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Long-term Outcome for Open and Endoscopically Resected Sinonasal Tumors

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Abstract

Objective. Endoscopic resection of sinonasal cancer has become an alternative to open craniofacial surgery and leads to safe and satisfying results in emerging numbers. Randomized study data comparing outcomes between approaches are missing. Hence, it remains unclear which subgroups of patients might profit most from each technique. We aimed to identify such patient and tumor characteristics and gather information for future prospective study design.

Study Design. Case series with chart review.

Setting. Tertiary academic center.

Subjects and Methods. This study is based on a retrospective chart review of 225 patients undergoing open craniofacial or endoscopic resection for sinonasal malignancy between 1993 and 2015 at Munich University Hospital. Statistical analyses include *t* test, chi-square, Kaplan-Meier charts, and univariate and multivariate analyses.

Results. The sample size was similar between the endoscopic and open surgery groups. Tumors were significantly larger in patients who underwent open craniofacial resection. The risk of notable bleeding ($P = .041$) was lower and hospital stay shorter ($P = .001$) for endoscopic interventions of all tumor stages. Rates of overall ($P = .024$) and disease-specific ($P = .036$) survival were significantly improved for endoscopic cases; improved recurrence-free survival rates did not achieve statistical significance ($P = .357$). For cases matched for tumor size, this improvement was confirmed for T3 tumors ($P = .038$). Regional and distant metastatic tumor spread generally worsened survival in both surgical subgroups. Multivariate Cox regression analysis revealed independent prognosticators for overall survival.

Conclusion. Endoscopic tumor resection remains a suitable option for distinct indications and showed improved outcome in intermediate-stage tumors in our collective. Further randomized studies acknowledging the here-identified factors are needed to improve future therapy guidelines and patient care.

Keywords

sinonasal cancer, head and neck cancer, endoscopic skull base surgery, endoscopic sinus surgery, CSF leak

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The surgical management of sinonasal malignant tumors remains a challenge despite new technical advances in the past years.[1] Much in contrast to other mucosal malignant tumors in the head and neck area, the group of sinonasal malignant tumors is highly heterogeneous. Despite standardization of the treatment algorithm with pretherapeutic tumor boards, current treatment choices can differ to a large extent between 2 similar tumor cases.

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Sinonasal malignant tumors are relatively rare, with reported incidences ranging from <1 to 1.5 per 100,000 men and women.[2] This limits availability of evidence-based studies that take notice of recent technical advances.

With open craniofacial surgery still being the gold standard for the resection of sinonasal malignant tumors, numerous studies analyzed the technical feasibility and outcome of endoscopic tumor resection, assessing if the endoscopic approach could serve as an alternative in distinct cases.[3,4] Studies showed that purely endoscopic resection of certain sinonasal malignant tumors led to a similar long-term outcome as studies evaluating open craniofacial surgery.[5-11] In addition, this similar outcome seems to come with a lower rate of perioperative complications and shortened hospital stay.[12,13] Earlier, concerns were raised over the piecemeal resection technique utilized during endoscopic surgery. However, it was demonstrated that it is negative surgical margins, not en bloc resection, that affect outcomes.[14-16]

This study aimed at analyzing the outcome and risk of perioperative complications after surgical removal of sinonasal malignant tumors in a large series and a long observation period. For distinct subgroups of patients, we compared endoscopic with open craniofacial surgery, with the goal of identifying disease and patient characteristics that would influence outcomes for either surgical approach.

Methods

A review by the ethics committee of the Ludwig-Maximilians University Faculty of Medicine was waived according to an exemption for retrospective chart analyses at our institution. Included in our analysis were cases with histologically confirmed diagnosis of malignant sinonasal tumor, surgical primary therapy, surgery between 1993 and 2015 at our institution, and sufficiently available charts and reports. Excluded from analysis were cases of benign sinonasal tumor, malignant tumor with an origin other than the nasal cavity or paranasal sinuses, nonsurgical primary therapy, intent of surgery being debulking or biopsy rather than gross total resection, and insufficient documentation.

The collected variables are presented in **Table 1**. Interventions with combined approaches were counted as open surgery, acknowledging similar invasiveness. Adjuvant therapy was performed at our institution or at outside centers. Documentation of complications was gathered from surgical reports and progress notes. Due to their clinical significance and reliable documentation, bleeding and the occurrence of cerebrospinal fluid (CSF) leaks were subjected to our analysis. The TNM classification of the Union for International Cancer Control was used for tumor staging.[17] For olfactory neuroblastoma cases, the UCLA (University of California, Los Angeles) staging system was used.[18]

Oncologic outcome was measured by determining overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS). Survival times were calculated as either median survival or mean survival, if median could not be calculated. Five- and 10-year survival proportions were determined from Kaplan-Meier tables. Follow-up consisted of clinical, endoscopic, and neck ultrasound outpatient examination in increasing intervals ranging from 4 weeks to once a year. In addition, magnetic resonance imaging and computed tomography imaging (cranial, paranasal sinuses and skull base, neck, thorax, abdomen) were performed at least once within the first 12 months, ideally 3 months after therapy. Last follow-up visits are marked as censored in Kaplan-Meier curves.

Statistical analysis comprised chi-square and *t* tests; survival was calculated through Kaplan-Meier analysis, log-rank test, and Cox regression models. A P value <.05 was considered statistically significant. All statistical analyses were performed with GraphPad Prism 6 (GraphPad Software, La Jolla, California) and SPPS 23 (IBM, Armonk, New York).

Results

Population

Following a retrospective chart review, 225 patients with 393 surgical tumor resections were included in this study (**Table 1**). The most common type of cancer was squamous cell carcinoma (45%), followed by adenocarcinoma (15%) and malignant melanoma (12%). Mean follow-up periods were similar for patients with endoscopic or open surgery: 52.4 months (95% CI, 43.8-61) and 45.4 months (95% CI, 35.9-55), respectively.

Table 1 shows that open craniofacial (45.3%) and endoscopic (54.6%) surgery was performed in similar numbers of cases across all common entities. However, the table does not reflect that the ratio between endoscopic and open surgery changed over time; the mean proportion of endoscopic interventions was 36% between 1993 and 2003 and 57% between 2004 and 2014. Average primary tumor size (T from TNM/UCLA classification) was statistically higher in the open surgery group (mean T, 3.19 vs 2.65 for endoscopic cases, $P = .002$; see Supplemental Figure S1, available in the online version of the article). Surgical approaches were distributed uniformly across sexes and age groups, but age >60 years did influence the outcome significantly regardless of surgery approach (OS, $P < .001$). Length of hospitalization was significantly shorter for endoscopic cases as compared with open surgery cases (8.67 vs 13.42 days, $P < .001$). Patients who required duraplasty during endoscopic tumor resection were hospitalized significantly shorter than matched patients with open surgery (12.25 vs 23.31 days, $P = .001$).

Complications and Dural Defects

The risk of (1) significant intraoperative bleeding resulting in a more difficult intervention and (2) postoperative bleeding and hematoma formation was significantly higher for patients undergoing open craniofacial surgery (35.4%) as compared with endoscopic cases (26%, $P = .042$). Interestingly, the risk of bleeding remained stable for all T stages among endoscopic approaches. However, bleeding risk increased significantly with increasing tumor size during or after open craniofacial surgery as compared with endoscopic cases ($P = .004$).

Table 1. Population and Univariate Analysis: Patients Undergoing Open Craniofacial and Endoscopic Resection.

Variable	Patients, n		Hazard Ratio, Exp(b_j)	95% CI	*P* Value
	Endoscopic	Open Craniofacial			
Sex					
Male	72	63	1.051	0.641-1.723	.845
Female	51	39	0.952	0.580-1.561	.845
Age, y					
<60	55	43	0.287	0.163-0.508	<.001
≥60	68	59	3.480	1.969-6.152	<.001
T stage					
T1	25	11	0.244	0.096-0.619	.003
T2	32	10	0.859	0.249- 2.970	.811
T3	16	11	2.397	0.800-7.179	.118
T4	33	67	4.100	1.616-10.401	.003
Tx	17	3	1.621	0.469-5.607	.445
Nodal status					
N0	81	69	0.459	0.242-0.869	.017
N+	11	14	2.180	1.154-4.119	.016
Nx	31	19	1.360	0.756-2.445	.304
Metastatic disease					
M0	72	72	0.328	0.145-0.742	.007
M+[a]	9	3	3.099	1.371-7.009	.007
Mx	42	27	1.437	0.857-2.411	.169
Histology					
SCC	51	52			
Adenocarcinoma	16	18	0.812	0.385-1.713	.585
Malignant melanoma	17	11	1.367	0.684-2.729	.376
Olfactory neuroblastoma	8	5	0.957	0.337-2.720	.935
ACC	7	3	0.675	0.205-2.226	.518
Sarcoma	7	4	0.514	0.123-2.156	.363
SNUC	3	6	1.017	0.242-4.269	.981
Lymphoma[a]	6	0	2.200	0.664-7.288	.197
Others	8	3	0.517	0.070-3.802	.517
Orbital infiltration	21	42	2.95	1.811-4.795	<.001
Orbital bone	13	21	2.157	1.121-4.151	.0212
Orbital soft tissue	8	21	3.915	2.213-6.926	<.001
Intracranial infiltration	16	34	2.483	1.482-4.160	.001
Dura mater	9	13	1.740	0.818-3.702	.150
Cerebrum	7	21	3.305	1.797-6.081	<.001
Duraplasty	15	33	2.098	1.225-3.593	.007
Postoperative CSF leak	1	8	2.486	0.984-6.277	.054
Clear margins: R0	10	15			
Positive margins: R1	13	17	2.544	0.894-7.242	.080
Positive margins: R2	9	7	4.631	1.524-14.072	.007
Adjuvant therapy	57	73	2.620	1.589-4.319	<.001
Radiation	33	52	2.545	1.380-4.694	.003
Chemoradiation	24	21	3.824	1.965-7.441	<.001
Recurrence	57	52	0.843	0.519-1.370	.490

Abbreviations: ACC, adenoid cystic carcinoma; CSF, craniospinal fluid; SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.
[a]Excluded from survival analyses, M+ except for Supplement Figure S2 (available in the online version of the article).

Forty-eight patients required duraplasty: 15 underwent endoscopic tumor resection, and 33 underwent open resection (**Table 1**). The majority of reconstructions involved the cribriform plate (55%). There was no significant difference between surgical groups ($P = .054$) for the development of postoperative CSF leaks, which occurred in 1 and 8 patients

in the endoscopic and open groups, respectively. The postoperative leaks were managed with Tuohy needle CSF drainage (n = 3), endoscopic (n = 3) or open (n = 1) revision surgery, or observation (n = 2) due to a spontaneous cessation of CSF drainage.

General Outcome

Local and regional tumor expansion is known to have a substantial impact on disease outcome. The OS significantly worsened with increasing T stage, from a mean 209 months for T1 and T2 tumors to 85 months for T4 tumors ($P < .001$; **Figure 1**). Five- and 10-year OS rates were 87.5% and 84.6% for T1/T2 tumors, 73.2% and 43.9% for T3 tumors, and 52% and 33% for T4 tumors, respectively. Aside from locoregional tumor expansion, negative resection margins are known to be predictive of outcome. OS significantly worsened with microscopically (R1) or macroscopically (R2) positive resection margins as compared with negative margins (mean OS, 140 months for negative margins vs 98 and 51 months for R1 and R2 margin cases, respectively; $P = .021$).

Similarly, patients without nodal and distant metastases had significantly longer OS than patients diagnosed with lymph node or distant metastases (mean OS, 171 months for N0 M0, 78 months for N+, and 69 months for M+; $P = .006$; Supplemental Figure S2, available in the online version of the article). Orbital tumor expansion was divided into infiltration of bone or further infiltration of fat and soft tissue. OS and DSS were significantly lower in either disease situation (mean OS, 99 months for bone and 62 months for soft tissue infiltration) as compared with patients with neither (mean OS, 176 months; $P < .001$; DSS not shown; **Figure 2**). Furthermore, skull base infiltration was a strong predictor of worse outcome for OS ($P < .001$; **Figure 3**) but did not achieve statistical significance as a predictor of DSS ($P = .094$).

Outcome after adjuvant therapy was analyzed for T4 tumors where it was oncologically imperative. RFS was significantly longer with radiation and chemoradiation for T4 tumors, with a median RFS of 59 and 44 months, respectively, versus 23 months for patients without adjuvant treatment ($P = .007$; Supplemental Figure S3, available in the online version of the article). Median OS for patients who received adjuvant radiation was 80 months, as opposed to 57 months for patients who did not receive radiation; this difference was not statistically significant ($P = .660$).

Specific Outcome: Surgical Approach

OS and DSS were significantly apart between the endoscopic and open surgery groups, with a mean OS of 175 versus 120 months ($P = .024$) and a mean DSS of 202 vs 149 months ($P = .036$; **Figure 4**), respectively. Five- and 10-year OS rates for the endoscopic surgery group were 76.1% and 69.9%, as opposed to 59.5% and 41.8% in the open craniofacial surgery group, respectively. Statistical significance was not achieved between the groups for RFS ($P = .357$). The corresponding analyses of OS for the most common histologic types of tumor are illustrated in Supplemental Table S1 (available in the online version of the article). Improved survival after endoscopic surgery was observed for squamous cell carcinoma, the most common type in our study ($P = .001$).

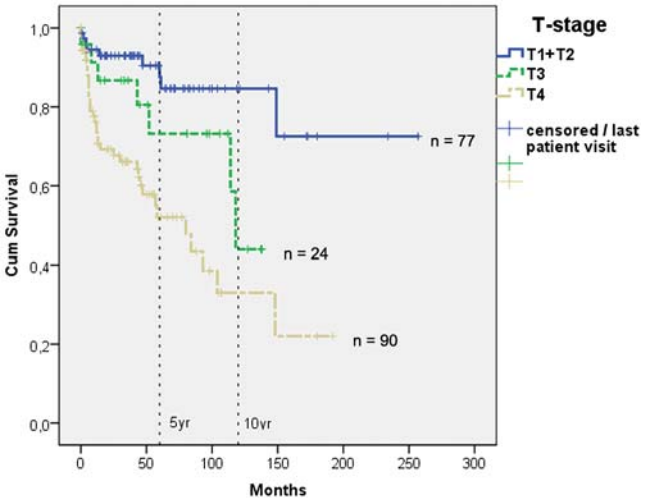

Figure 1. Kaplan-Meier overall survival curve per tumor size (T stage). Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P < .001$.

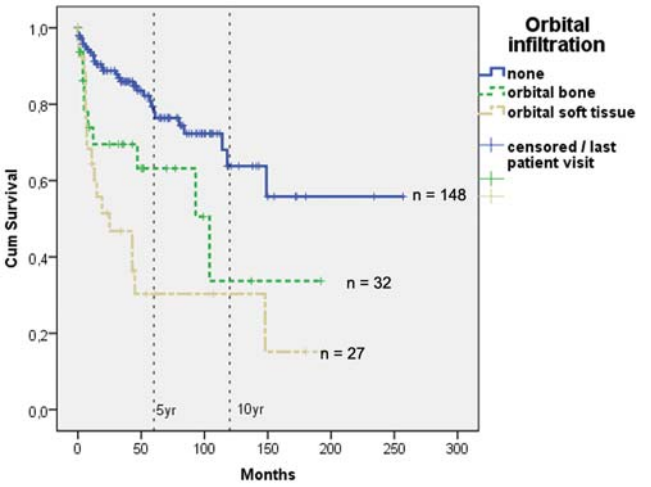

Figure 2. Kaplan-Meier overall survival curve per extent of orbital infiltration. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P < .001$.

With the mean T stages being significantly different between surgical groups, we needed to perform Kaplan-Meier analysis stratified for T stage. There was no significant difference between OS and DSS after endoscopic or open surgery for T1 and T2 tumors (OS, $P = .285$; **Figure 5**). We found a significantly higher OS after endoscopic removal of T3 tumors (mean OS, 127 vs 80 months; 10-year OS, 92.3% vs 18.8%; $P = .038$; **Figure 6**). Statistical significance was not demonstrated for DSS ($P = .149$) or median RFS ($P = .881$) for T3 tumors. Statistical significance of improved OS after endoscopic surgery was not achieved for the T4 subgroup ($P = .613$; **Figure 7**).

Additionally, we tried to determine if outcomes were different between the endoscopic and open surgery groups in

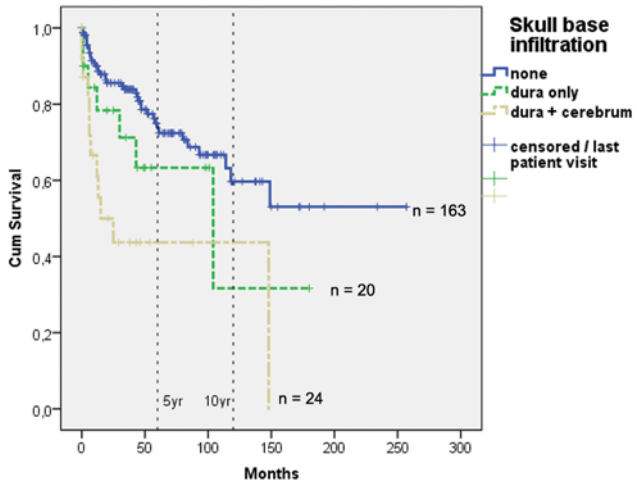

Figure 3. Kaplan-Meier overall survival curve per extent of skull base infiltration. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P < .001$.

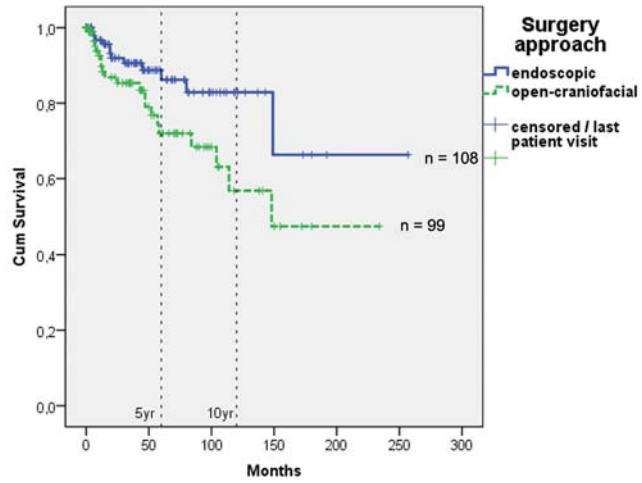

Figure 4. Kaplan-Meier disease-specific survival curve per surgery approach for the primary intervention. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P = .036$.

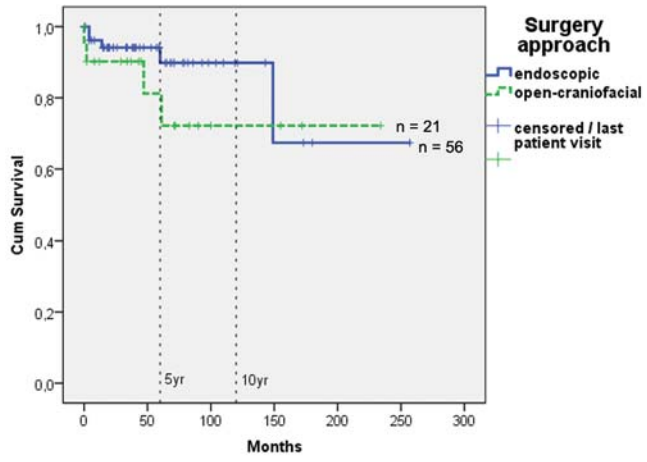

Figure 5. Kaplan-Meier overall survival curve for T1 and T2 tumors per surgery approach. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P = .285$.

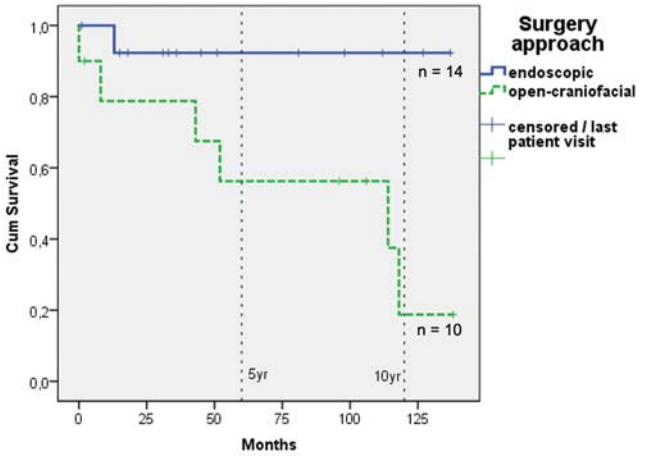

Figure 6. Kaplan-Meier overall survival curve for T3 tumors per surgery approach. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P = .038$.

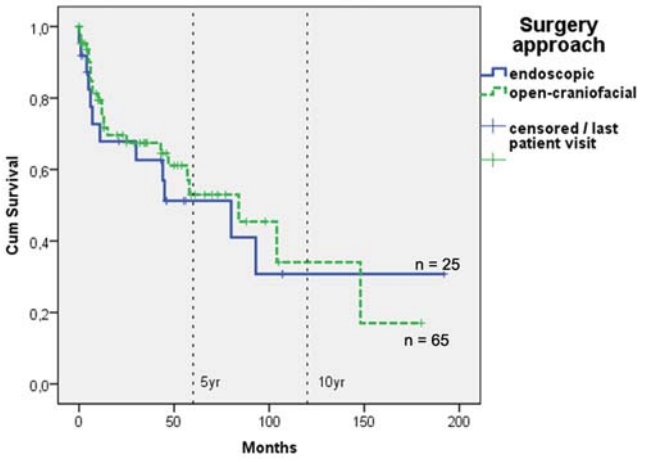

Figure 7. Kaplan-Meier overall survival curve for T4 tumors per surgery approach. Broken lines represent 5- and 10-year survival. Log rank (Mantel-Cox), $P = .613$.

those cases with skull base or orbital infiltration. Skull base involvement was further divided into dural and cerebral infiltration. We did not demonstrate statistical significance in mean OS for patients with skull base ($P = .752$), dural involvement ($P = .818$), or cerebral involvement ($P = .648$). In regard to orbital infiltration, soft tissue invasion by tumor usually dictates an open surgery approach. Thus, comparison between surgical groups was limited to cases with bone infiltration only. OS and DSS were longer for the endoscopic surgical group; however, due to a large proportion of censored data and a low number of cases (n = 32), results did not reach statistical significance (DSS, $P = .292$; **Figure 8**). There was no significant difference in RFS between surgery groups in cases with orbital bone involvement ($P = .271$).

Multivariate Analysis

To gather information about relevant factors that influence OS, we performed a Cox regression model. Orbital

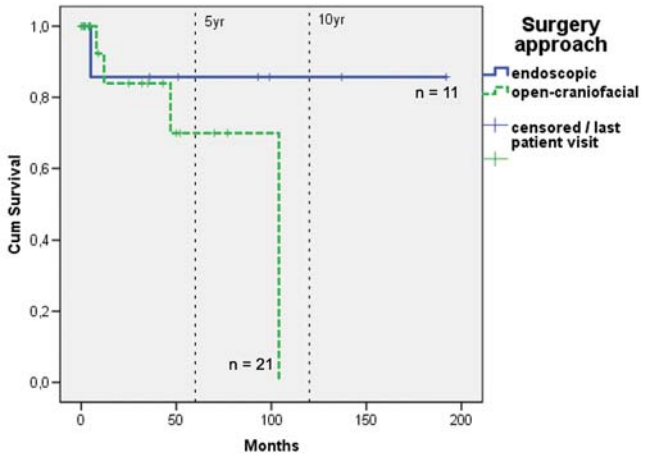

Figure 8. Kaplan-Meier disease-specific survival curve for patients with orbital bone but not soft tissue infiltration per surgery approach. Broken lines represent 5- and 10-year survival. Log rank, $P = .292$.

Table 2. Multivariate Cox Regression Analysis on Overall Survival.

Variable	*P* Value	Hazard Ratio, Exp(b_j)	95% CI
Surgical approach	.457	1.459	0.539-3.951
Skull base infiltration	.685	1.225	0.460-3.262
Orbital infiltration	.049[a]		
Orbital bone	.115	2.693	0.768-9.233
Orbital soft tissue	.014[a]	4.160	1.332-12.998
Margin status	.226		
Positive: R1	.215	2.032	0.663-6.232
Positive: R2	.088	2.850	0.857-9.478

[a]$P < .05$.

infiltration and margin status were found to have a strong influence on survival, with hazards between 2.032 and 4.160 (**Table 2**). There was a detectable and significant difference between patients with infiltration limited to bone and those with soft tissue infiltration of the orbit ($P = .014$). Open surgery as compared with endoscopic surgery had a hazard of 1.459 on OS ($P = .457$). These observations were confirmed for multivariate analysis on DSS (not shown).

Discussion

Our data suggest that endoscopic and open craniofacial surgical resections of sinonasal malignant tumors are valuable and successful treatment options for resectable malignant tumors. In addition, our data suggest that endoscopic resection of specific tumors is favorable for outcome and prevention of certain complications.

The 5- and 10-year OS rates for all patients combined were 87.5% and 84.6% for smaller tumors (T1 and T2) and 52% and 33% for T4 tumors, respectively. Comparison with other studies remains difficult due to population heterogeneity and different presentation of data. Higgins et al compared both surgical approaches and found 5-year OS rates of 87.4% and 76.8% for endoscopic and open surgery, respectively.[3] These data applied to low-stage tumors (T1/T2 and Kadish A/B) and range around our numbers of 89.8% and 81.2% for the same low-stage group (**Figure 5**).

In accordance with previous studies, the rate of notable perioperative bleeding and the length of hospitalization were significantly higher in the open surgery group. There was no significant difference in the frequency of CSF leaks between open surgery cases and endoscopic cases. Finally, both approaches were successfully used for the management of dural defects.

Various studies on short- and long-term outcome, as well as occurrence of complications, exist for endoscopic and open craniofacial resection of sinonasal malignant tumors.[5-11,19] Previous studies did not always perform separate analysis of the study population according to low- and high-stage tumors. To our knowledge, our study ranges among the largest monocentric studies on this topic in terms of mere patient numbers and includes a more detailed stratification for tumor stage and extent of local invasion. No prospective and controlled studies exist comparing surgical approaches to date. Rawal et al performed a meta-analysis in 2016 of many studies evaluating the endoscopic approach, concluding that the outcome of endoscopic surgery was similar or sometimes greater than survival data from published open surgery studies.[4] Cancer grading had a significant impact on OS, whereas cancer staging did not. However, a direct comparison of the 2 surgery approaches was waived due to lack of controlled and prospective data.

This large collective of patients was observed over a long period and thus takes into account technical advances over time and gain of experience as a surgical center for the management of this disease. Because endoscopic resection became more common and feasible, we were able to find out that OS and DSS were significantly longer for patients who underwent endoscopic surgery as their primary intervention (**Figure 4**). This represents a novel finding that needs to be analyzed and interpreted in a critical and detailed manner. First, tumor stage was significantly higher in the open surgery group. Chi-square correlation analysis revealed that T stage influenced the choice of surgery in a significant matter and can be regarded as a confounder ($\chi^2 = 37.622$, $P < .001$). Further subanalyses stratified for tumor stage were necessary. Kaplan-Meier analysis by tumor stage showed similar OS and DSS between endoscopic and open surgery groups for low stage tumors (T1/2) and locally extensive high-stage tumors (T4); in contrast, for the intermediate tumor stage (T3), we could show a significant difference in OS and DSS between groups (**Figures 5-7**). This finding is interesting, with T3 tumors being a heterogeneous group that can grow more extensively than what the ''middle position'' of the T-staging system suggests. T3 tumors can reach UICC stage IV(a/b) depending on the extent of lymph node involvement, which is the highest stage and usually has limited survival in terms of OS, DSS, and RFS.[17] The infiltration of anatomic structures surrounding the paranasal sinuses, such as orbital walls, palate,

subcutaneous tissue, or cribriform plate, defines the T3 category. Thus, just the crossing of an anatomic compartment can have a tremendous effect on outcome.

Currently, despite open craniofacial surgery still being referred to as the gold standard for the resection of malignant tumors in the nasal cavity and paranasal sinuses, the choice of surgery is usually made on the basis of how comfortable a surgeon feels with any approach. Endoscopic surgery is becoming more and more common according to recent data.[4] The contraindications for endoscopic resection correspond only partially with TNM classification.[20] Infiltration of subcutaneous tissue anteriorly to the maxillary sinus and skull base infiltration lateral to the middle portion of the orbit are among known contraindications and could be independent prognostic factors for outcome. We identified orbital involvement to be a strong prognostic factor for OS and DSS in our collective. Besides our study, only 1 other report, from Howard et al, differentiated orbital involvement into orbital bone and soft tissue infiltration.[19] They compared a cohort of 308 patients who underwent open craniofacial surgery for sinonasal malignant tumors. In accordance with Howard et al, we could illustrate that outcome worsens significantly with tumorous orbital soft tissue invasion as compared with orbital wall infiltration only. Future studies are needed to investigate which surgical approach is the most appropriate for tumors adjacent to the orbital soft tissue in terms of long-term survival, as our data could not show significant differences between groups. Prospective studies would minimize loss to follow-up bias, which was the case for our data. Additionally, the effect of local tumor invasion on outcome has to be analyzed in an even more detailed fashion than our study.

The presented study reports on a large collective of patients (N = 225) who were observed for a long time span (>10 years), which renders this study a valuable data source for further assessment and improvement of current treatment standards. However, consequences for current treatment standards should be assessed carefully. The limitations of our study arise from the study design, which is nonrandomized and retrospective. The margin status could be obtained in only a subgroup of cases due to insufficient documentation (n = 71). In accordance with current literature, margin status had a significant impact on OS and was an independent prognosticator.[16] In clinical reality, however, 3-dimensional margin status remains difficult to acquire for endoscopy-guided and open sinonasal tumor resections.

Cases with distant metastases (M0+) were excluded from survival analyses, as surgical treatment is usually not a curative treatment option. Mx cases were treated in curative intent; however, no precise TNM classification was available to our review. The M+ situations in **Table 1** affected cases of adenocarcinoma, adenoid cystic carcinoma, olfactory neuroblastoma, and squamous cell carcinoma. With the exception of adenoid cystic carcinoma where occult metastases are not uncommon, the decision for surgery could have been made on the grounds of functional improvement or organ preservation. This also applies to lymphoma cases, which were left out of survival analyses.

For the subanalyses, losses to follow-up have to be acknowledged and can lead to misinterpretation of results. This also applies for our T3 category tumors, where censored data exceeded 80%. The results reported here are likely not uniformly valid for all known entities of malignant sinonasal tumors. Several performing surgeons were involved in this study throughout the years, as were technical advances, namely regarding endoscopic technology. Experience and training are 2 factors that not only improve surgical outcome over time but also affect the choice of surgery to begin with.

The results of our multivariate Cox regression model demonstrated a powerful influence of orbital involvement, among others, on OS and DSS. The differentiation between orbital bone and soft tissue infiltration highlighted an important significant factor that could be of tremendous implication for the design of future, desirably prospective, studies. Current views on indications and contraindications for endoscopic resection for sinonasal malignant tumors could be supported in great parts by our data. Future prospective trials should be designed on the basis of existing findings to validate currently emerging endoscopic surgery approaches.

Author Contributions

Jan Hagemann, study design, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Jana Roesner**, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Soenke Helling**, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript accountable for entire manuscript; **Christian Jacobi**, study design, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Johannes Doescher**, study design, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Matthias Engelbarts**, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Julian Kuenzel**, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Philipp Krauss**, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Sven Becker**, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript; **Christian Stephan Betz**, study design, conduct of study/acquisition of data, analysis/interpretation, revising/drafting manuscript, final approval of the manuscript, being accountable for entire manuscript.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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