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ENDOSCOPIC NASAL VERSUS OPEN APPROACH FOR THE MANAGEMENT OF SINONASAL ADENOCARCINOMA: A POOLED – ANALYSIS OF 1826 PATIENTS.

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ABSTRACT

Background: Surgical resection represents the gold standard for the treatment of sinonasal malignancies. This study reviewed the published outcomes on endoscopic (ES) or endoscopic-assisted surgery (EAS) versus open approach (OP) for the management of sinonasal adenocarcinomas.

Methods: PubMed, EMBASE, the Cochrane Library and CENTRAL electronic databases were searched for English language articles on ES, EAS and OP for sinonasal adenocarcinomas. Each article was examined for patient data and outcomes for analysis.

Results: Thirty-nine articles including 1826 patients were used for the analysis. The ES and EAS showed low rates of major complications (6.6% and 25.9%, respectively) compared to OPs (36.4%, $p<0.01$). The incidence of local failure was lower in the ES group as compared with OP patients (17.8% vs. 38.5%, $p<0.01$, respectively). The multivariate Cox regression model showed a worst overall survival related to advanced T classification and OP.

Conclusion: From the existing body of data there is growing evidence that endoscopic nasal resection is a safe surgical option in the management of sinonasal adenocarcinomas.

INTRODUCTION

Sinonasal malignancies pose a diagnostic and therapeutic challenge because of their location, resulting symptoms and presentation mimicking benign lesions¹. The incidence of nasal and paranasal cancers in most relevant series is less than 1 per 100,000 per year. The ethmoid sinuses are mostly involved (between 5% to 30%), and adenocarcinoma is the most frequent malignancy of the ethmoid sinuses². Primary adenocarcinomas of the sinonasal tract are a diverse group of malignancies that can be initially classified as salivary (5% to 10%) and non-salivary types³. The World Health Organization (WHO) classification of non-salivary gland type sinonasal adenocarcinomas considers the categories: high- and low-grade adenocarcinomas of non-intestinal type and intestinal type adenocarcinoma (ITAC) of colonic and mucinous subtypes⁴. Since symptoms are usually similar to inflammatory sinusitis, the diagnosis may be delayed and tumors are diagnosed at advanced stages. As with other malignancies the presence of unilateral symptoms, typically obstruction, rhinorrhea, and epistaxis, should serve as a warning sign for the clinician. Males are affected 2- to 6 times more often than females, reflecting occupational factors. In most series the cohorts are relatively small and often no distinction is made between the several subtypes of adenocarcinomas⁵. Surgical resection with negative margins, followed by adjuvant radiotherapy for advanced lesions, represents the gold standard for the management of sinonasal adenocarcinomas. Inability to control local disease is recognized as cause of death in sinonasal malignancies, highlighting the importance of complete surgical resection at the primary site⁶. In this light, numerous open surgical approaches were used to deal with the complex anatomy of the paranasal sinuses and adjacent structures. Although traditional surgical management is successful in yielding 5-year survival rates ranging from 40% to 70%, open approaches carry specific complications, functional, and cosmetic risks, even with proper execution⁷⁻⁹. Recently, endoscopic

techniques gained popularity in the management of benign and malignant sinonasal tumors.

However, endoscopic management of malignant neoplasms, such as sinonasal adenocarcinoma, is still under evaluation⁵. Evidence based guidelines on this topic are lacking due to the absence of randomised control trials, the low incidence of sinus adenocarcinoma that renders prospective studies difficult and because of the widely variable reporting methods widely used with data from various histopathological types often aggregated together. Consequently, the aim of this study is to compile and analyse outcome data in patients who received surgical treatment (endoscopic or open surgery) for sinonasal adenocarcinoma taking into account the variety of reporting methods for outcomes and tumor characteristics found across the literature on this entity.

METHODS

Literature Search Protocol

A comprehensive review of the English language literature on the surgical management of sinonasal adenocarcinomas was performed using PubMed, EMBASE, the Cochrane Library and CENTRAL electronic databases (see Figure 1). Three searches using the keywords (1) surgery OR endoscopic OR craniofacial OR open approach, (2) adenocarcinoma OR malignancy OR tumor, and (3) paranasal OR sinonasal OR nasal were performed. These searches were combined with the AND function to find all relevant articles. The following inclusion criteria were applied to each article: (1) available information on outcome data with survival statistics related to the treatment of sinonasal or skull base adenocarcinomas and (2) data concerning the type of surgical resection: endoscopic, or endoscopic assisted, or open approaches/craniofacial resection^{7,9-46}. When multiple papers were published by a single institution^{8,47,48,49} with updated follow-up on their patient populations, the most recent publication was used for analysis to maximize accuracy of follow-up data and reduce the risk of redundancy.^{9,35,41} Papers not meeting the inclusion criteria were excluded. Further exclusion criteria were: case reports without significant outcome data⁵⁰, reports

on surgical debulking, and studies regarding local 5-FU applications⁵¹⁻⁵⁴. To further reduce the risk of incomplete literature search, a manual search through the references of the included papers was performed.

Analysis Protocol

Data from the studies were first extracted and assessed by the principal investigator (M.G.) and thereafter independently by 2 co-authors (D.A. and G.C.) using standardized data forms. Articles were examined for data resolution with the intent to perform a meta-analysis. Different methods of meta-analyses were considered in reviewing the literature to seek results that would provide meaningful analysis with the least risk of introducing biases. The quality assessment of studies (QUADAS-2) tool was used to evaluate relevant study design characteristics of the included studies⁵⁵. A graphical display of QUADAS-2 results is shown in Figure 2. Based on the surgical treatment, three groups were defined: endoscopic surgery (ES), endoscopic assisted surgery (EAS), and open approach (OP). The manuscripts were analysed to extrapolate all information for each treated patient about age, gender, occupational exposure, smoking, tumor staging, total admission time, adjuvant therapies, disease free survival (in months), events of local recurrence, regional recurrence, distant metastasis, total follow-up time (in months) and survival. However survival data were limited in the EAS group, thus we compared only survival data from ES and OP groups. The articles were also reviewed for data concerning the occurrence of perioperative and postoperative complications. A major complication was defined as at least one reported event of: cerebrospinal fluid (CSF) leak, haemorrhage or severe epistaxis, stroke, severe pneumocephalus, meningitis, brain abscess, sepsis, post-operative death. Minor complication was noted as at least one reported event of: light or moderate epistaxis, light or moderate pneumocephalus, agitation, minor subdural blood collection, central venous catheter infection, fever, deep venous thrombosis, epilepsy, headache, pneumonia, hallucinations, cranial nerve palsy, anisocoria, diplopia, epiphora.

Statistical analysis

To test the differences among groups the Fisher's exact test was used for categorical data, while the Student's t-test was used for continuous data. The role of each possible prognostic factor (univariate analysis) and their independent effect (multivariate analysis) was explored using logistic regression model or cox-proportional hazard model as appropriate. Unfortunately due to discrepancies in the presentation of survival data, including follow up, it was impossible to calculate Kaplan-Meier curves. Probability values lower than 0.05 were considered statistically significant. All analyses were performed with STATA 12.0 software (Stata Corp., College Station, TX, USA).

RESULTS

The search was performed in October 2014 and yielded 1360 articles, of which 39 articles met inclusion's criteria^{7,9-46}, comprising a total of comprising a total of resulting in 1826 cases patients for initial analysis (see Figure 1 for flowchart). Thirty-six studies^{7,9,10-14,16-20,22,23,25-46} with 1404 cases included at least 3 years of follow-up and were included in the final analysis. All series were retrospective. Most series presented outcome data from heterogeneous histologies^{7,9,14-17,20-22,25-27,31,32,34,37-39,43}, at differing stages, who received a variety of treatment strategies over a relatively long time frame. The largest series of ethmoid adenocarcinomas was published by the French GETTEC group³⁰. Table 1 summarizes the extrapolated data from each included study. Palliative treatment was administered in 94(5.1%) patients, 431 patients (23.6%) received ES, 31 (1.7%) received EAS and 1270 patients (69.6%) underwent an OP. Table 2 shows the patients' characteristics among surgical groups. In 2002 (with implementation starting from 2003), the American Joint Committee on Cancer(AJCC) and the International Union Against Cancer(UICC) published staging protocols for epithelial tumors arising from sinonasal complex. Of 29 articles published after 2003, 11 studies specifically used the 6th or 7th edition of the TNM staging system^{24,29-31,35-37,41,42,44-46}. The remaining articles did not provide any information on the staging of treated adenocarcinomas except for 5 manuscripts published before the 2003 which used an earlier version of these guidelines^{13,15-19}. All but few studies mentioned only the staging of the primary

tumor (see Table 2), only 8 papers reported N classification at diagnosis although these studies account for the larger series^{17,19,27,30,35,36,44,46}. In total we had T classification information for 1221 patients. In 937 N-classified cases, only 9 (1%) N1, 3(0.3%) N2a, 3(0.3%) N2b and 1 (0.1%) N3 were recorded, the remaining 921 (98.3%) cases were staged N0. Unfortunately only 9 studies (364 patients) reported hospital discharge times^{7,9,21,26,33,40,42,44,46}. The available data showed a shorter hospitalisation in the ES group (4.7 ± 4.6 days) compared to the EAS and OP groups (9.2 ± 3.7 and 11.5 ± 4.9 days, respectively) which is statistically significant ($p<0.01$, Fig.3). Furthermore, 19 published articles recorded peri-operative and post-operative complications comprising a total of 938 patients^{13,15,21,23,24,26,27,29,31,33,36,39-46}. The ES and EAS showed low rates of major complications (6.6% and 25.9%, respectively) compared to OPs (36.4%), $p<0.01$. Post-operative deaths were recorded in 1 case of EAS and in 7 cases of OPs, no post-operative death was registered among patients who underwent ES($p=0.04$). Minor complications occurred in 10% of the ES group and in 7.4% of the OP group, whilst these were recorded in 33.3% of EAS patients who underwent combined endoscopic and open approach (Fig.4). In 9 studies adjuvant therapy was not documented or impossible to deduce^{9,13,14,21,22,25,31,34,37}. According to T classification, adjuvant radiotherapy (RT) was administered in 27.1% of T1 cases, 80% T2, 92.4% T3, 90.8% T4a, 91% T4b. In ES group, 78.9% of the cases received adjuvant RT whilst EAS and OP patients had adjuvant RT in 73.1% and 85.2%, respectively($p<0.01$).

For what concerns the outcome and survival, statistics varied among the articles, and in some studies data were not amenable for meta-analysis^{24,25,30-32,34}. The mean follow-up time was 51.9 ± 45.8 months (range 1–360), with 46.4 ± 37.6 (range 2-180) in ES group and 53.6 ± 47.6 (range 1-360) in OP group($p=0.09$). Within the available data, 536 failure events were reported: 424(31.5%) local, 15(1.1%) regional, and 97(7.2%) distant failures, resulting in crude Disease Free Survival (DFS) of 60.7% and Local Recurrence Free Survival (LRFS) of 67.6%. The crude DFS, LRFS and overall survival (OS) according to T classification between ES and OP groups is shown

in Table 3. Univariate and multivariate logistic regression analysis demonstrated that advanced T classification and OP are statistically related to a high rate of major complications (Odd Ratio=6.1, $p<0.01$ and Odd Ratio=3.5, $p<0.01$, respectively). Univariate and multivariate Cox regression model showed that advanced T classification and OP are statistically related to high rate of local relapses (see Table 4). Regarding the OS, the univariate Cox regression model highlighted the relationship among non-ITAC, advanced T classification and bad prognosis, albeit the statistical significance persisted only for advanced T classification and OP in a multivariate model (see Table 5).

DISCUSSION

ES is increasingly and effectively used for sinonasal inflammatory diseases, even showing intracranial extension, and benign tumors⁵⁶; nevertheless for malignant tumors this approach is in its relative infancy. A comprehensive analysis of the existing evidence would help serve as a barometer for the state of the art and to suggest future directions. Given that different types of tumors have several treatment survival implications for patients, we focused this analysis on the surgical management of sinonasal adenocarcinomas comparing outcomes between ES and traditional OPs. The potential benefits of endoscopic resections in sinonasal adenocarcinomas are numerous, including lack of facial incisions, excellent visualization and illumination of the surgical site, minimal trauma, shorter hospital stay, and lower costs⁵⁷. However, any treatment in sinonasal malignancies must be primarily judged by its efficacy. In that respect our study is not conclusive. This is indeed a pooled analysis of patient data, rather than a comparative meta analysis. This is inevitable, as, up to now, there are no comparative studies (and certainly no randomized controlled trials) comparing endoscopic with external approaches for adenocarcinomas. The main problem in comparing different interventions, is Simpson's paradox i.e. the effect of case mix (in our case the proportion of patients with T1/T2 versus T3/T4 tumors) in the endoscopic

versus the open approaches, which could erroneously lead to false conclusions regarding their efficacy.

It is true that smaller tumors are more likely to be treated endoscopically, and this is indeed what we found within our data. However, comparing results by T stage, we found that endoscopic management was associated with better overall and disease free survival across almost all tumor stages.

An issue is the possible reporting bias. It is true, that the most experienced surgeons with the best results would be the first to publish their results. This is unfortunately true in all surgical series, and we can only acknowledge it.

In our analysis, we found a statistically lower rate of major and minor complications in ES (16.6%) compared to OPs (43.8%, $p < 0.01$). Post-operative deaths were recorded only within patients who underwent either EAS or OP. Of note, the open craniectomy might represent a risk factor in itself for the development of post-operative complications; in fact the higher rate of complications in EAS and OP groups is mainly related to this external approach. Furthermore, the hospital stay in the ES group was statistically shorter compared to the EAS and OP groups ($p < 0.01$). Almost all series largely used postoperative radiotherapy in the majority of the cases and its use is reasonable in a district surrounded by noble structures where wide clear margins are often difficult to obtain^{7,10-12,15-20,23,24,26-30,32,33,35,36,39-46}; Nevertheless no randomised nor even controlled trials of its precise role for sinonasal adenocarcinomas are available. This does not mean that radiotherapy plays no role in the management of sinonasal adenocarcinomas but highlights the importance of a complete surgical resection. Outcomes are reported as combined results with and without radiotherapy. Patients treated with adjuvant radiotherapy are more likely to have locally advanced tumors and to be high-grade and/or to have positive margins, and are not comparable with those treated with surgery alone. Because of this understandable bias a conclusion cannot be drawn on its precise role. The overall local recurrence rate was reported as 32.5% with a rate of 17.8% for the ES group and

38.5% in the OP group. Nevertheless, a recurrence can occur even 10 years or more after the initial treatment. The application of endoscopic techniques for the management of malignant sinonasal tumors is still controversial. The primary concern worries about the adherence to the oncological principle of en bloc excision with adequate margins. However, many sinonasal tumors have a small area of tissue invasion despite filling the nasal cavity and paranasal sinuses; furthermore, tumor growth into sinuses and skull base regions often occurs by compression of bony structures rather than by direct invasion. En bloc excision of the entire tumor is not necessary; instead, en bloc resection of the area of invasion is performed with frozen sections control confirming clear margins. In order to gain access to the area of invasion, it is frequently necessary to debulk the tumor first. Albeit this clearly violates the tumor, it does not violate normal tissue planes surrounding the malignant proliferation since the tumor is residing in an air-filled cavity, and furthermore there is no evidence that this intraoperative debulking increases the risk of local recurrence. In fact, there are multiple examples of other neoplasms that are removed in a piece-meal fashion without jeopardizing the results: inverted papillomas, laser resection of laryngeal and pharyngeal carcinomas. Even with an open surgical approach (craniofacial resection), en bloc resection is not always possible because of the fragility and fragmentation of the specimen and the proximity to vital structures. Thus it is the final resection margin that is crucial, and not the method of tumor removal⁵⁸. Nevertheless there is no consensus regarding the indication and contraindication for ES as treatment for sinonasal adenocarcinomas. Some authors identified orbital involvement as a contraindication^{28,48} while others argued that ES would still be an acceptable method²⁷. Dural and intracranial extension, however, served as a nearly universal contraindication to ES^{15,25,26}, but also this dogma has also been challenged with the constant evolution of techniques, technology and surgeons expertise^{44,46,59}. Histopathologic typing is strictly related to outcome with the poorly differentiated subtypes faring worse. Thus, survival is better in papillary and colonic (ITAC) type than in solid or mucinous type adenocarcinomas⁶⁰. Wood dust exposure as an etiologic factor that

confers a better prognosis in the larger, but not all, series^{30,35,36}. As ITAC is a subtype of adenocarcinoma showing histological features reminiscent of colonic adenomas and adenocarcinomas, new therapeutic approaches such as targeted therapy with monoclonal antibodies against epidermal growth factor receptor (EGFR) might, in the future, be helpful in the therapeutic approach of these lesions⁶¹.

The variability encountered in the reported data was detailed in this study. This variability is partially indicative of the rare nature of this tumor and the changes in staging with time. Another aspect is the difficulty in the interpretation of the oncologic results reported in some studies, given that different histologies with different patterns of behaviour and prognosis were mixed. Furthermore the staging information were not available in all series, thus this potential bias might distort the results of this study. Nevertheless for advanced T classifications, surprisingly, the ES showed better outcomes in survival than the traditional OP.

CONCLUSION

Based on the available published data, endoscopic management of sinonasal adenocarcinomas appears be a safe and effective treatment modality. Recommendations for future studies include the implementation of prospective multi-institutional studies with detailed data regarding histology, staging, surgical treatment, adjuvant treatment, minor/major complications and oncologic results.

DISCLOSURE

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FIGURE LEGEND

Figure 1. Flowchart of study selection.

Figure 2. Graphical Display for QUADAS-2 results.

Figure 3. Hospital Stay according to the surgical techniques ($p < 0.01$).

Figure 4. Distribution of complications.