Journal of Surgical Oncology 2015;112:561–567

Treatment Strategies for Primary Early-Stage Sinonasal Adenocarcinoma: A Retrospective Bi-institutional Case-Control Study

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Objective: To investigate different treatment strategies for primary early-stage (pT1-T2) sinonasal adenocarcinomas.
Methods: Retrospective case-control study. From 2000 to 2011, 61 cases were radically resected using an endoscopic endonasal approach. Surgery as a single treatment modality was adopted for 33 patients (study group) while it was followed by postoperative radiotherapy (poRT) in 28 patients (control group).
Results: Median follow-up was 61 and 67 months for the study and control group respectively. Patients were stratified according to the pT classification and no statistically significant differences were found in terms of Overall (OS) and Recurrence-free (RFS) survival. When analyzing the high-grade tumors (47 cases), statistically significant differences were observed between the control and study groups both in terms of OS ($90.5\% \pm 6.5\%$ versus $57.6\% \pm 15.4\%$, $P = 0.03$) and RFS ($92.3\% \pm 7.39\%$ versus $80.2\% \pm 8.88\%$, $P = 0.05$). Using multivariate analysis, OS was independently determined by poRT (Hazard Ratio = 0.16; $P = 0.03$) thus confirming its protective role for high-grade adenocarcinomas.
Conclusion: Our preliminary results suggest that endoscopic endonasal surgery could be used as a single treatment modality for primary early-stage low-grade sinonasal adenocarcinoma, resected with negative margins. Surgery followed by poRT offers the best treatment strategy not only for advanced-stage lesions but also for high-grade adenocarcinomas, regardless of the stage of disease at presentation.
J. Surg. Oncol. 2015;112:561–567. © 2015 Wiley Periodicals, Inc.

KEY WORDS: **adenocarcinoma; adjuvant radiotherapy; endoscopic endonasal; paranasal sinus cancer; skull base**

INTRODUCTION

Malignancies of the paranasal sinuses and nasal cavities are rare, accounting for approximately 3% of head and neck cancers. Of these, adenocarcinoma is the most frequently occurring malignancy of the ethmoid sinuses in Europe and is usually associated with occupational exposure to wood dusts or leather tanning [1].

The treatment of choice for sinonasal adenocarcinoma is the complete surgical excision of the tumor followed by postoperative radiotherapy (poRT) [2–3]. Surgical removal is traditionally performed using open approaches such as midfacial degloving, later rhinotomy or craniofacial resection. In recent years, endoscopic endonasal resection has proved to be a safe and feasible method by which to radically resect selected sinonasal malignancies, obtaining valid oncologic outcomes and dramatically reducing the rates of surgical complications and morbidity [4]. Similarly, advances in irradiation modalities have improved on conventional radiotherapy with the introduction of modern techniques such as 3D-conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). These offer the potential to spare the maximum amount of healthy tissue and to escalate doses to the gross tumor volume via optimized non-uniform beam intensities [5].

These innovations have been vital in maximizing tumor control and minimizing morbidity for the large majority of patients affected by sinonasal adenocarcinoma, which generally presents in an advanced stage of disease at diagnosis. However, with the philosophy of minimal invasiveness and maximum effectiveness in mind, there is the potential that new treatment strategies could be designed for specific subsets of patients. In this regard, several centers worldwide have suggested

This work was presented at the International Federation of Head and Neck Oncologic Societies (IFHNOS) 5th World Congress and American Head and Neck Society (AHNS) Annual Meeting, New York, NY, July 26–30, 2014.

Conflict of interest: None.

All the authors certify that they have no conflict of interest or financial relationship with any entity mentioned in the paper.

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work. No sponsor or grants are involved in the paper.

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Received 21 April 2015; Accepted 26 August 2015

DOI 10.1002/jso.24038

Published online 8 September 2015 in Wiley Online Library (wileyonlinelibrary.com).

sparing poRT for selected patients who are affected by primary early stage sinonasal adenocarcinoma resected with adequate margins. However, the cohorts analyzed were small and the criteria used for the selection of patients eligible to undergo surgery as a single treatment modality were conflicting, thus precluding any widely accepted conclusions. Additionally, comparative studies between the two treatment options are lacking meaning that, at present, the appropriate management of this subset of patients remains unclear.

The aim of this study was to analyze the different treatment strategies in the management of primary early-stage sinonasal adenocarcinoma by retrospectively reviewing the experiences of two tertiary-care referral centers for sinonasal cancers sharing the same treatment policies.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed all patients treated for sinonasal adenocarcinoma between January 2000 and December 2011 at two tertiary-care referral centers sharing the same treatment philosophy.

Of these, only those patients who met all of the following criteria were included in this study: (1) histology-proven sinonasal adenocarcinoma; (2) primary tumor which had not previously been treated; (3) early stage cancer with local disease classified as pT1-T2; (4) no regional or distant metastasis at presentation, N0-M0; (5) patients surgically treated through an endoscopic endonasal approach able to obtain microscopic negative margins both on frozen sections and definitive histology; (6) minimum follow-up of 24 months for surviving patients.

In the absence of universally accepted guidelines concerning adjuvant treatments for primary early-stage sinonasal adenocarcinoma excised with negative margins, the option of poRT was suggested (but not recommended) to all patients during counseling with discussion of the potential pros and cons of this adjuvant treatment. Eventually only a few of them decided to undergo poRT.

A retrospective case-control study was designed by matching the "study" group of patients undergoing surgery as a single treatment modality with the "control" group of those treated by means of surgical resection followed by poRT. The two groups were compared statistically with regard to demographic and clinical characteristics as well as disease stage distribution in order to exclude any selection bias. Statistical analyses were performed by an independent center to remove bias and ensure objectivity. The study has been performed in compliance with the Helsinki Declaration and with policies approved by the Local Board of Ethics.

Preoperative Work-Up

Pretreatment evaluation consisted of complete physical examination, nasal endoscopy, routine blood counts, liver function tests, neck ultrasound, and total body CT scan with contrast enhancement. The local extension of disease was estimated with multiplanar CT and contrast-enhanced MRI in all cases. All tumors were staged according to the 2010 AJCC TNM classification (7th Edition). Written informed consent was obtained from all patients prior to any diagnostic or therapeutic procedure.

Surgical Treatment

All patients were treated using an endoscopic endonasal approach tailored according to the extension of disease. Resection may involve only the sinonasal complex (EER, exclusive endoscopic resection), or it may be extended to include the ethmoidal roof and dura of the anterior skull base, from the posterior wall of the frontal sinus back to the sphenoidal planum and between the orbits (ERTC, endoscopic resection with transnasal craniectomy) [6].

Transnasal skull base reconstruction was performed according to a multilayer technique using autologous materials such as fascia lata or iliotibial tract [6]. The entire bilateral ethmoid labyrinth was included in the resection in those cases associated with exposure to leather tanning or wood dust since such exposure renders all the mucosa of the naso-ethmoidal complex vulnerable to developing adenocarcinoma foci [7–8].

Surgical margins were assessed intraoperatively by sending for frozen section multiple biopsies taken from selected places at the surgical site after the tumor resection and these were confirmed postoperatively by analyzing the surgical specimen on definitive histology.

A brain CT scan was performed on the 1st post-operative day in all the patients who underwent skull base reconstruction in order to rule out complications and to evaluate the extent of pneumocephalus. Nasal packing was gradually removed within 48 hours. Intravenous third-generation cephalosporin was started the day before surgery and continued for at least 5 days.

Adjuvant Radiotherapy

The patients included in the "control" group received poRT with 3D-CRT or IMRT technique and 6 MV photons. All patients were simulated after immobilization with a thermoplastic mask before getting the treatment-planning CT scan, which was obtained with 3 mm slice thickness from the head down to the clavicles. The volumes of interest (VOI) and organs at risk (OARs) for poRT were delineated on the simulation CT scan.

Pre-operative imaging was used to reconstruct the pre-operative gross tumor volume (GTV) using the image-fusion package of the Varian-Eclipse® treatment planning systems at both institutions. The clinical target volume (CTV), defined by the pre-operative GTV combined with the surgical margin status and assessed on the final histological examination, usually consisted of the whole resection cavity and involved paranasal sinuses.

Planning target volume (PTV) was generated by an automatic anisotropic 6 mm expansion of CTV. At least 95% of the PTV had to be encompassed by a 90% and 95% isodose for 3D-CRT and IMRT, respectively. Evidence in the literature for elective treatment of the first-echelon lymph nodes being absent in early-stage sinonasal adenocarcinoma, this was never performed [9].

Histopathological Analysis

Tissue specimens were available from all patients and were retrieved from the Department of Pathology of our Institutes. The histological slides were independently reviewed by two senior pathologists in order to confirm the diagnosis and to stratify tumors according to the histopathological features. Well-differentiated tumors (G1) were classified as "low-grade" while moderately (G2) and poorly differentiated (G3) tumors were classified as "high-grade". In addition, intestinal-type adenocarcinomas (ITAC) were separated from those not further classified and then analyzed according to the Barnes system [10] and according to the Kleinsasser and Schroeder classification [11].

Follow-Up

Follow-up data were available for all patients and included endoscopic evaluation every two months and MR every four months over the first year and both endoscopic evaluation and MR every 6 months until the fifth year with clinical evaluation and MR yearly thereafter. Total body CT scan was performed every year to rule out systemic dissemination of disease. Additional imaging was performed when a suspicion of recurrence was clinically or endoscopically detected.

Statistical Analysis

Continuous variables with skewed distribution are shown as median and range, comparing differences between the 'control' and 'study' groups using the Wilcoxon signed rank test. Variables with normally distributed data are shown as mean and standard deviation, and comparisons between the 'control' and 'study' groups have been performed with the T test. Categorical variables are presented as frequency and percentage, comparing differences between the "control" and "study" groups with the χ^2 test or the Fisher exact test.

The main endpoints analyzed were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the time from surgical treatment to death for all causes. RFS was defined as the time from surgical treatment until relapse at any site or death related to the disease. The Kaplan–Meier method was used to estimate the probability of RFS and OS with Greenwood standard errors (SE); values were compared using the log-rank test.

A multivariate proportional hazard Cox-regression model was implemented for the RFS and OS. Results are shown in term of hazards ratios (HR), 95% confidence intervals (CIs) and p values. All statistical tests were two tail and p values were considered significant when ≤ 0.05. All analyses were carried out using the SAS program, version 9.2 (Cary, North Carolina).

RESULTS

Considered eligible for the present analysis were 61 consecutive patients and their demographic and clinico-pathological characteristics are detailed in Table I. Of these, 33 patients were included in the 'study' group and 28 in the "control" group.

Exposure to wood and leather was observed in the large majority of patients (82% and 78.8% in the "control" and "study" group, respectively), with a mean latency of 44.7 years (range, 12–8 years).

TABLE I. Demographics Data, Clinic-Pathological Features, Therapeutic Strategies and Patients Status at the End of the Follow-up, In 61 Patients Affected By Primary Early stage Sinonasal Adenocarcinoma

	Control Group (surgery + poRT) 28 patients	Study Group (surgery) 33 patients	Total 61 patients	P value
Mean Age				
(Range)	62 yrs (29–79)	67 yrs (17–84)	64.5 yrs (17–84)	0.168
Gender				
Male	24 (85.7%)	28 (84.8%)	52 (85.3%)	0.924
Female	4 (14.3%)	5 (15.2%)	9 (14.7%)	
Occupational exposure				
Wood	16 (57%)	18 (54.6%)	34 (55.7%)	0.947
Leather	7 (25%)	8 (24.2%)	15 (24.6%)	
None	5 (18%)	7 (21.2%)	12 (19.7%)	
pT classification				
pT1	14 (50%)	15 (45.5%)	29 (47.5%)	0.723
pT2	14 (50%)	18 (54.5%)	32 (52.5%)	
Grading				
Low-grade	2 (7.1%)	12 (36.3%)	14 (23%)	0.061
High-grade	26 (92.9%)	21 (63.7%)	47 (77%)	
Histology				
ITAC	27 (96.4%)	30 (90.9%)	57 (93.4%)	0.617
non-ITAC	1 (3.6%)	3 (9.1%)	4 (6.6%)	
Barnes classification (57 cases of ITAC)				
Papillary	2 (7.2%)	10 (30.3%)	12 (19.7%)	0.067
Colonic	15 (53.5%)	8 (24.2%)	23 (37.7%)	
Solid	1 (3.5%)	1 (3%)	2 (3.3%)	
Mucinous	7 (25%)	6 (18.2%)	13 (21.3%)	
Mixed	2 (7.2%)	5 (15.2%)	7 (11.4%)	
Kleinsasser classification (57 cases of ITAC)				
PTCC-I	2 (7.2%)	9 (27.2%)	11 (18%)	0.065
PTCC-II	15 (53.5%)	8 (24.2%)	23 (37.7%)	
PTCC-III	1 (3.5%)	1 (3%)	2 (3.3%)	
Alveolar-goblet	7 (25%)	6 (18.2%)	13 (21.3%)	
Signet-ring	—	—	—	
Transitional	2 (7.2%)	6 (18.2%)	8 (13.1%)	
Extent of Surgery				
ER	12 (42.8%)	16 (48.5%)	28 (45.9%)	0.523
ERTC	16 (57.2%)	17 (51.5%)	33 (54.1%)	
Radiation therapy				
3D-CRT	17 (60.7%)	n.a.	17 (27.8%)	n.a.
IMRT	11 (39.3%)	n.a.	11 (18%)	
Follow-up				
Range	19-148 mths	8-146 mths	8-148 mths	0.073
Median	67 mths	61 mths	62 mths	
Recurrence				
Local	1 (3.5%)	3 (9%)	4 (6.5%)	n.a.
Local, Regional	1 (3.5%)	—	1 (1.6%)	
Local, Distant	—	1 (3%)	1 (1.6%)	
Status				
NED	24 (85.7%)	25 (75.8%)	49 (80.4%)	n.a.
AWD	0	1 (3%)	1 (1.6%)	
DOD	0	2 (6%)	2 (3.2%)	
DOC	4 (14.3%)	5 (15.2%)	9 (14.8%)	

ITAC, intestinal-type adenocarcinoma; PTCC, papillary tubular cylinder cell; poRT, post-operative radiotherapy; ER, endoscopic endonasal resection; ERTC, endoscopic resection with transnasal craniectomy; n.a., not applicable; 3D-CRT, 3D conformal radiotherapy; IMRT, intensity-modulated radiotherapy; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DOC, dead of other causes; mths, months; yrs, years.

Male/female ratio was comparable between the two groups, with males far more frequently affected than females (6:1), reflecting the occupational factor.

The extent of surgical resection ranged from the EER to the ERTC and was equally distributed between the two groups (Table I). Notably, no intra or post-operative complications were observed and the mean hospitalization time was 8 days with a range of 2–12 days.

Additionally, no statistically significant differences between the "control" and "study" groups were found in terms of stage of disease, histological classifications and follow-up time, suggesting that the patients were equally distributed and the two groups were fully comparable. These results are detailed in the last column of Table I.

Patients included in the 'control' group received poRT with 3D-CRT in 17 (60.7%) cases and IMRT in 11 (39.3%) cases. The median interval between time of surgery and the commencement of poRT was 35 days (range, 24–58 days). The median prescription dose of poRT was 58.3 Gy (range 52-64 Gy), in fractions of 1.9 Gy/day (range, 1.8-2 Gy/day). The prescribed doses were delivered to all patients without noticeable treatment interruptions with a mean overall treatment time of 46 days, ranging from 38 to 57 days. The worst grades of acute and late radiotherapy-induced toxicities are reported in Tables II and III, respectively. To note, no severe toxicities (Grade 3 or 4) were observed.

No patient was lost to follow-up. The mean and median follow-up times were 63 and 61 months for the "study" group, similar to those observed in the "control" group which were 68 and 67 months, respectively. After a median follow-up time of 26.5 months, 6 (9.8%) patients developed recurrences. Four of these were local, one was local and regional and one was local and distant. Five out of the six recurrences were treated with curative intent using endoscopic endonasal surgery in three cases, craniofacial resection in one case and a transcranial approach with functional neck dissection in one case. The remaining patient presented with diffuse systemic spread of disease and was treated with palliative chemotherapy. At present three of the six patients have not been cured: two of these have died of their disease and the third is alive but with disease remaining. All three belong to the "study" group (Table I).

Histopathological Prognosticators

Correlations between clinical outcomes and histopathological features have been investigated in the whole cohort of 61 patients by performing univariate analyses. No statistically significant differences in term of 5-year OS were found between the histological subtypes proposed by Barnes (Papillary, $91.6\% \pm 7.9\%$; Colonic, $79.4\% \pm 11.1\%$; Solid, $50\% \pm 35.3\%$; Mucinous, $70.3\% \pm 14.7\%$; Mixed 100%; non-ITAC 100%; with $P = 0.11$). Likewise, the Kleinsasser and Schroeder histological classification had no statistically significant influence on 5-year OS (PTCC-I, $90.9\% \pm 8.6\%$; PTCC-II, $79.4\% \pm 11.1\%$; PTCC-III, $50\% \pm 35.3\%$; Alveolar-goblet, $70.3\% \pm 14.7\%$; Transitional, 100%; non-ITAC 100%; with $P = 0.11$). Also when analyzing the 5-year RFS, no statistically significant values were obtained for both the histological classifications (data not shown).

On the other hand, the grade of differentiation of tumor emerged as a statistically significant prognostic factor for both 5-year OS (G1, $92.8\% \pm 6.9\%$; G2, $79.8\% \pm 8.5\%$; G3; $37.5\% \pm 28.6\%$; with $P = 0.02$) and 5-year RFS (G1, $95.2\% \pm 5.6\%$; G2, $74.9\% \pm 9.1\%$; G3; $34.1\% \pm 14.7\%$; with $P = 0.03$). In addition all recurrences (6/6, 100%) were observed among the "high-grade" adenocarcinomas (G2-G3), emphasizing the prognostic implication of this histopathological parameter.

TABLE II. Maximum Grade of Acute Radiation Toxicity Scored According to the RTOG/EORTC Schema, Assessed in the Patients That Underwent a Multimodal Treatment With Endoscopic Surgery Followed by Adjuvant Radiotherapy (Control Group, 28 cases)

Organ at risk	Grade 1 (%)	Grade 2 (%)
Skin	9 (32.1%)	3 (10.7%)
Mucosa	16 (57.2%)	5 (17.8%)
Salivary glands	13 (46.4%)	3 (10.7%)
Conjunctiva	7 (25%)	4 (14.2%)
Pharynx	4 (14.2%)	1 (3.5%)

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer.

TABLE III. Late Radiation Toxicity Scored According to the CTCAE System, Version 4.0, Assessed in the Patients That Underwent a Multimodal Treatment With Endoscopic Surgery Followed by Adjuvant Radiotherapy (Control Group, 28 cases)

Adverse event	Grade 1 (%)	Grade 2 (%)
Lacrimal pathways stenosis (epiphora)	2 (7.1%)	2 (7.1%)
Sense of smell reduction	—	16 (57.2%)
Taste disturbance	1 (3.5%)	—
Xerostomia	1 (3.5%)	—

CTCAE, Common Terminology Criteria for Adverse Events.

Case-Control Survival Analysis

The 5-year OS was $91.3\% \pm 5.9\%$ and $74.3\% \pm 9.4\%$ in the "control" and "study" group, respectively, without statistically significant difference ($P = 0.44$). Similarly, no significant differences were found between the two groups in term of 5-year RFS ($93.3\% \pm 6.4\%$ versus $87.6\% \pm 5.8\%$, $P = 0.51$).

The analysis was then repeated by stratifying study population according to the stage of disease. Among the 29 patients affected by pT1 adenocarcinoma, no significant differences in terms of 5-year OS and RFS were found between the "study" group of patients treated solely with surgery and the 'control' group of patients treated mutimodally with surgery and poRT (Table IV). Similar results were obtained when analyzing the 32 patients affected by pT2 tumors. Here the outcomes of the "control" group were better than those observed in the 'study' group but without statistically significant differences for 5-year OS and RFS (Table IV).

Considering the significant impact on survival of the grade of differentiation, statistical analysis has been repeated stratifying the patient cohort into "low-grade" and "high-grade" tumors, in order to determine whether such grading might be a useful parameter in identifying patients who could benefit from poRT. The 5-year OS calculated in the patients affected by 'low-grade' adenocarcinoma was 100% and $91.6\% \pm 8\%$ in the 'control' and "study" group respectively, without significant differences ($P = 0.68$). Similar results were obtained with analysis of the 5-year RFS (Table IV), suggesting that poRT does not affect patient survival in the well-differentiated subset of tumors. However, when analyzing the 47 patients affected by "high-grade" adenocarcinoma, the 5-year OS was $90.5\% \pm 6.5\%$ in the 'control' group and $57.6\% \pm 15.5\%$ in the "study" group, with statistically significant difference ($P = 0.03$) (Fig. 1A). Similarly, a statistically significant difference was observed in terms of 5-year RFS ($92.3\% \pm 7.4\%$ vs $80.2 \pm 8.9\%$, $P = 0.05$) (Fig. 1B), suggesting that poRT could have a protective role in treating moderately and poorly differentiated adenocarcinoma, since it significantly affects the survival rates.

To validate this hypothesis, a multivariate analysis was performed considering only those patients affected by "high-grade" tumors. The administration of poRT emerged as the only statistically significant

TABLE IV. Univariate Analysis of 5 Years Overall and Recurrence-Free Survivals (percentage ± Standard Error), Using the Kaplan Meier Method and the Log-rank Test

	5-years OS			5-years RFS		
	Control Group (surgery + poRT)	Study Group (surgery)	p-value	Control Group (surgery + poRT)	Study Group (surgery)	p-value
Cohort	91.3% ± 5.9%	74.3% ± 9.4%	0.44	93.3% ± 6.4%	87.6% ± 5.8%	0.51
Low grade	100%	91.6% ± 8%	0.68	100%	100%	n.a.
High grade	90.5% ± 6.5%	57.6% ± 15.5%	0.03*	92.3% ± 7.4%	80.2% ± 8.9%	0.05*
pT1	82.5% ± 11.5%	92.3% ± 7.4%	0.53	100%	93.3% ± 6.4%	0.33
pT2	100%	55.5% ± 16%	0.09	88.9% ± 10.5%	82.6% ± 9.1%	0.63

poRT, post-operative radiotherapy; OS, overall survival; RFS, recurrence-free survival; n.a., not applicable; *, statistically significant values.

prognostic factor for OS (Hazard Ratio of 0.16 with 95% confidence interval of 0.03–0.88, $P = 0.03$) and was independently associated with a lower risk of death (Table V). Conversely, the patient's age at diagnosis, pT classification of tumor and year of treatment did not show any prognostic role in this subset of patients (Table V).

DISCUSSION

Treatment of sinonasal adenocarcinoma often involves the integration of multiple modalities and discussion by a multidisciplinary tumor board is crucial to set up an optimized and individualized treatment strategy. At present, complete surgical excision followed by poRT is considered the mainstay in the management of sinonasal adenocarcinoma, regardless of the stage of disease at presentation, because it improves survival rates and local control [2,3,8–9,12].

Data regarding the possibility of minimizing the indications for poRT in early stage lesions which are excised with negative margins are limited and inconclusive. DeGabory suggested that poRT should be avoided in T1-T3 adenocarcinomas when resected with adequate margins, reporting 31% of recurrences at a median time of 3 years from a series of 95 patients in different stages (T1-T4b) [13]. Similarly, other authors confined poRT to lesions resected with invaded margins [14] and for advanced stage tumors invading the dura or sphenoid [15]. Recently, Vergez proposed treating pT1 adenocarcinomas solely with surgery and supported the addition of poRT for tumors classified as pT2 or greater, reporting acceptable survival rates [16].

However, the rarity of sinonasal adenocarcinoma has so far prevented any prospective randomized study. All the published series have been retrospective and comparison is hindered by disparities in stages of disease as well as in surgical approaches and poRT indications and protocols.

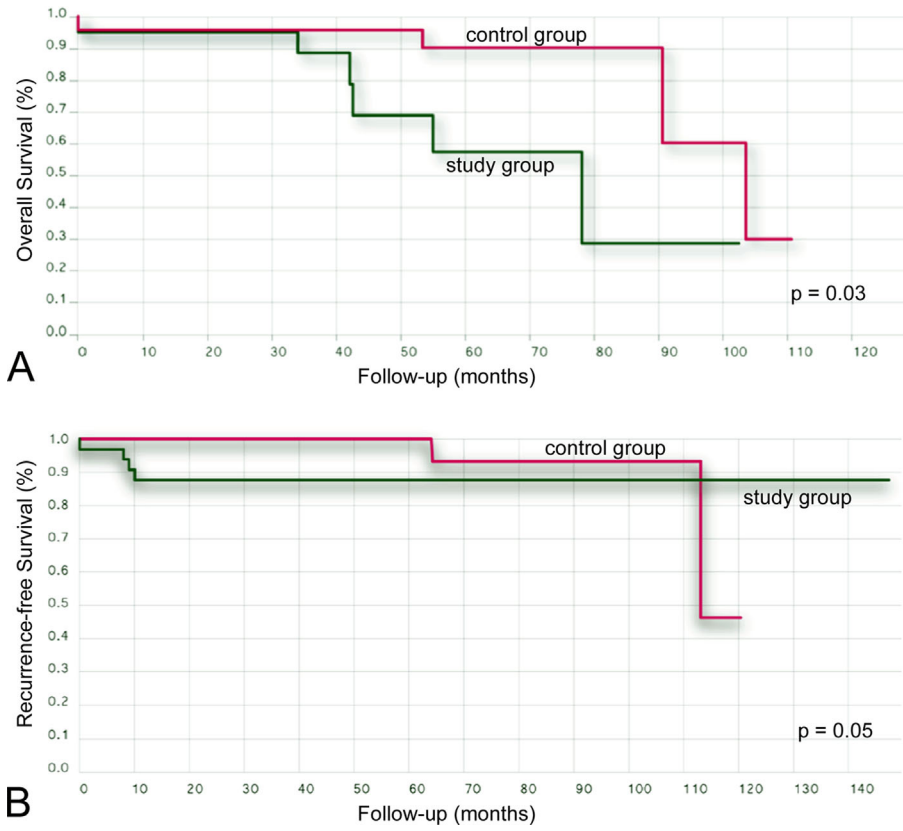

Fig. 1. Overall (A) and Recurrence-free survivals (B), calculated among the 'high-grade' sinonasal adenocarcinoma (47 cases), comparing the outcomes of the 'control' and 'study' group.

TABLE V. Multivariate Analysis Using the Cox Regression Model in the Group of Patients Affected by High-Grade Adenocarcinoma (47 Cases)

	5-years OS			5-years RFS		
Variable	HR	HR confidence interval (95%)	p-value	HR	HR confidence interval (95%)	p-value
poRT	0.16	0.03–0.88	0.03*	0.17	0.01–1.71	0.13
Age of Patient	1.03	0.98–1.09	0.19	1.02	0.94–1.10	0.58
Year of Treatment	0.72	0.47–1.09	0.12	0.94	0.66–1.33	0.74
pT Classification	0.58	0.09–3.68	0.56	2.35	0.25–22.07	0.45

HR, hazard ratio; poRT, postoperative radiotherapy; *, statistically significant values.

Our study analyzed a homogenous and well-selected cohort of patients with primary early stage sinonasal adenocarcinoma, managed through a uniform treatment policy, with a long-term follow-up (mean 66 months, median 62 months).

From a surgical standpoint, the endoscopic endonasal approach obtained free-margin resection while minimizing functional and cosmetic sequelae for the patients. This surgical approach, even when combined with transnasal craniectomy, is less traumatic and more tolerable than external approaches [17] and has now replaced the traditional transfacial/craniofacial resection in the surgical management of sinonasal adenocarcinomas, especially for early-stage lesions [18].

As regards the extent of surgery, we advocate a complete bilateral ethmoidectomy, even in cases of unilateral tumor, in order to prevent local recurrences contralaterally, particularly in cases of ascertained occupational exposure, as reported by previous studies [7–9]. In fact recently, the Belgian groups who until now have supported unilateral surgery have also suggested a more aggressive/complete resection to improve local recurrences rates, based on a large series of 123 cases with 38% of recurrences on a long-term follow-up (mean, 66 months) [19].

By using modern irradiation techniques such as 3D-CRT and even more IMRT, high-dose areas can be sculpted around defined target volumes with sharp dose fall-off to limiting organs at risk, thus significantly decreasing radiation-induced toxicities while maintaining an optimal coverage of the target volume [5,20]. In our series, acute and late toxicities were, if present, always mild (Grade 1–2) and no severe dry eye syndrome or any radiation-induced blindness occurred. Significantly, these promising results were obtained without compromising local control and survival rates. To note, we observed a high incidence of dry sinonasal mucosae and nasal crusting, an annoying side effect for many patients and requiring daily nose rinsing for some time.

Globally, poRT, despite its advances, is still associated with deterioration in quality of life and potential complications and so must be reserved only for patients for whom it is strictly necessary.

For these reasons, we designed a retrospective case-control study to identify those patients who might really benefit from poRT, and therefore to determine whether in future others might be spared unnecessary adjuvant treatments. The proportion of males to females, the mean age at presentation and the distribution of staging, grading and histological features were fully comparable between the "control" and "study" group from a statistical viewpoint.

Although no significant differences were found between the two groups in terms of 5-year OS and RFS, we repeated the case-control survival analysis after filtering the "low-grade" tumors from the cohort. The significant differences observed between the "control" and "study" group in this new cohort may be explained from a statistical viewpoint as the result of some event-free individuals having been removed from the study population therefore increasing the number of disease-related events in that remaining. Nonetheless, it indicated that primary early stage sinonasal "low-grade" adenocarcinoma, when radically resected, did not present any event related to the disease (death or recurrence) regardless of whether the patients received poRT. Our preliminary results therefore suggest that poRT may be considered an overtreatment for this subset of low-risk tumor. On the other hand, the impact on survival rates of poRT in "high-grade" adenocarcinomas has been emphasized by our data. In this group, on univariate analysis, statistically significant differences were found between patients treated with or without poRT both in terms of 5-year OS and RFS. Moreover, on multivariate analysis, OS was independently determined by poRT (Hazard Ratio=0.16; $P = 0.03$), thus confirming its protective role in the treatment of high-grade adenocarcinomas, despite the early stages.

Our study clearly suggests that the grade of differentiation of tumor cells could be a useful parameter in selecting those patients who can be safely followed up after surgery alone as opposed to those who would really benefit from the addition of poRT. These results are consistent with other reports showing that lower grade adenocarcinomas are associated with improved survival rates and could be less intensively treated [21,22]. Interestingly, this is in contrast with a large pooled series by Choussy who did not find significant differences in survival in relation to differentiation status [2].

Data from our study concerning the implications of the stage of disease are less revealing. When analyzed separately, the pT2 tumors showed better trends of survival in the control group than in the study group, but no statistically significant difference were found for both 5-year OS and RFS. In light of this, poRT could still be prudently suggested for the pT2 adenocarcinomas, but no evidence concerning the best treatment strategy is available at present.

The main limitations of this study are its retrospective design and the non-randomized selection of the therapy. However, the rarity of the disease and ethical concerns hampered prospective studies and precluded any sort of randomization in the distribution of patients between the two treatment groups in the present analysis.

Furthermore, our series confirms that local recurrence is the most frequent cause of treatment failure in sinonasal adenocarcinoma, even in its early stages, with a mean interval of 26.5 months. Notably, local recurrences are often amenable to further endoscopic or combined resections, with favorable results. For this reason we strongly recommend a strict post-operative endoscopic and radiologic surveillance for early detection of relapse. These findings are consistent with data emerging from recent case-series showing a downsloping prognosis for sinonasal adenocarcinoma after long follow-up periods, even if these present in early-stage, and recommending that all patients remain in follow-up for longer than ten years [19,23]. With this in mind, it is crucial to set up long-term multidisciplinary outpatient clinics to follow up survivors of sinonasal adenocarcinoma.

CONCLUSIONS

Endoscopic endonasal surgery may be proposed as a single treatment modality for primary early-stage low-grade sinonasal adenocarcinoma, resected with negative margins. If poRT could be considered as an

overtreatment in low-grade adenocarcinoma staged pT1, data concerning pT2 tumors offer less evidence and poRT could prudently remain indicated.

Multimodal therapy with surgery followed by poRT is recommended not only in cases of positive surgical margins and for advanced-stage lesions (pT3-pT4) but also for high-grade adenocarcinomas, regardless of the stage of disease at presentation.

Prospective randomized trials on a larger cohort of patients are difficult because of the rarity of the disease but would be desirable in order to validate our preliminary findings. Additionally, future endeavors will be devoted to better defining prognostic-relevant histological subtypes and to gaining a deeper understanding of the molecular profile of this tumor in order to refine treatment strategies towards a minimally-invasive, patient-tailored, and biology-driven perspective.

REFERENCES

1. Bonzini M, Battaglia P, Parassoni D, et al.: Prevalence of occupational hazards in patients with different types of epithelial sinonasal cancers. Rhinology 2013;51:31–36.
2. Choussy O, Ferron C, Védrine PO, et al.: Adenocarcinoma of Ethmoid: a GETTEC retrospective multicenter study of 418 cases. Laryngoscope 2008;118:437–443.
3. Van Gerven L, Jorissen M, Nuyts S, et al.: Long-term follow-up of 44 patients with adenocarcinoma of the nasal cavity and sinuses primarily treated with endoscopic resection followed by radiotherapy. Head Neck 2011;33:898–904.
4. Castelnuovo P, Battaglia P, Turri-Zanoni M, et al.: Endoscopic Endonasal Surgery for Malignancies of the Anterior Cranial Base. World Neurosurg 2014;82: S22.
5. Duprez F, Madani I, Morbée L, et al.: IMRT for sinonasal tumors minimizes severe late ocular toxicity and preserves disease control and survival. Int J Radiat Oncol Biol Phys. 2012;83:252–259.
6. Nicolai P, Battaglia P, Bignami M, et al.: Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: A 10-year experience. Am J Rhinol 2008;22:308–316.
7. Cantu G, Solero CL, Mariani L, et al.: Intestinal type adenocarcinoma of the ethmoid sinus in wood and leather workers: A retrospective study of 153 cases. Head Neck 2011;33:535–542.
8. Antognoni P, Turri-Zanoni M, Gottardo S, et al.: Endoscopic resection followed by adjuvant radiotherapy for sinonasal intestinal-type adenocarcinoma: Retrospective analysis of 30 consecutive patients. Head Neck. 2014;5:DOI:10.1002/hed.23660.
9. Lund VJ, Chisholm EJ, Takes RP, et al.: Evidence for treatment strategies in sinonasal adenocarcinoma. Head Neck 2012;34:1168–1178.
10. Barnes L: Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Surg Pathol 1986;10:192–202.
11. Kleinsasser O, Schroeder HG: Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. Arch Otorhinolaryngol 1988;245:1–15.
12. Jardeleza C, Seiberling K, Floreani S, et al.: Surgical outcomes of endoscopic management of adenocarcinoma of the sinonasal cavity. Rhinology 2009;47:354–361.
13. de Gabory L, Maunoury A, Maurice-Tison S, et al.: Long-term single-center results of management of ethmoid adenocarcinoma: 95 patients over 28 years. Ann Surg Oncol 2010;17:1127–1134.
14. Dilhuydy JM, Lagarde P, Allal AS, et al.: Ethmoidal cancers: A retrospective study of 22 cases. Int J Radiat Oncol Biol Phys 1993;25:113–116.
15. Catalano PJ, Hecht CS, Biller HF, et al.: Craniofacial resection. An analysis of 73 cases. 1994;120:1203–1208.
16. Vergez S, Martin-Dupont N, Lepage B, et al.: Endoscopic vs transfacial resection of sinonasal adenocarcinomas. Otolaryngol Head Neck Surg 2012;146:848–853.
17. Castelnuovo P, Lepera D, Turri-Zanoni M, et al.: Quality of life following endoscopic endonasal resection of anterior skull base cancers. J Neurosurg. 2013;119:1401–1409.
18. Grosjean R, Gallet P, Baumann C, et al.: Transfacial versus endoscopic approach in the treatment of woodworker's nasal adenocarcinomas. Head Neck 2014;10:DOI:10.1002/hed.23601.
19. Camp S, Van Gerven L, Vander Poorten V, et al.: Long-term follow-up of 123 patients with adenocarcinoma of the sinonasal tract treated with endoscopic resection and postoperative radiation therapy. Head Neck 2014;21:DOI:10.1002/hed.23900.
20. Dirix P, Vanstraelen B, Jorissen M, et al.: Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:998–1004.
21. Bhayani MK, Yilmaz T, Sweeney A, et al.: Sinonasal adenocarcinoma: A 16-year experience at a single institution. Head Neck 2014;36:1490–1496.
22. Orvidas LJ1, Lewis JE, Weaver AL, et al.: Adenocarcinoma of the nose and paranasal sinuses: A retrospective study of diagnosis, histologic characteristics, and outcomes in 24 patients. Head Neck 2005;27:370–375.
23. Nicolai P, Schreiber A, Villaret AB, et al.: Intestinal type adenocarcinoma of the ethmoid: Outcomes of a treatment regimen based on endoscopic surgery with or without radiotherapy. Head Neck 2015;DOI:10.1002/hed.24144.