Incidence Of Atrophic Rhinitis After Endoscopic Sinonasal Surgery: A Retrospective Review

by

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DECLARATION

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LIST OF ABBREVIATIONS

AR	Atrophic Rhinitis
PAR	Primary Atrophic Rhinitis
SAR	Secondary Atrophic Rhinitis
IT	Inferior Turbinate
MT	Middle Turbinate
MM	Medial Maxillectomy
RR	Relative Risk
CI	95% Confidence Interval
IP	Incidence Proportion

ABSTRACT

INCIDENCE OF ATROPHIC RHINITIS AFTER ENDOSCOPIC SINONASAL SURGERY: A RETROSPECTIVE REVIEW

BACKGROUND:

Sinonasal tumours have been resected endoscopically at Groote Schuur Hospital Cape Town South Africa since 2003. Surgery, although seen as minimally invasive because no external incisions are visible, is often very aggressive and destructive to the nasal structures. The removal of the nasal turbinates has always been seen as sacrilege due to the risk of developing atrophic rhinitis. If the theory regarding developing atrophic rhinitis after a simple turbinectomy stands true, one would expect a high incidence of atrophic rhinitis after radical resection of the sinonasal structures. This has not been our experience.

METHODS:

The study population includes a retrospective case review of all patients that had endoscopic sinonasal tumour resection by the same surgeon between 2006 and 2010. All patients were assessed for symptoms and signs suggestive of atrophic rhinitis up to two years post resection.

RESULTS:

51 patients (34M: 17F) were included in the study. Patients with residual or recurrent tumour (n=19) and patients who had received adjuvant radiotherapy (n=17) had a statistically significant chance of developing symptoms and signs suggestive of atrophic rhinitis over time. Variables such as age, gender, extent of surgery, bilateral disease, benign or malignant tumour, were not statistically significant in the development of symptoms and signs suggestive of atrophic rhinitis over time.

CONCLUSIONS:

Atrophic rhinitis is not more common in patients who undergo endoscopic sinonasal surgery without adjuvant therapy. However, patients with residual tumour (after debulking surgery) or recurrent tumour and those who had received adjuvant radiotherapy had a statistically significant chance of developing symptoms and signs suggestive of atrophic rhinitis over time.

Keywords: atrophic rhinitis, endoscopic resection, turbinectomy, medial maxillectomy, sinonasal tumours.

PART A: PROTOCOL

INCIDENCE OF ATROPHIC RHINITIS AFTER ENDOSCOPIC SINONASAL SURGERY: A RETROSPECTIVE REVIEW

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BACKGROUND

Atrophic Rhinitis (AR) is a chronic debilitating disease of the nasal passages that is characterized by progressive atrophy of the nasal mucosa, nasal crusting, fetor (foul smelling nasal discharge) and enlargement of the nasal space with paradoxical subjective nasal congestion. Patients with AR may also complain of a disordered sense of smell, but complete anosmia is rare until late in the disease process.[1] Much confusion exists in the literature regarding the diagnosis, aetiologic factors, and treatment of AR. Different terminologies have been used interchangeably in the literature (atrophic rhinitis, rhinitis sicca/dry nose, ozaena and even empty nose syndrome[2, 3]) and this has made investigation of the causes and treatment of the condition difficult.

Since the middle of the century, various authors have divided AR into two separate entities. Primary atrophic rhinitis (PAR) is of spontaneous onset, progresses slowly and has an unspecified aetiology. Secondary atrophic rhinitis (SAR) develops after chronic rhinosinusitis, chronic granulomatous disease, excessively aggressive surgery in inflammatory/infectious nasal and sinus surgery, nasal trauma or irradiation. PAR may represent early ozaena before the submucosal destructive processes brought on by inheritable or infections causes have progressed to their end state.[4] SAR is much more commonly encountered, although it is no more completely understood. Characteristic findings in both forms include nasal crusting, enlarged nasal cavities, resorption of the turbinates, mucosal atrophy, and paradoxical nasal congestion.[5] The distinction between the two diseases lie in the aetiology. Frequent attention is given to SAR because of numerous debates that have addressed the association between atrophic rhinitis and modified or total reductive turbinate surgery.[6-15] If the theory regarding developing atrophic rhinitis after turbinectomy stands true, one would expect all patients undergoing radical resection of the nasal structures to develop atrophic rhinitis. This has not been the case in our experience.

PURPOSE OF THE STUDY

We hypothesise that atrophic rhinitis is not common after extensive endoscopic sinonasal surgery. The primary aim of the study is to determine the incidence of developing signs and symptoms suggestive of atrophic rhinitis after endoscopic sinonasal surgery. We challenge the current literature that suggest a simple turbinectomy can lead to atrophic rhinitis and postulate that an underlying systemic disorder or other mechanism is required to develop this condition.

METHODOLOGY

STUDY DESIGN

A retrospective case review includes all patients who had sinonasal tumours endoscopically resected by the same surgeon from 2006 – 2010 at Groote Schuur Hospital, Cape Town South Africa. All patients included in the study were given standard post-operative instructions and were followed up for at least two years after surgery. They were assessed for symptoms and signs suggestive of atrophic rhinitis at each visit.

The same surgeon assessed all patients pre-operatively. A thorough history and examination, including nasendoscopy was performed prior to each surgery. Special investigations included a histological diagnosis and imaging (CT and/or MRI scans of the sinuses). Tumour location and extent of surgery was documented and patients followed up as per routine. All patients were given instructions on post-operative care in terms of nasal douching and nasal hygiene. Post-operative follow-up was done at the following intervals: 2 weeks, 6 weeks, 3 months, 6 months , 12 months, 18 months and 24 months or sooner at the discretion of the surgeon. At each visit the patient was assessed for symptoms and signs suggestive of atrophic rhinitis.

CHARACTERISTICS OF THE STUDY POPULATION

All adult patients at Groote Schuur hospital who were assessed and diagnosed with a sinonasal tumour (benign or malignant) and proceeded to have an endoscopic excision (curative or palliative) by the same surgeon, were included in the study. A time frame between 2006 and 2010 was chosen, allowing for a minimum 2 - year follow-up. The study is aimed at recording symptoms and signs suggestive of atrophic rhinitis and to assess the presence / absence of a 'cause – effect' relationship.

RESEARCH PROCEDURES AND DATA COLLECTION METHODS

The primary investigator will record data in relation to certain patient demographics, type and extent of tumour, procedure performed and follow-up symptoms and signs at the post-operative visits.

Post-operative care is performed according to standard existing management protocols which includes nasal douching and nasal hygiene. Follow-up is performed at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months. At each visit the patient will be assessed for symptoms and signs suggestive of atrophic rhinitis.

DATA SAFETY AND MONITORING

The primary investigator will act as study co-ordinator and will be responsible for the safety of the collected data.

DATA ANALYSIS

Statistical data analysis will be performed using a statistical program and interpreted with the help of a statistician to evaluate our hypothesis.

RESULTS / OUTCOME MEASURES

The incidence of atrophic rhinitis in post-operative patients will be assessed. Patient demographics and other factors which may influence the development of the disease process will be looked at. Post- operative follow up of at least 2 years will be looked at.

PROJECTED COSTS

None

RISKS TO PATIENT

None

PRIVACY AND CONFIDENTIALITY

The primary investigator will act as study coordinator and will be responsible for the safety of the collected data. Data collected and recorded on data sheets will be recorded electronically using Microsoft Excel. All materials will be kept in a locked room within the ENT ward. A hospital number will be recorded as a patient identifier within the raw data in order to permit verification of information at later stages during analysis.

Patient-specific information will neither be required nor included during data analysis.

WHAT HAPPENS AT THE END OF THE STUDY?

Should the hypothesis be proven, the investigators plan to submit findings of the study to an international scientific journal for publication.

No proprietary interests to declare.

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PART B: STRUCTURED LITERATURE REVIEW

INCIDENCE OF ATROPHIC RHINITIS AFTER ENDOSCOPIC SINONASAL TUMOUR RESECTION

Introduction

Over the past decade, there has been a natural evolution in the capabilities of endoscopic sinus surgeons. Advances in endoscopic instrumentation, the availability of intraoperative imaging and increased experience with endoscopic repair of even large skull base defects, have led to a shift from open surgery to the endoscopic resection of advanced sinonasal tumours. Many endoscopic surgeons have continued to fine-tune their skills and improve their knowledge of the complex orbital and skull base anatomy. Initially advocated for obstructive inflammatory disease, endoscopic approaches are now being used increasingly for the definitive treatment of nasal and paranasal sinus tumours, previously resected through more traditional (transfacial or craniofacial) approaches. Endoscopic management of benign and malignant lesions, reflects a fundamental change from the more traditional therapeutic concepts and modalities.[1-3]

Sinonasal tumours have been resected endoscopically at Groote Schuur Hospital in Cape Town since 2003. Almost all benign and intermediate tumours are removed endoscopically as well as malignant tumours amenable to this minimally invasive surgical approach. Surgery, although seen as minimally invasive because no external incisions are visible, is often very aggressive and destructive to the nasal structures. Current literature suggests that one of the causes of secondary atrophic rhinitis is overaggressive nasal surgery, particularly turbinate surgery.[6-9] If the theory regarding developing atrophic rhinitis after a simple turbinectomy stands true, one would expect all patients undergoing radical resection of the nasal structures to develop atrophic rhinitis.

Objectives and Search Strategy

The objective of the literature review is firstly to review the existing evidence relating to the aetiology of atrophic rhinitis and more specifically the role of nasal surgery, particularly endoscopic nasal surgery and the development of atrophic rhinitis. Existing levels of evidence and research methods employed will also be examined. Deficiencies in current published knowledge and scope for further research will be identified.

A systematic search for relevant literature, not restricted to English literature only, was conducted using Medline® and PubMed® systems. The following key words were used: endoscopic nasal resection, endoscopic medial maxillectomy, atrophic rhinitis, complications of turbinate surgery. No relevant review was found in the Cochrane database, and to our knowledge, no studies published on the development of atrophic rhinitis after endoscopic sinonasal tumour resection.

Studies have examined the likely aetiology and diagnosis of secondary atrophic rhinitis (SAR). The largest study to date by Moore and colleagues (Mayo Clinic Otorhinolaryngology) published in 2001, identified 242 cases of atrophic rhinitis of which 197 cases were SAR. According to this study, 24%(47) were due to complete removal of the lower and middle turbinates, 56%(110) were due to partial removal of the lower and/or middle nasal turbinates, 10%(20) to endonasal sinus surgery without turbinectomy, 6%(12) tumour removal with partial maxillectomy, 2%(4) due to sinonasal irradiation and 2%(4) due to nasal trauma/granulomatous disease.[4]

Some of the older studies done between 1987 – 1999, have authors reporting 15 – 89% of their own patients experiencing post – operative atrophic rhinitis symptoms after nasal tissue removal particularly in the form of turbinectomy. A retrospective study by Moore and colleagues published in 1985 (University of Nabraska) identified 18 patients who had undergone total inferior turbinectomies for nasal obstruction (1977 – 1982). They were followed up for 3 to 5 years and 16 of 18(89%) developed symptoms and signs of atrophic rhinitis.[5]

Warwick – Brown and colleagues published another retrospective study in 1987 where 24 out of 207 patients with nasal obstruction were found to have undergone partial inferior turbinectomy (Royal Berkshire Hospital, Reading UK). Follow up period was 16 years and 18 of 24(75%) developed atrophic rhinitis.[6] In 1993 a publication by Salam and colleagues (Hull Royal Infirmary, Hull) showed in a prospective trial of 25 patients, that total inferior turbinectomy resulted in 4 of 25(16%) developing atrophic rhinitis after a 6 month follow up period.[7] Another prospective trial published in 1995 by Oburra (Aga Khan Hospital, Nairobi) revealed 5 of 34(15%) patients who had bilateral total inferior turbinectomies developed atrophic rhinitis.[8] The follow up period was not stated in this study. One further prospective study published in 1999 by Passali and colleagues (Siena Medical School, Siena, Italy) confirmed atrophic rhinitis in 10 of 45(22%) patients who had undergone total inferior turbinectomy and followed up for 4 years.[9]

Other authors report that they have never encountered a case of atrophic rhinitis after total removal of the inferior turbinates. Martinez and colleagues (Nebraska University – Otorhinolaryngology), in 1983, found 29 patients who underwent total inferior turbinectomy for nasal obstruction. This was a prospective study and patients were followed for 2 – 60 months.[10] Only 1 patient developed excessive dryness but no atrophy. Odetoyinbo in 1987 (Department of Surgery – Nigeria) reported that none of their 39 patients who underwent total inferior turbinectomy had developed atrophic rhinitis after a 2 year follow up. This too was a prospective study.[11] A retrospective study done by Courtiss and colleagues, (Division of Plastic surgery, Harvard Medical School) published in 1989, showed a 10-year follow up of patients who had total inferior turbinectomy with none developing symptoms of atrophic rhinitis.[12] This study involved 25 patients age range from 24 to 74 years (mean 39 years). A retrospective study published in 1989 by Ophir, (Kaplan Hospital – Israel) showed 38 patients who also underwent total inferior turbinectomy for nasal obstruction. There were no signs or symptoms of atrophic rhinitis postoperatively and the follow up was from 1 to 7 years.[13]

The first prospective study involving resection of the middle turbinate for nasal obstruction was published in 1995 by Cook and colleagues (University of Missouri School of Medicine). This study looked at the effect of partial middle turbinectomy on nasal airflow and resistance. Thirty-one patients were included in the study and were followed up for 3 to 10 months post – operatively. No patients developed atrophic rhinitis and nasal function was enhanced.[14] In 2000 Talmon and collegues (Western Gallilee Hospital – Israel) reported on 357 patients who underwent total inferior turbinectomy. This was a prospective study and patients were followed up for 6 years. No patient developed atrophic rhinitis.[15] They also commented that even though the climate was hot, dry and dusty, no patients developed excessive dryness or atrophy.

Searching for studies reporting atrophic rhinitis as a result of endoscopic sinonasal tumour surgery, delivered no results. There are reports on the endoscopic management of sinonasal inverted papillomas but no studies mention atrophic rhinitis as a complication of the surgery. The studies were mainly concerned with tumour recurrence rates.[3]

Two studies published in 2005 and 2008 respectively, compared endoscopic and open approaches for sinonasal tumour (benign and malignant) resection. Again no mention is made of atrophic rhinitis as a postoperative complication, with the main focus again being recurrence rates.[1, 2]

Published literature evaluating the cause – effect relationship of atrophic rhinitis as a result of nasal surgery is not clear. Also the incidence of atrophic rhinitis after endoscopic sinonasal tumour resection cannot be identified by an extensive literature review. This represents a significant gap both in the existing literature and in evidenced-based practice.

To summarize, the literature is not clear with regards to nasal surgery as a possible causative factor in the development of atrophic rhinitis. No reports could be found on atrophic rhinitis as a result of endoscopic sinonasal tumour resection. This generates an interesting research question. Would the endoscopic resection of tumours lead to the development of atrophic rhinitis in patients where the normal nasal structures (such as the turbinates and septum) have been sacrificed?

The aim of the study is to review all our endoscopic sinonasal tumour resection cases done at Groote Schuur hospital, Cape Town South Africa, by the same surgeon between 2006-2010 and assess the incidence of atrophic rhinitis as a consequence/complication of this surgery.

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PART C: PUBLICATION-READY MANUSCRIPT

INCIDENCE OF ATROPHIC RHINITIS AFTER ENDOSCOPIC SINONASAL SURGERY: A RETROSPECTIVE REVIEW

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Keywords
Atrophic rhinitis, endoscopic resection, sinonasal tumours, medial maxillectomy, turbinectomy

STRUCTURED ABSTRACT

BACKGROUND:

Sinonasal tumours have been resected endoscopically at Groote Schuur Hospital in Cape Town South Africa since 2003. Surgery, although seen as minimally invasive because no external incisions are visible, is often very aggressive and destructive to the nasal structures. The removal of nasal turbinates have always been seen as sacrilege due to the risk of developing atrophic rhinitis. If the theory regarding developing atrophic rhinitis after a simple turbinectomy stands true, one would expect all patients undergoing radical resection of the nasal structures to develop atrophic rhinitis. This has not been our experience.

METHODS:

This restrospective case review includes all patients with both benign and malignant sinonasal tumours that have been endoscopically resected by the same surgeon from 2006 – 2010 at Groote Schuur Hospital, Cape Town South Africa. We recorded the incidence of post – operative atrophic rhinitis over a 2-year follow-up period.

RESULTS:

51 patients (34M: 17F) were included in the study. Patients with residual or recurrent tumour (n=19) and patients who had received adjuvant radiotherapy (n=17) had a statistically significant chance of developing symptoms and signs suggestive of atrophic rhinitis over time. Variables such as age, gender, extent of surgery, bilateral disease, benign/malignant tumour were not statistically significant in the development of symptoms and signs suggestive of atrophic rhinitis over time.

CONCLUSIONS:

In our series, atrophic rhinitis is not more common in patients who have had extensive endoscopic sinonasal tumour resection (with curative intent) without adjuvant radiotherapy. Factors that did influence the development of atrophic rhinitis were residual/recurrent disease and adjuvant radiotherapy.

INTRODUCTION

Atrophic Rhinitis (AR) is a chronic debilitating disease of the nasal passages that is characterized by progressive atrophy of the nasal mucosa, nasal crusting, fetor (foul smelling nasal discharge) and enlargement of the nasal space with paradoxical subjective nasal congestion. Patients with AR may also complain of a disordered sense of smell, but complete anosmia is rare until late in the disease process.[1] Much confusion exists in the literature regarding the diagnosis, aetiologic factors, and treatment of AR. Different terminologies have been used interchangeably in the literature (atrophic rhinitis, rhinitis sicca/dry nose, ozaena and even empty nose syndrome[2, 3]) and this has made investigation of the causes and treatment of the condition difficult.

Since the middle of the century, various authors have divided AR into two separate entities. Primary atrophic rhinitis (PAR) is of spontaneous onset, progresses slowly and has an unspecified aetiology. Secondary atrophic rhinitis (SAR) develops after chronic rhinosinusitis, chronic granulomatous disease, excessively aggressive surgery in inflammatory/infectious nasal and sinus surgery, nasal trauma or irradiation. PAR may represent early ozaena before the submucosal destructive processes brought on by inheritable or infections causes have progressed to their end state.[4] SAR is much more commonly encountered, although it is no more completely understood. Characteristic findings in both forms include nasal crusting, enlarged nasal cavities, resorption of the turbinates, mucosal atrophy, and paradoxical nasal congestion.[5] The distinction between the two diseases lie in the aetiology. Frequent attention is given to SAR because of numerous debates that have addressed the association between atrophic rhinitis and modified or total reductive turbinate surgery.[6-15] If the theory regarding developing atrophic rhinitis after turbinectomy stands true, one would expect all patients undergoing radical resection of the nasal structures to develop atrophic rhinitis. This has not been the case in our experience.

MATERIALS AND METHODS

Study population

All patients with sinonasal tumours (benign or malignant) who had endoscopic resection by the same surgeon at Groote Schuur Hospital, over a five year period (2006-2010) were eligible for inclusion. The patients required follow-up for at least two years post op.

Study Design

A retrospective case review includes all patients who had sinonasal tumours endoscopically resected by the same surgeon from 2006 – 2010 at Groote Schuur Hospital, Cape Town South Africa. All patients included in the study were given standard post-operative instructions and were followed up for at least two years after surgery. They were assessed for symptoms and signs suggestive of atrophic rhinitis at each visit.

The same surgeon assessed all patients pre-operatively. A thorough history and examination, including nasendoscopy was performed prior to each surgery. Special investigations included a histological diagnosis and imaging (CT and/or MRI scans of the sinuses). Tumour location and extent of surgery was documented and patients followed up as per routine. All patients were given instructions on post-operative care in terms of nasal douching and nasal hygiene. Post-operative follow-up was done at the following intervals: 2 weeks, 6 weeks, 3 months, 6 months , 12 months, 18 months and 24 months or sooner at the discretion of the surgeon. At each visit the patient was assessed for symptoms and signs suggestive of atrophic rhinitis.

Statistical analysis

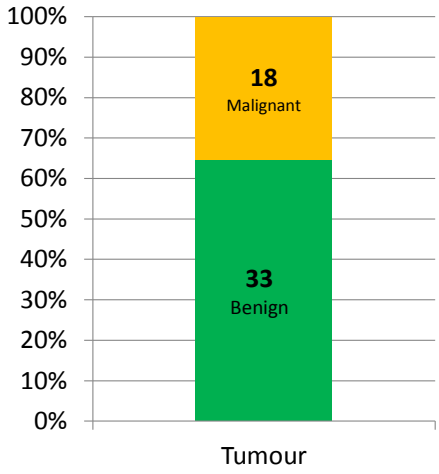
Incidence proportions, mean and median values were calculated for all patient characteristics, as appropriate. Relative ratios, p-values and 95% confidence intervals were used to estimate the relative risk of developing the outcome of interest with respect to various categorical predictors by generalized linear regression models at time 12 weeks. The statistical significance of the association between outcome and exposure over the 7 time periods was assessed by the xtreg (cross-sectional time dependent regression) procedure. Stata 12 software, StataCorp, College Station, Texas, USA was used to carry out all analyses and results interpreted with the help of a statistician.

The University of Cape Town Human Research Ethics Committee as well as the Department of Research Council approved this study.

RESULTS

A total of 51 patients (34 male and 17 female) had sinonasal tumours endoscopically excised by the same surgeon at our institution from 2006 – 2010 and met our inclusion criteria. There were 18 patients with malignant lesions and 33 patients with benign lesions (Figure 1). Mean patient age was 51.1 years (range 13-78 years); this was normally distributed.

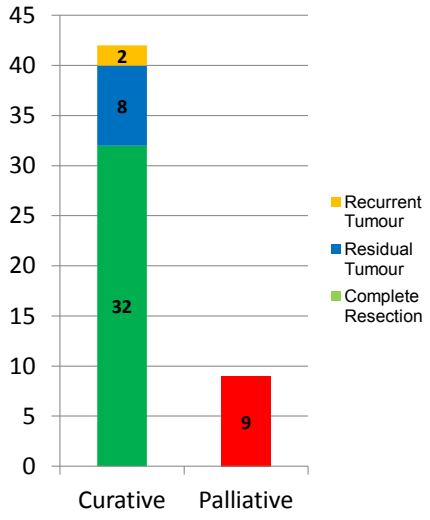
Figure 1 :
Benign and Malignant Tumours (n= 51)



N	Tumour
5	Squamous Cell Ca
3	Adenoid Cystic Ca
3	Sinonasal Melanomas
2	Esthesioneuroblastoma
2	Neuroendocrine Ca
1	Chondrosarcoma
1	Sinonasal Adeno Ca
1	Sinonasal Carcinoid
22	Inverted Papilloma
3	Ossifying Fibroma
2	Benign Nasal Mass
2	Hemangiopericytoma
1	Fibrous Dysplasia
1	Meningioma
1	Osteoclastoma
1	Schwannoma

In our series, 42 patients were planned to have curative surgery and 9 patients had extensive tumours planned for palliative debulking and adjuvant treatment (Figure 2).

Figure 2 :
Curative Surgery (n=42)
Palliative Debulking (n=9)
2 years Post Op



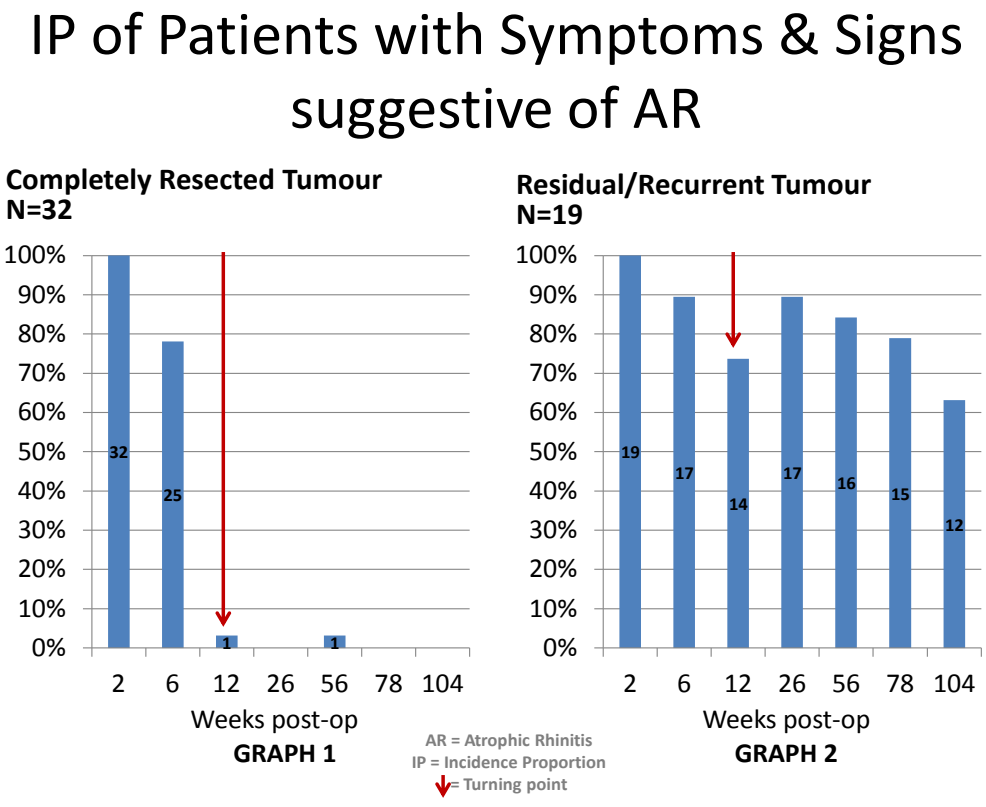
N	Tumour
2	Squamous Cell Ca
1	Adenoid Cystic Ca
1	Esthesioneuroblastoma
1	Hemangiopericytoma
1	Meningioma
1	Ossifying Fibroma
1	Osteoclastoma
1	Schwannoma
2	Inverted Papilloma
2	Squamous Cell Ca
2	Sinonasal Melanoma
1	Adenoid Cystic Ca
1	Esthesioneuroblastoma
1	Ossifying Fibroma
1	Sinonasal Adeno Ca
20	Inverted Papilloma
2	Benign Nasal Mass
2	Neuroendocrine Ca
1	Adenoid Cystic Ca
1	Chondrosarcoma
1	Fibrous Dysplasia
1	Hemangiopericytoma
1	Ossifying Fibroma
1	Sinonasal Carcinoid
1	Sinonasal Melanoma
1	Squamous Cell Ca

Patients reporting symptoms of nasal obstruction and nasal discharge together with clinical findings of nasal discharge/excessive crusting and a wide nasal cavity were used as criteria to label patients as having atrophic rhinitis. Biopsies of suspicious areas were taken and sent for microbiology and histopathological examination. No swabs were taken and the only medical treatment throughout the course was normal saline nasal douches and nasal hygiene. Potential recall bias was minimal as the symptoms patients' reported and clinical signs seen by the same clinician were documented in the notes.

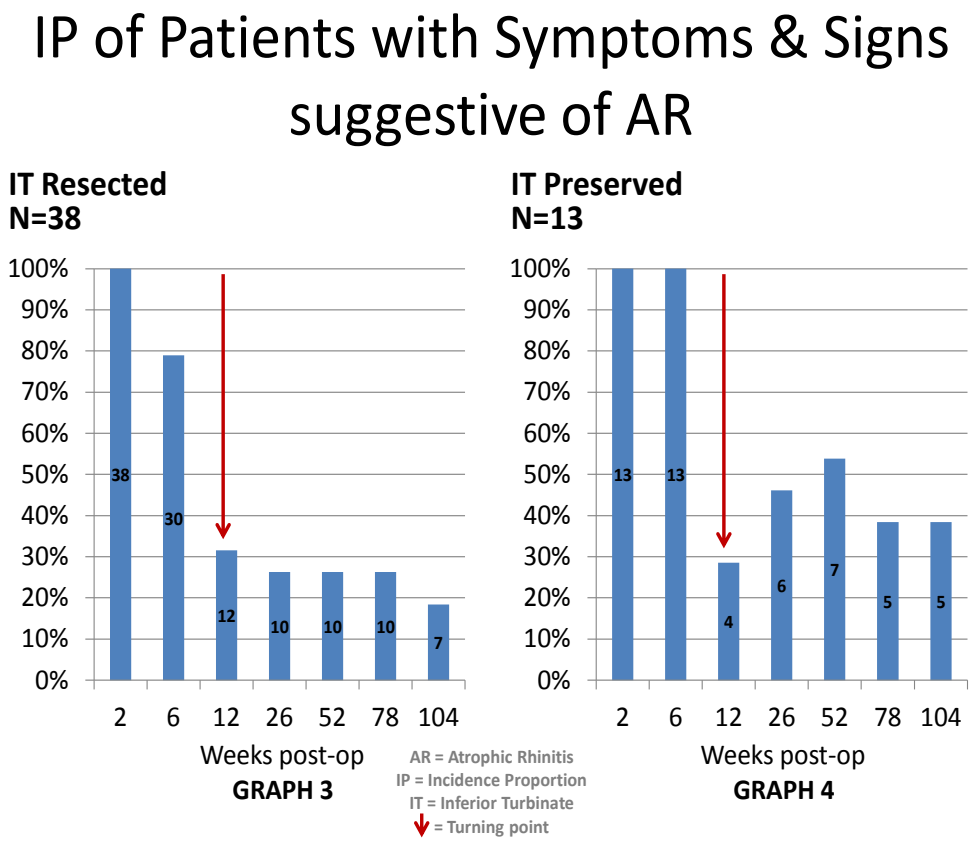
It was evident that after the initial post - operative follow up, all patients reported symptoms of nasal obstruction and nasal discharge. There were also clinical signs of nasal discharge and crusting which were suggestive of atrophic rhinitis. These findings were also evident in the majority of patients at the 6 week follow up despite proper nasal hygiene.

However, we noticed a significant change in symptoms and signs at a turning point of 12 weeks (3 months) post – operatively, when taking certain variables into account. This is possibly due to the time taken for appropriate re-epithelialisation, but further studies need to be done to evaluate and verify this.

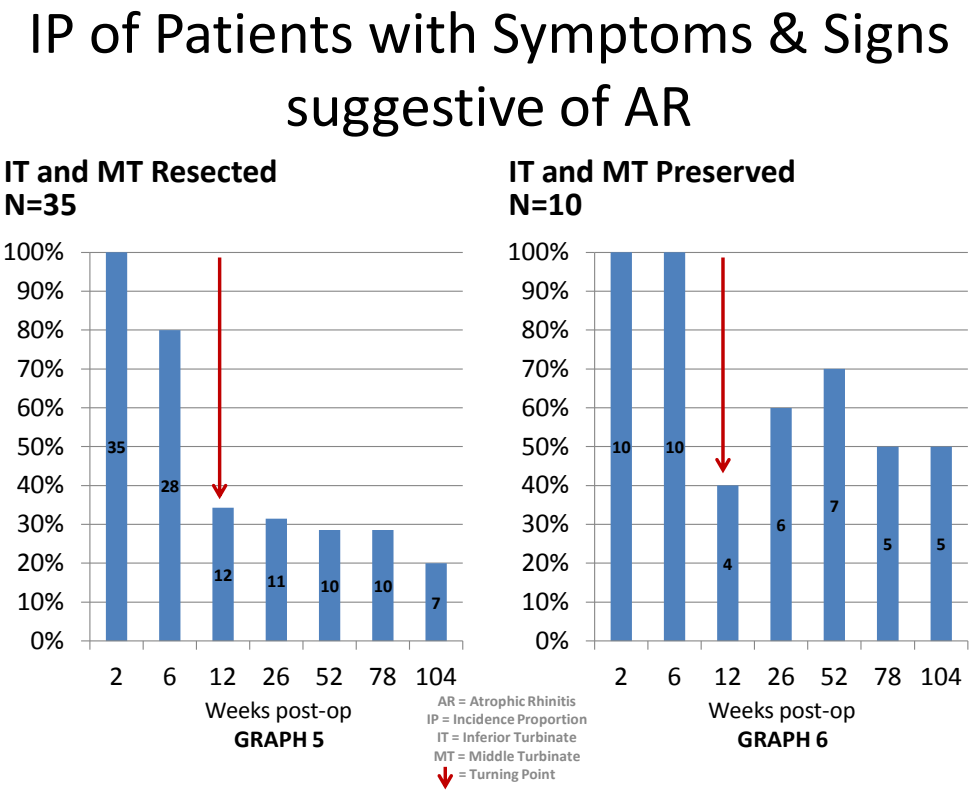
The most striking difference would be the patients who had residual/recurrent sinonasal tumour (n=19) compared with those patients who had tumour completely resected (n=32). The incidence proportion (IP) for developing symptoms and signs suggestive of atrophic rhinitis in those with residual/recurrent tumour relative to those with complete resection of tumour at the turning point of 12 weeks was 78.9% and 3.1% respectively. This results in a relative risk (RR) of 25.3, 95 % confidence interval (CI) of 3.7 – 179.6 at week 12. Comparing the IPs over time in these two groups resulted in an overall p-value < 0.001 suggesting that patients with residual/recurrent tumour develop symptoms and signs suggestive of atrophic rhinitis over time relative to those in whom the tumour was completely excised (Comparative Graphs 1 & 2/Table 1).



We investigated patients who had the inferior turbinate (IT) resected during surgery (n=38) and compared them to patients who had their IT preserved (n=13). The IP for developing symptoms and signs of atrophic rhinitis in those who had the IT resected relative to those who had the IT preserved at turning point 12 weeks was 31.6% and 30.8% respectively. This results in a RR of 1.0, 95 % CI 0.4 – 2.63 at week 12. Comparing the IPs over time in these 2 groups resulted in an overall p-value = 0.96 which is not statistically significant. Thus resecting the IT was not a factor in the development of atrophic rhinitis over time (Comparative Graphs 3 & 4/Table 1).



We also looked at the patients who had both inferior turbinate (IT) and middle turbinate (MT) resected (n=35) and compared them to patients who had the IT an MT preserved (n=10). The IP for developing symptoms and signs suggestive of atrophic rhinitis in those who had both IT and MT resected relative to those who had the IT and MT preserved at the turning point of 12 weeks was 34.3% and 40.0% respectively. This results in a RR of 0.9, 95% CI of 0.5 – 3.6 at week 12. Comparing the IPs over time in these 2 groups resulted in an overall p-value = 0.75 which is not statistically significant. Thus resecting the IT and MT did not influence the development of atrophic rhinitis over time (Comparative Graphs 5 & 6/Table 1).



A significant variable found was with patients who received adjuvant radiotherapy (n=17). We compared these patients with those who did not receive adjuvant radiotherapy (n=34). The IP for developing symptoms and signs suggestive of atrophic rhinitis in those who had adjuvant radiotherapy relative to those we did not receive adjuvant radiotherapy at the turning point of 12 weeks was 47.1% and 23.5% respectively. This results in a RR of 2.0, 95% CI 0.9 – 4.4 at week 12. This seems not to be statistically significant at this point, but comparing the IPs over time in these two groups resulted in an overall p-value < 0.001 suggesting that patients who received adjuvant radiotherapy develop symptoms and signs suggestive of atrophic rhinitis over time relative to those who did not receive adjuvant radiotherapy. This is possibly due to the long term side effects radiotherapy has on tissues and bone resulting in mucosal damage, destruction of ciliary function, longstanding mucositis and radiogenic osteitis of the underlying bony structures. Again, further studies are needed to evaluate this. (Comparative Graphs 7 & 8/Table 1).

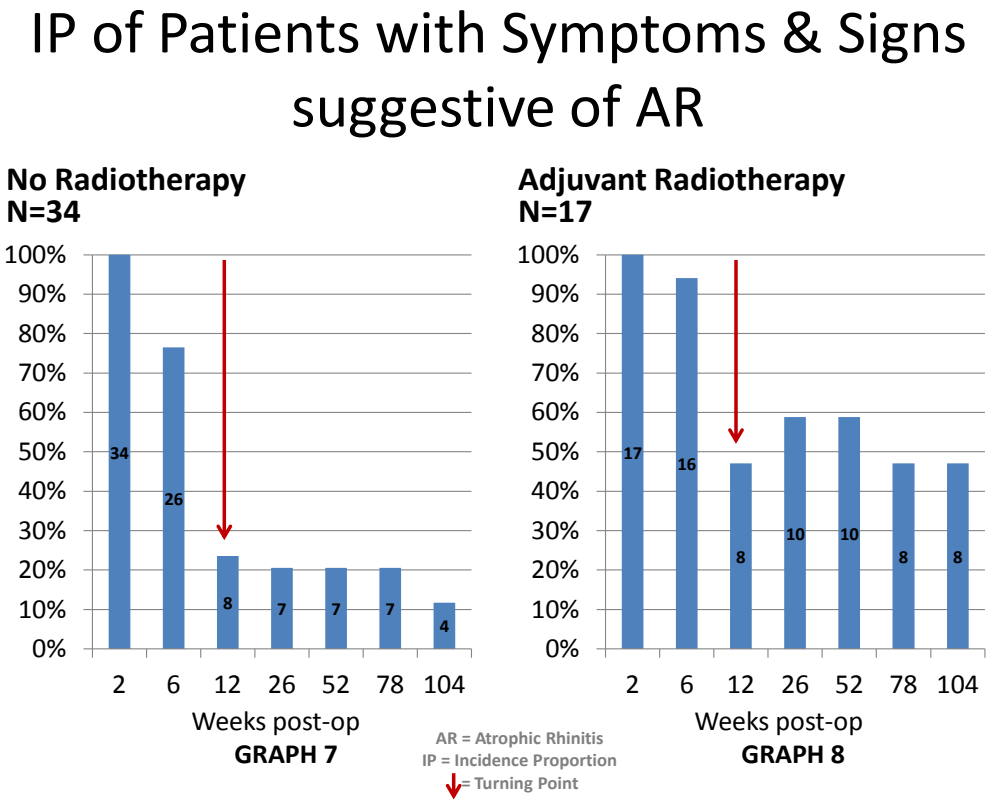


Table 1: Evaluation of relative risk of atrophic rhinitis (12 weeks post – op) and overall p-values

Variable		N	% AR at 12 weeks	Risk ratio (95% CI) at 12 weeks	Overall p-value for IP over the 7 time periods
Tumour	Complete excision	32	3.1	**1.0** (ref)	
	Residual/Recurrent disease	19	78.9	**25.3** (3.6 – 176.3)	<0.001
IT	Preserved	13	30.8	**1.0** (ref)	
	Resected	38	31.6	**1.0** (0.4 – 2.63)	=0.96
IT & MT	Preserved	10	40.0	**1.0** (ref)	
	Resected	35	34.3	**0.9** (0.5 – 3.6)	=0.75
Adjuvant Radiotherapy	Yes	34	23.5	**1.0** (ref)	
	No	17	47.1	**2.0** (0.8 – 4.4)	<0.001

Abbreviations: IT, inferior turbinate; MT, middle turbinate; AR, atrophic rhinitis; IP, incidence proportion

Variables such as age, gender, bilateral disease and whether tumour was benign or malignant or extent of surgery was not statistically significant in the development of atrophic rhinitis over time.

DISCUSSION

Over the past decade, there has been a natural evolution in the capabilities of endoscopic sinus surgeons. Advances in endoscopic instrumentation, along with intraoperative imaging, and increased experience with endoscopic repair of even large skull base defects, have opened up new and exciting possibilities. At the same time, many endoscopic surgeons have continued to fine-tune their skills and improve their knowledge of the complex orbital and skull base anatomy. Initially advocated for obstructive inflammatory disease, endoscopic approaches are now being used increasingly for the definitive treatment of nasal and paranasal sinus tumours, previously resected through more traditional (transfacial or craniofacial) approaches. Endoscopic management of benign lesions and even some malignant lesions, reflects a fundamental change from the more traditional therapeutic concepts and modalities.[1-3]

Sinonasal tumours have been resected endoscopically at Groote Schuur Hospital in Cape Town South Africa since 2003. Almost all benign and intermediate tumours are removed endoscopically as well as malignant tumours amenable to this minimally invasive surgical approach. Surgery, although seen as minimally invasive because no external incisions are visible, is often very aggressive and destructive to the nasal structures.

Current literature suggests that one of the causes of secondary atrophic rhinitis is overaggressive nasal surgery, particularly turbinate surgery.[6-9]

If the theory regarding developing atrophic rhinitis after a simple turbinectomy stands true, one would expect all patients undergoing radical resection of the nasal structures to develop atrophic rhinitis. This has not been the case in our study as shown by our results.

Studies have examined the likely aetiology and diagnosis of secondary atrophic rhinitis (SAR). The largest study to date by Moore and colleagues (Mayo Clinic Otorhinolaryngology) published in 2001, identified 242 cases of atrophic rhinitis of which 197 cases were SAR. According to this study, 24%(47) were due to complete removal of the lower and middle turbinates, 56%(110) were due to partial removal of the lower and/or middle nasal turbinates, 10%(20) to endonasal sinus surgery without turbinectomy, 6%(12) tumour removal with partial maxillectomy, 2%(4) due to sinonasal irradiation and 2%(4) due to nasal trauma/granulomatous disease.[4]

Some of the older studies done between1987 – 1999 have authors reporting 15 – 89% of their own patients experiencing post - operative atrophic rhinitis symptoms after nasal tissue removal particularly in the form of turbinectomy.

A retrospective study by Moore and colleagues published in 1985 (University of Nabraska) identified 18 patients who had undergone total inferior turbinectomies for nasal obstruction (1977 – 1982). They were followed up for three to five years and 16 of 18(89%) developed symptoms and signs of atrophic rhinitis.[5]

Warwick – Brown and colleagues published another retrospective study in 1987 where 24 out of 207 patients with nasal obstruction were found to have undergone partial inferior turbinectomy (Royal Berkshire Hospital, Reading UK). Follow up period was 16 years and 18 of 24(75%) developed atrophic rhinitis.[6] In 1993 a publication by Salam and colleagues (Hull Royal Infirmary, Hull) showed in a prospective trial of 25 patients, that total inferior turbinectomy resulted in 4 of 25(16%) developing atrophic rhinitis after a 6 month follow up period.[7] Another prospective trial published in 1995 by Oburra (Aga Khan Hospital, Nairobi) revealed 5 of 34(15%) patients who had bilateral total inferior turbinectomies developed atrophic rhinitis.[8] The follow up period was not stated in this study. One further prospective study published in 1999 by Passali and colleagues (Siena Medical School, Siena, Italy) confirmed atrophic rhinitis in 10 of 45(22%) of patients who had undergone total inferior turbinectomy and followed up for 4 years.[9]

Other authors report that they have never encountered a case of atrophic rhinitis after total removal of the inferior turbinates. Martinez and colleagues (Nebraska University – Otorhinolaryngology), in 1983, found 29 patients who underwent total inferior turbinectomy for nasal obstruction. This was a prospective study and patients were followed for 2 – 60 months.[10] Only 1 patient developed excessive dryness but no atrophy. Odetoyinbo in 1987 (Department of Surgery – Nigeria) reported that none of their 39 patients who underwent total inferior turbinectomy had developed atrophic rhinitis after a 2 year follow up. This too was a prospective study.[11] A retrospective study done by Courtiss and colleagues, (Division of Plastic surgery, Harvard Medical School) published in 1989, showed a 10-year follow up of patients who had total inferior turbinectomy with none developing symptoms of atrophic rhinitis.[12] This study involved 25 patients age range from 24 to 74 years (mean 39 years).

A retrospective study published in 1989 by Ophir, (Kaplan Hospital – Israel) showed 38 patients who also underwent total inferior turbinectomy for nasal obstruction. There were no signs or symptoms of atrophic rhinitis post – operatively and the follow up was from 1 to 7 years.[13]

The first prospective study involving resection of the middle turbinate for nasal obstruction was published in 1995 by Cook and colleagues (University of Missouri School of Medicine). This study looked at the effect of partial middle turbinectomy on nasal airflow and resistance. Thirty-one patients were included in the study and were followed up for 3 to 10 months post – operatively. No patients developed atrophic rhinitis and nasal function was enhanced.[14] In 2000 Talmon and collegues (Western Gallilee Hospital – Israel) reported on 357 patients who underwent total inferior turbinectomy. This was a prospective study and patients were followed up for 6 years. No patient developed atrophic rhinitis.[15] They also commented that even though the climate was hot, dry and dusty, no patients developed excessive dryness or atrophy.

Searching for studies reporting atrophic rhinitis as a result of endoscopic sinonasal tumour surgery, delivered no results. There are reports on the endoscopic management of sinonasal inverted papillomas but no studies mention atrophic rhinitis as a complication of the surgery. The studies were mainly concerned with tumour recurrence rates.[3]

Two studies published in 2005 and 2008 respectively, compared endoscopic and open approaches for sinonasal tumour (benign and malignant) resection. Again no mention is made of atrophic rhinitis as a post-operative complication, with the main focus again being recurrence rates.[1, 2]

Published literature evaluating the cause effect relationship of atrophic rhinitis as a result of nasal surgery is not clear. Also the incidence of atrophic rhinitis after endoscopic sinonasal tumour resection cannot be identified by an extensive literature review. This represents a significant gap both in the existing literature and in evidenced-based practice.

To summarize, the literature is not clear with regards to nasal surgery as a possible causative factor in the development of atrophic rhinitis. No reports could be found on atrophic rhinitis as a result of endoscopic sinonasal tumour resection. This generates an interesting research question. Would the endoscopic resection of tumours lead to the development of atrophic rhinitis in patients where the normal nasal structures (such as the turbinates and septum) have been sacrificed?

Certainly from our series of patients the surgery or extent of surgery did not significantly affect the development of atrophic rhinitis. We did however show that residual or recurrent disease and those who received adjuvant radiotherapy had a statistically significant chance of developing the symptoms and signs of atrophic rhinitis over time.

CONCLUSIONS

Development of atrophic rhinitis is not more common in patients having endoscopic sinonasal surgery according to our study. However having residual or recurrent sinonasal disease and/or having adjuvant radiotherapy did have a statistically proven effect on the development of symptoms and signs of atrophic rhinitis over time.

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No conflicts of interest to declare.

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APPENDIX I: DATA COLLECTION

PATIENT FACTORS

- Hospital number
- Age
- Sex
- Smoking and alcohol intake history
- Diabetic / Non-diabetic
- Other major medical co-morbidity (COPD, CCF, HTN, liver disease)

DISEASE-RELATED

- Histological diagnosis
- Areas involved with tumour

PROCEDURE-RELATED

- Extent of tumour resection
- Complications
- Repeat surgery
- Post op adjuvant treatment

POST-OPERATIVE FACTORS

- Patient symptoms on each visit
- Clinical signs on each visit
- Strict follow up period
- Routine post - operative care and management
- Residual/recurrence of disease

IN CASES OF ATROPHIC RHINITIS

- Patient symptoms
- Clinical signs
- Site

ATROPHIC RHINITIS POST ENDOSCOPIC SINONASAL TUMOUR RESECTION STUDY
Data sheet to be completed for all patients

Name:

Hospital number:

Age at surgery:

Sex: M / F

Smoking history: Current smoker / Ex – smoker / Lifetime non-smoker
Cigs / day:

Alcohol use: Teetotal / Ex-drinker / Drinker
(No. of units / week)

Diabetic: Y / N

Symptoms pre-op

Signs pre-op

Histology pre-op post-op

ENDOSCOPIC SINONASAL SURGERY

Date of surgery:

Areas involved:

Extent of surgery:

Curative surgery: Y / N

Repeat surgery: Y / N

If yes, date(s) of repeat surgery:

POST-OPERATIVE PERIOD

2 wks: Symptoms:

Signs:

6 wks: Symptoms:

Signs:

3 mo: Symptoms:

Signs:

6 mo: Symptoms:

Signs:

1 yr: Symptoms:

Signs:

18 mo: Symptoms:

Signs:

2 yrs: Symptoms:

Signs:

Adjuvant Treatment: Y / N

If yes, what treatment:

Residual/Recurrence: Y / N

IN CASES OF ATROPHIC RHINITIS:

Diagnostic criteria: Symptoms:

Signs:

Gender	Age	IP	Mening	Schwan	OF	FiDys	Hemangio	NasMass	MalMel	Esthesio	AdenoCa	SqCellCa	NeuroEnd	ChondroSarc	Carcinoid	Muco	Benign
1	62	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	30	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
0	50	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	48	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	66	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	24	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
1	37	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	65	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	35	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	75	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
0	65	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	46	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	52	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	42	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
1	63	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	59	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	66	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	13	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
0	70	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	23	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
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1	38	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
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1	30	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	13	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
1	59	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	28	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
1	44	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	68	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	45	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
0	70	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
0	76	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
1	48	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
1	47	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
0	75	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1	19	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1	56	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1	72	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1	76	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
1	51	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
1	49	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
1	54	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
0	64	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1	68	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
0	57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
1	78	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
1	70	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
1	63	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0

Right	Left	Bilateral	IT	MT	Latwall	Sept	Ft	Et	Sph	Crib	Intraorb	Intracran	Ittk	Mttk	MM	Septtk	Ftk	Etk	Sphtk	Cribtk
0	1	0	1	1	1	0	1	0	0	0	0	0	1	1	1	0	0	1	1	0
0	0	1	1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0
1	0	0	1	0	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
1	0	0	1	1	1	0	1	0	0	0	0	0	1	1	1	0	0	0	0	0
1	0	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
1	0	0	1	1	1	1	0	0	1	0	0	1	1	1	0	0	0	0	0	0
1	0	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
0	0	1	1	1	1	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
0	1	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
0	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
0	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
1	0	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0
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w2symNO	w2symND	w6symNO	w6symND	m3symNO	m3symND	m6symNO	m6symND	m12symNO	m12symND	m18symNO	m18symND	m24symNO	m24symND
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1	1	1	1	0	0	0	0	0	0	0	0	0	0
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w2siND	w2siNC	w2siNcav	w6siND	w6siNC	w6siNcav	m3siND	m3siNC	m3siNcav	m6siND	m6siNC	m6siNcav	m12siND	m12siNC	m12siNcav	m18siND	m18siNC	m18siNcav	m24siND	m24siNC	m24siNcav
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RadioRx	ChemoRx	Residual/Recurrence Histologically confirmed	Repeat surgery	Maj Complications		
0	0	1	1	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	1	0	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	1	1	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	1	1	0		
0	0	1	1	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	0	0	0		
0	0	1	1	0		
0	0	0	0	0		Key
0	0	0	0	0		1 = yes
0	0	0	0	0		0 = no
0	0	0	0	0		Red = Different tumour types
0	0	0	0	0		Green= Areas involved with tumour
0	0	0	0	0		Light blue = Structures excised during surgery
0	0	0	0	0		Purple = Patient symptoms
0	0	0	0	0		symNO = Nasal obstruction
0	0	0	0	0		symND = Nasal discharge
0	0	1	1	0		Orange = Clinical Signs
0	0	0	0	0		siND = Nasal discharge
0	0	0	0	0		siNC = Nasal crusts
1	0	1	0	0		siNcav = sign Normal cavity
0	0	0	0	0		Gender
1	0	0	0	0		1 = Male
1	0	1	0	0		0 = Female
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1	1	1	1	0		
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0	0	1	1	0		
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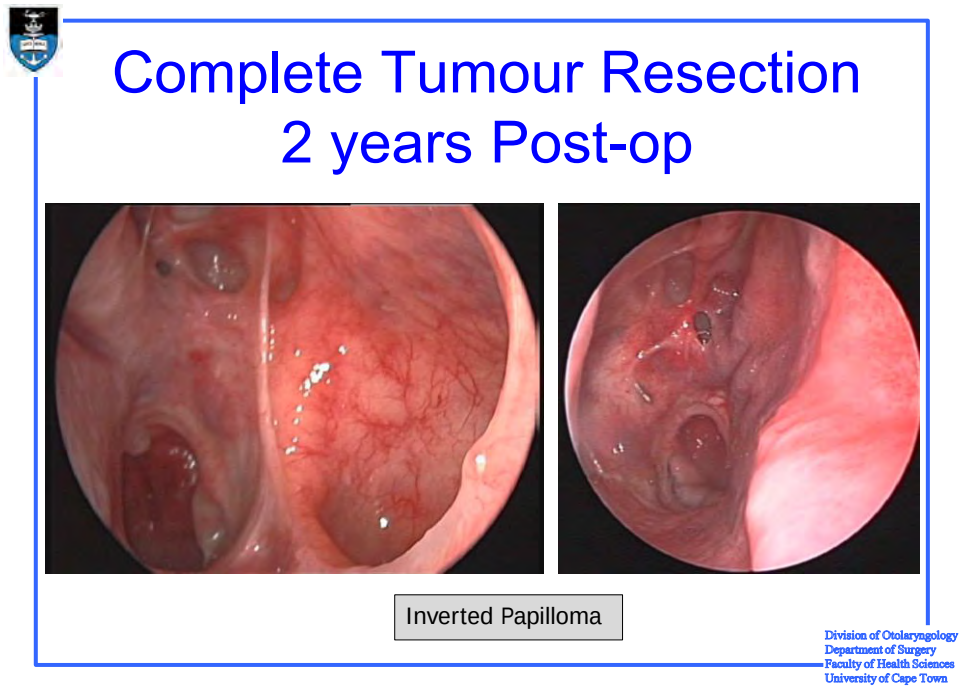
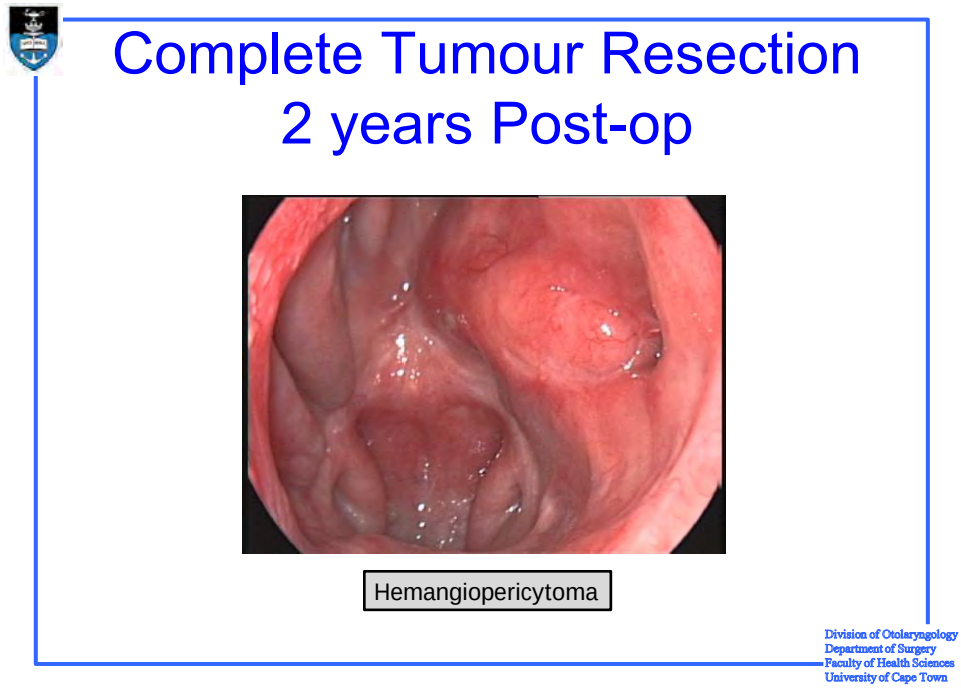
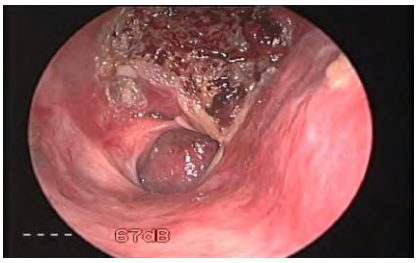
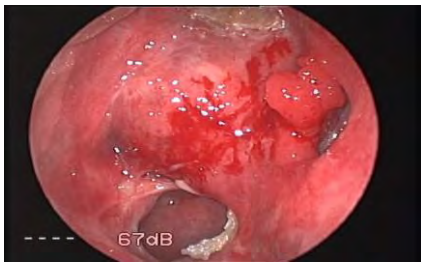
APPENDIX II: ENDOSCOPIC PICTURES

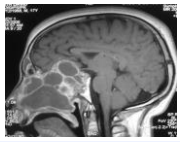


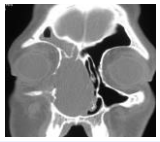


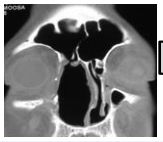
Recurrent Tumour
2 years Post-op











Ossifying fibroma

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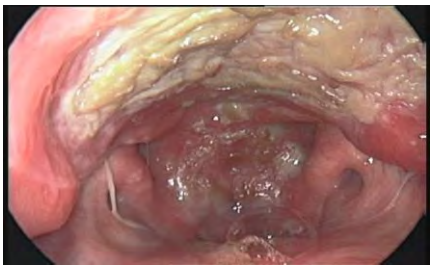
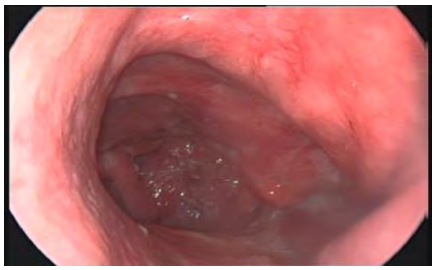
University of Cape Town

Residual Tumour
2 years Post-op

Osteoclastoma





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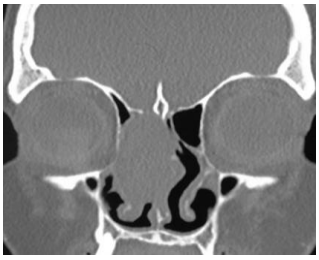
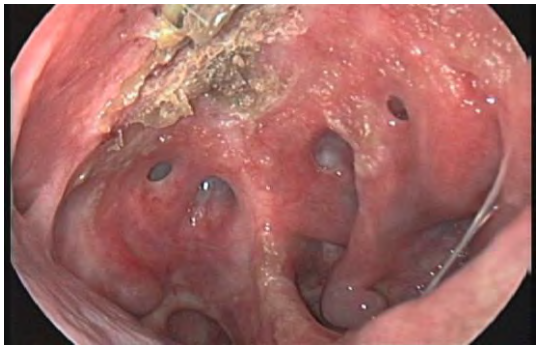
Faculty of Health Sciences
University of Cape Town

Adjuvant Radiotherapy
2 years Post-op



Malignant Melanoma



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Department of Surgery
Faculty of Health Sciences
University of Cape Town

APPENDIX III:
HUMAN RESEARCH ETHICS COMMITTEE APPROVAL

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone (021) 406 6338 • Facsimile (021) 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

12 April 2013

HREC REF: 228/2013

Dr M S Kamedien
Department of Otolaryngology
ENT
OMB

Dear Dr Kamedien

PROJECT TITLE: INCIDENCE OF ATROPHIC RHINITIS AFTER ENDOSCOPIC SINO-NASAL TUMOUR RESECTION

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 15 April 2014.

Please submit a progress form, using the standardised Annual Report form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please provide assurance that confidentiality will be protected and how?

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

APPENDIX IV:
DEPARTMENTAL RESEARCH ETHICS COMMITTEE APPROVAL

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee

Professor Anwar Suleman Mall

J-45 Room Old Main Building Groote Schuur Hospital

Observatory 7925 South Africa

Tel [021] 406 6148/6233/6227 Fax [021] 448 6461

Email: AnwarMall@uct.ac.za

18th March 2013

Dr MS Kamedien
Department of Surgery
Division of Otolaryngology
Groote Schuur Hospital
University of Cape Town

Dear Dr Kamedien,

RE: PROJECT 2013/018

PROJECT TITLE: Incidence of Atrophic Rhinitis after Endoscopic Sino-nasal Tumour Resection

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

signature removed

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

APPENDIX V: AUTHOR GUIDELINES: RHINOLOGY

Submission

Please go to our website at 'www.rhinologyjournal.com/review/' to submit your article. If this is your first manuscript, a new user account should be made where you will make a username and password. Before you prepare your manuscript, download the **template** at 'www.rhinologyjournal.com/review/' to submit your article. If this is your first manuscript, a new user account should be made where you will make a username and password. Before you prepare your manuscript, download the **template** and use that as a starting point for your manuscript. If you already had prepared your paper, please use 'copy - paste special - unformatted text' to enter your text in the **template**. In the submission module you can enter your new manuscript by filling out the required fields and upload your manuscript. Please prepare a complete manuscript in the Word **template** and save it in .doc(x) or .rtf format. Upload all figures and tables in separate files. Further instructions are available on the **template**.

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In younger patients operative repair is advised. It entails exposure of the tendon from above by splitting the acromion in the coronal plane, and reattachment of the tendon by sutures through drill holes in the tuberosity of the humerus (1,2). Thereafter a long course of supervised exercises may be required before a full range of active movement is restored. As would be expected, the results of operation tend to be poorer in cases of large musculo-teninous defects than when the rent is small (2).

- Debeyre J, Patte D, Elmelik E. Repair of ruptures of the rotator cuff of the shoulder. J Bone Joint Surg Br. 1965; 47B: 36-42.
- Kessel L, Bayley I. Clinical disorders of the shoulder. 2nd ed. Edinburgh: Churchill Livingstone, 1986.

Journal

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- A corporate author: The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977; 2: 242-244.
- No author given: Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981; 283: 628.

Books and other monographs

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- A chapter in a book:
Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974; 457-472.

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ACKNOWLEDGEMENTS

People who contributed to the work but do not fit criteria for authorship should be listed in the Acknowledgments, along with their contributions. Details of the funding sources that have supported the work should be mentioned here.

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