	3.03 (0.62-5.74)

Data are expressed as N (%) or as median (IQR).

* The amount of patients with a positive result is too small to give a median (IQR).

Appendix 11: Correlation between biomarkers measured in 2000 and the total symptom score at each time of contact.

		Total symptom score		
		2000	2006	2012
Tissue IL-5 (pg/ml)	r_s*	**,405**	-,149	,256
	P	,013	,478	,120
	N	37	25	38
Tissue IL-5Ra (pg/ml)	r_s	,209	,162	**,344**
	P	,214	,439	,034
	N	37	25	38
Ratio Tissue IL-5Ra/IL-5	r_s	-,094	,348	,170
	P	,580	,088	,309
	N	37	25	38
Tissue TGF-B1 (pg/ml)	r_s	,264	,182	,168
	P	,167	,470	,384
	N	29	18	29
Tissue MPO (ng/ml)	r_s	,177	,373	,097
	P	,348	,116	,611
	N	30	19	30
Tissue IL-18 (pg/ml)	r_s	,153	,243	,123
	P	,428	,331	,524
	N	29	18	29
Tissue ECP (µg/l)	r_s	**,334**	-,005	**,390**
	P	,043	,982	,017
	N	37	25	37
Tissue albumin (g/l)	r_s	,208	-,284	-,174
	P	,224	,179	,311
	N	36	24	36
Tissue IgE (kUA/l)	r_s	,120	,214	,225
	P	,485	,315	,187
	N	36	24	36
Tissue grass mix (kUA/l)	r_s	,096	,245	,182
	P	,573	,238	,281
	N	37	25	37
Tissue house dust mite mix (kUA/l)	r_s	,282	,275	,280
	P	,091	,183	,093
	N	37	25	37
Tissue SAE A (kUA/l)	r_s	,054	,218	**,378**
	P	,751	,295	,021
	N	37	25	37
Tissue SAE B (kUA/l)	r_s	,239	,280	,208
	P	,153	,175	,217
	N	37	25	37
Tissue SAE C (kUA/l)	r_s	,055	,115	,059

	P	,745	,585	,729
	N	37	25	37
Tissue SAE D (kUA/l)	r_s	,138	,115	,185
	P	,414	,585	,272
	N	37	25	37
Tissue SAE E (kUA/l)	r_s	,108	,115	,180
	P	,526	,585	,287
	N	37	25	37
Tissue SAE TSST (kUA/l)	r_s	,030	,164	,243
	P	,862	,432	,148
	N	37	25	37
Tissue mold mix (kUA/l)	r_s	,009	,260	,202
	P	,959	,242	,267
	N	32	22	32
Tissue tree mix (kUA/l)	r_s	,111	,166	,241
	P	,554	,459	,192
	N	31	22	31
Ratio tissue IgE/albumin	r_s	,092	,367	,236
	P	,598	,085	,172
	N	35	23	35
IL-5 in nasal secretions (pg/ml)	r_s	**,349**	-,037	**,408**
	P	,037	,862	,013
	N	36	25	36
IL-5Ra in nasal secretions (pg/ml)	r_s	,179	,031	,285
	P	,297	,882	,092
	N	36	25	36
Ratio IL-5Ra/IL-5 in nasal secretions	r_s	-,125	,108	,081
	P	,468	,608	,640
	N	36	25	36
ECP in nasal secretions (µg/l)	r_s	,209	-,098	,280
	P	,222	,641	,098
	N	36	25	36
IgE in nasal secretions (µg/l)	r_s	,409	-,264	,406
	P	,187	,493	,190
	N	12	9	12
sIgE(SEA,C,TSST)*factor in nasal secretions (µg/l)	r_s	**,650**	-,140	,432
	P	,022	,720	,161
	N	12	9	12
Serum IL-5Ra (pg/ml)	r_s	,230	-,250	-,161
	P	,302	,388	,474
	N	22	14	22
Serum eosinophils count (#/µl)	r_s	**,416**	,203	,351
	P	,031	,420	,073
	N	27	18	27
Serum eosinophils %	r_s	**,489**	,265	**,400**
	P	,010	,287	,039

	N	27	18	27
Serum albumin (g/l)	r_s	,211	-,084	-,262
	P	,400	,806	,294
	N	18	11	18
Serum ECP (µg/l)	r_s	**,512**	-,087	,108
	P	,015	,767	,632
	N	22	14	22
Serum IgE (kUA/l)	r_s	,026	,154	-,160
	P	,907	,599	,477
	N	22	14	22
Serum grass mix (kUA/l)	r_s	-,269	,015	-,056
	P	,266	,964	,821
	N	19	11	19
Serum house dust mite mix (kUA/l)	r_s	,088	,283	-,006
	P	,720	,399	,982
	N	19	11	19
Serum SAE A (kUA/l)	r_s	,175	,514	,390
	P	,474	,106	,099
	N	19	11	19
Serum SAE B (kUA/l)	r_s	,294	,514	,203
	P	,222	,106	,405
	N	19	11	19
Serum SAE C (kUA/l)	r_s	,226	/ [#]	-,010
	P	,353	/ [#]	,968
	N	19	11	19
Serum SAE D (kUA/l)	r_s	/ [#]	/ [#]	/ [#]
	P	/ [#]	/ [#]	/ [#]
	N	19	11	19
Serum SAE E (kUA/l)	r_s	,294	,514	,203
	P	,222	,106	,405
	N	19	11	19
Serum SAE TSST (kUA/l)	r_s	,175	,514	,390
	P	,474	,106	,099
	N	19	11	19
Serum mold mix (kUA/l)	r_s	/ [#]	/ [#]	/ [#]
	P	/ [#]	/ [#]	/ [#]
	N	21	13	21
Serum tree mix (kUA/l)	r_s	,091	,471	**,500**
	P	,696	,104	,021
	N	21	13	21
Ratio serum IgE/albumin	r_s	-,016	-,117	-,242
	P	,950	,732	,332
	N	18	11	18
Detectable tissue IL-5	P	0.066	0.152	0.327
Detectable tissue SAE	P	0.596	0.936	0.089

[*] r_s: Spearman rank correlation coefficient

[#] Spearman correlation test could not be performed.

Appendix 12: Correlation between biomarkers measured in 2000 and the NP score at each time of contact.

		NP score		
		2000	**2006**	**2012**
Tissue IL-5 (pg/ml)	r_s*	,252	,103	,147
	P	,126	,648	,400
	N	38	22	35
Tissue IL-5Ra (pg/ml)	r_s	,214	,213	,104
	P	,198	,341	,551
	N	38	22	35
Ratio Tissue IL-5Ra/IL-5	r_s	,073	,173	,073
	P	,665	,443	,678
	N	38	22	35
Tissue TGF-B1 (pg/ml)	r_s	-,106	,053	-,039
	P	,584	,844	,850
	N	29	16	26
Tissue MPO (ng/ml)	r_s	,265	,246	,086
	P	,157	,342	,670
	N	30	17	27
Tissue IL-18 (pg/ml)	r_s	-,103	,390	,205
	P	,594	,135	,314
	N	29	16	26
Tissue ECP (µg/l)	r_s	,197	,067	,124
	P	,242	,767	,484
	N	37	22	34
Tissue albumin (g/l)	r_s	,159	-,190	-,067
	P	,354	,408	,711
	N	36	21	33
Tissue IgE (kUA/l)	r_s	,327	**,492**	,184
	P	,051	,024	,305
	N	36	21	33
Tissue grass mix (kUA/l)	r_s	**,431**	**,575**	,247
	P	,008	,005	,159
	N	37	22	34
Tissue house dust mite mix (kUA/l)	r_s	,216	,198	,232
	P	,200	,376	,186
	N	37	22	34
Tissue SAE A (kUA/l)	r_s	,203	**,556**	,265
	P	,228	,007	,130
	N	37	22	34
Tissue SAE B (kUA/l)	r_s	,198	,297	,069
	P	,239	,180	,697
	N	37	22	34
Tissue SAE C (kUA/l)	r_s	**,364**	**,472**	,184

	P	,027	,026	,298
	N	37	22	34
Tissue SAE D (kUA/l)	r_s	,309	**,474**	,063
	P	,063	,026	,721
	N	37	22	34
Tissue SAE E (kUA/l)	r_s	,223	,234	,123
	P	,185	,295	,488
	N	37	22	34
Tissue SAE TSST (kUA/l)	r_s	,169	,390	,232
	P	,316	,073	,186
	N	37	22	34
Tissue mold mix (kUA/l)	r_s	,343	**,478**	**,380**
	P	,055	,038	,042
	N	32	19	29
Tissue tree mix (kUA/l)	r_s	,161	,296	,366
	P	,387	,219	,056
	N	31	19	28
Ratio tissue IgE/albumin	r_s	,267	**,561**	,260
	P	,120	,010	,150
	N	35	20	32
IL-5 in nasal secretions (pg/ml)	r_s	,287	,118	**,377**
	P	,090	,602	,031
	N	36	22	33
IL-5Ra in nasal secretions (pg/ml)	r_s	,304	,042	,084
	P	,072	,853	,644
	N	36	22	33
Ratio IL-5Ra/IL-5 in nasal secretions	r_s	,043	-,074	-,157
	P	,804	,743	,384
	N	36	22	33
ECP in nasal secretions (µg/l)	r_s	,135	,020	,147
	P	,431	,930	,414
	N	36	22	33
IgE in nasal secretions (µg/l)	r_s	,023	,162	-,065
	P	,944	,676	,848
	N	12	9	11
sIgE(SEA,C,TSST)*factor in nasal secretions (µg/l)	r_s	,104	,492	,139
	P	,747	,179	,684
	N	12	9	11
Serum IL-5Ra (pg/ml)	r_s	,155	-,127	-,287
	P	,490	,678	,221
	N	22	13	20
Serum eosinophils count (#/µl)	r_s	,291	,333	,147
	P	,142	,225	,493
	N	27	15	24
Serum eosinophils %	r_s	,279	,265	,100
	P	,159	,341	,642

	N	27	15	24
Serum albumin (g/l)	r_s	**,589**	,399	-,066
	P	,010	,253	,809
	N	18	10	16
Serum ECP (µg/l)	r_s	,208	-,082	-,130
	P	,353	,790	,584
	N	22	13	20
Serum IgE (kUA/l)	r_s	-,036	,238	,045
	P	,873	,434	,851
	N	22	13	20
Serum grass mix (kUA/l)	r_s	,273	-,061	,078
	P	,258	,868	,766
	N	19	10	17
Serum house dust mite mix (kUA/l)	r_s	-,093	-,310	,030
	P	,705	,383	,909
	N	19	10	17
Serum SAE A (kUA/l)	r_s	-,271	,546	,381
	P	,263	,103	,132
	N	19	10	17
Serum SAE B (kUA/l)	r_s	-,069	,546	-,112
	P	,778	,103	,669
	N	19	10	17
Serum SAE C (kUA/l)	r_s	,088	/[#]	-,357
	P	,720	/[#]	,160
	N	19	10	17
Serum SAE D (kUA/l)	r_s	/[#]	/[#]	/[#]
	P	/[#]	/[#]	/[#]
	N	19	10	17
Serum SAE E (kUA/l)	r_s	-,069	,546	-,112
	P	,778	,103	,669
	N	19	10	17
Serum SAE TSST (kUA/l)	r_s	-,271	,546	,381
	P	,263	,103	,132
	N	19	10	17
Serum mold mix (kUA/l)	r_s	/[#]	/[#]	/[#]
	P	/[#]	/[#]	/[#]
	N	21	12	19
Serum tree mix (kUA/l)	r_s	-,260	,499	,370
	P	,256	,099	,119
	N	21	12	19
Ratio serum IgE/albumin	r_s	,042	,308	,027
	P	,868	,386	,922
	N	18	10	16
Detectable tissue IL-5	P	0.269	**0.695**	0.563
Detectable tissue SAE	P	0.063	0.014	0.051

[*] r_s: Spearman rank correlation coefficient

[#] Spearman correlation test could not be performed·

Appendix 13: Logistic regression between biomarkers measured in 2000 and NP recurrence during the 12-year follow-up period.

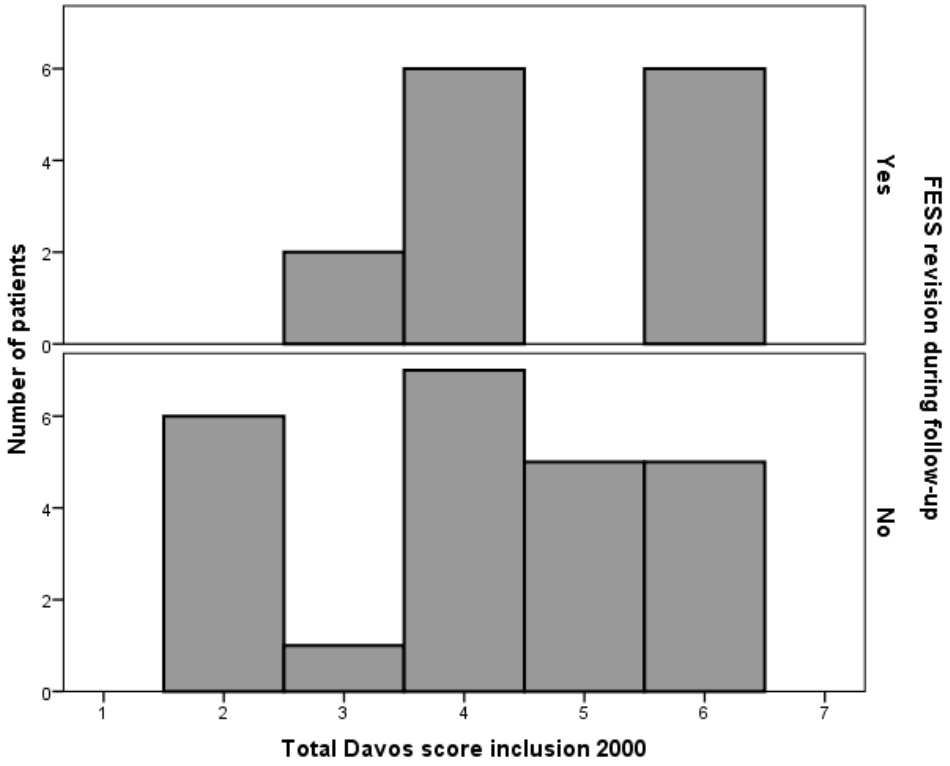
Logistic regression: Biomarkers and recurrence			
Biomarker	**OR**	**95% CI**	**P**
Tissue IL5	1,003	,998-1,008	,221
Detectable tissue IL-5	2.750	0.553-13,687	0.217
Tissue IL5Ra	1,000	1,000-1,000	,300
Ratio tissue IL5Ra.IL5	1,005	,995-1,014	,328
Tissue TGFB1	1,000	1,000-1,000	,732
Tissue MPO (ng/ml)	1,000	1,000-1,000	,263
Tissue IL-18 (pg/ml)	1,000	1,000-1,000	,249
Tissue ECP (µg/l)	1,000	1,000-1,000	,311
Tissue albumin (g/l)	,922	,772-1,100	,366
Tissue IgE (kUA/l)	1,000	,999-1,001	,614
Tissue grass mix (kUA/l)	1,048	,930-1,181	,443
Tissue house dust mite mix (kUA/l)	,993	,974-1,013	,493
Tissue SAE A (kUA/l)	,980	,725-1,324	,894
Tissue SAE B (kUA/l)	,875	,678-1,129	,303
Tissue SAE C (kUA/l)	1,000	,848-1,179	,998
Tissue SAE D (kUA/l)	,991	,663-1,481	,964
Tissue SAE E (kUA/l)	,973	,888-1,066	,560
Tissue SAE TSST (kUA/l)	,964	,894-1,040	,340
Detectable tissue SAE	1.354	0.271-6,758	0.712
Tissue mold mix (kUA/l)	1,011	,865-1,183	,887
Tissue tree mix (kUA/l)	1,016	,866-1,192	,846
Ratio Tissue IgE/albumin	1,007	,984-1,031	,563
IL-5 in nasal secretions (pg/ml)	1,006	,994-1,019	,324
IL-5Ra in nasal secretions	1,000	1,000-1,000	,502
Ratio IL-5Ra/IL-5 in nasal secretions	1,007	,989-1,024	,451
ECP in nasal secretions (µg/l)*	/	/	/
IgE in nasal secretions (µg/l)	1,000	,996-1,004	,947
sIgE(SEA,C,TSST)*factor in nasal secretions (µg/l)	,895	,676-1,186	,441
Serum IL-5Ra (pg/ml)*	/	/	/
Serum eosinophils count (#/µl)	1,001	,999-1,003	,438
Serum eosinophils %	1,054	,908-1,223	,487
Serum albumin (g/l)	1,035	,883-1,214	,668
Serum ECP (µg/l)	,997	,976-1,017	,748
Serum IgE (kUA/l)	,997	,994-1,000	,065
Serum grass mix (kUA/l)	1,614	,415-6,281	,490

Serum house dust mite mix (kUA/l)	,847	,669-1,072	,166
Serum SAE A (kUA/l)*	/	/	/
Serum SAE B (kUA/l)	,023	,000-27,963	,298
Serum SAE C (kUA/l)*	/	/	/
Serum SAE D (kUA/l)*	/	/	/
Serum SAE E (kUA/l)	,017	,000-3,299	,130
Serum SAE TSST (kUA/l)*	/	/	/
Serum tree mix (kUA/l)*	/	/	/
Ratio serum IgE/albumin	,826	,658-1,038	,101

* Logistic regression could not be performed, because of a significant Hosmer-Lemeshow test.

Appendix 14: Distribution of NP score in patients with and without revision FESS.

NP score could not be included in logistic regression processing because of a significant Hosmer-Lemeshow test (P = 0.035). The distribution of NP score in patients with and without revision FESS is shown in the histogram below.



Appendix 15: Logistic regression between biomarkers measured in 2000 and revision surgery during the 12-year follow-up period.

Logistic regression: Biomarkers and revision surgery			
Biomarker	**OR**	**95% CI**	**P**
Tissue IL5	**1,004**	1,001-1,008	,021
Detectable tissue IL-5	2,200	,481-10,066	,310
Tissue IL5Ra	1,000	1,000-1,000	,651
Ratio tissue IL5Ra.IL5	,999	,996-1,002	,551
Tissue TGFB1	1,000	1,000-1,000	,958
Tissue MPO (ng/ml)	1,000	1,000-1,000	,326
Tissue IL-18 (pg/ml)*	/	/	/
Tissue ECP (µg/l)	1,000	1,000-1,000	,931
Tissue albumin (g/l)	1,041	,896-1,211	,599
Tissue IgE (kUA/l)	1,000	,999-1,001	,677
Tissue grass mix (kUA/l)	1,007	,960-1,057	,775
Tissue house dust mite mix (kUA/l)	1,009	,989-1,029	,385
Tissue SAE A (kUA/l)	1,144	,882-1,484	,310
Tissue SAE B (kUA/l)	1,101	,862-1,406	,443
Tissue SAE C (kUA/l)	1,071	,923-1,243	,364
Tissue SAE D (kUA/l)	1,098	,783-1,541	,587
Tissue SAE E (kUA/l)	1,049	,950-1,158	,345
Tissue SAE TSST (kUA/l)	1,026	,952-1,105	,503
Detectable tissue SAE	3,200	,787-13,017	,104
Tissue mold mix (kUA/l)	1,028	,890-1,188	,703
Tissue tree mix (kUA/l)	1,093	,941-1,270	,243
Ratio Tissue IgE/albumin	1,003	,989-1,018	,687
IL-5 in nasal secretions (pg/ml)	1,005	,998-1,013	,172
IL-5Ra in nasal secretions	1,000	1,000-1,000	,733
Ratio IL-5Ra/IL-5 in nasal secretions	1,001	,996-1,006	,750
ECP in nasal secretions (µg/l)	1,000	1,000-1,000	,744
IgE in nasal secretions (µg/l)	1,000	,997-1,003	,928
sIgE(SEA,C,TSST)*factor in nasal secretions (µg/l)	1,052	,809-1,368	,703
Serum IL-5Ra (pg/ml)	,997	,993-1,002	,249
Serum eosinophils count (#/µl)	1,000	,999-1,001	,735
Serum eosinophils %	1,007	,892-1,136	,914
Serum albumin (g/l)	1,043	,902-1,206	,571
Serum ECP (µg/l)	,948	,862-1,042	,268
Serum IgE (kUA/l)	1,000	,997-1,003	,860
Serum grass mix (kUA/l)	,873	,325-2,347	,788

Serum house dust mite mix (kUA/l)	,980	,822-1,168	,823
Serum SAE A (kUA/l)*	/	/	1,000
Serum SAE B (kUA/l)	,848	,063-11,489	,901
Serum SAE C (kUA/l)*	/	/	,999
Serum SAE D (kUA/l)*	/	/	
Serum SAE E (kUA/l)	1,873	,031-113,499	,764
Serum SAE TSST (kUA/l)*	/	/	1,000
Serum tree mix (kUA/l)*	/	/	,998
Ratio serum IgE/albumin	,937	,752-1,167	,559

* Logistic regression could not be performed, because of a significant Hosmer-Lemeshow test.