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Single modality and multimodality treatment of nasal and paranasal sinuses cancer: A single institution experience of 229 patients

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Abstract

Aims: To assess the single and multimodal treatment results and prognostic factors for sinonasal carcinoma.
Methods: Overall survival (OS), disease-specific survival (DSS), local control (LC), and disease-free survival (DFS) in 229 patients with sinonasal carcinoma treated from 1967 to 2003 were calculated. Prognostic factors were univariately and multivariately analyzed. The median follow-up period for survivors was 126 months.
Results: 32% of the patients were operated only, 47% underwent multimodal therapy, and 20% were treated without operation. The 5-year OS rate was 41%, and the DSS rate was 51%. The LC rate was 64%, and the DFS rate was 34%. Prognostic for DSS were M status ($p < 0.001$), UICC stage ($p < 0.001$), T classification ($p = 0.001$), N status ($p = 0.002$), intracranial tumor infiltration ($p = 0.008$), infiltration of the pterygopalatine fossa ($p = 0.02$), infiltration of the skull base ($p = 0.021$), infiltration of the orbita ($p = 0.041$), and the type of therapy ($p < 0.001$): The 5-year DSS rate was 63% for patients operated only, 56% for all operated patients, 46% for patients undergoing surgery and radiotherapy, but only 21% for patients treated with radiotherapy ± chemotherapy. Multivariate analysis revealed that T classification ($p = 0.042$), N classification ($p = 0.035$), M classification ($p = 0.007$), UICC stage ($p = 0.038$), and type of therapy ($p = 0.038$) were independent prognostic factors for DSS.
Conclusions: Radical surgery is recommended for stage I/II sinonasal carcinomas. Stage III/IV carcinomas still have a poor prognosis, but multimodal treatment seems to favor the outcome.

Keywords: Carcinoma; Nose; Paranasal sinus; Multivariate; Treatment results; Prognostic factors

Introduction

Carcinoma of the paranasal sinuses or the nasal cavity is a rare disease, representing 3–5% of all head and neck tumors. The annual incidence rate is 0.5–1.0 per 100,000 population.[1] There is a great variety of histologic subtypes, and the correct classification can be difficult.[2] Moreover, the proximity of the nasal cavity and paranasal sinuses to the orbit, dura, brain, cranial nerves, and carotid arteries mandates careful diagnostic evaluation and treatment planning. The inherent difficulty in generalizing treatment approaches is obvious, given the numerous variables influencing the disease.[3] Because of the low incidence of sinonasal carcinoma, only a few centers have published large series reporting extensive experience with the treatment of patients with these tumors,[1,4–6] and large controlled trials are lacking.

Nevertheless, it is generally accepted that the majority of epithelial malignancies of this region treated with curative intent require surgical intervention as part of any treatment regimen.[3] A recent meta-analysis of large retrospective studies showed that the local control and cure rates are better with surgery (5-year local control: 70%) and combined

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surgery and radiation (56%) than with radiotherapy alone (33%).[1] The role of chemotherapy is unclear. Theoretically, patients with advanced squamous carcinomas should benefit from postoperative chemotherapy added to radiotherapy like in other head and neck areas. There is some evidence that chemotherapy is useful for certain special histologic types of sinonasal carcinomas, namely sinonasal undifferentiated carcinoma, certain sarcoma, and possibly neuroendocrine carcinoma and advanced esthesioneuroblastoma.[2]

The most frequent site of treatment failure, which in most cases is a fatal event, remains local recurrence (about 35%). Isolated regional recurrences (5%) or distant metastasis (5%) are a rare event if the primary is controlled.[1] The data on prognostic factors for tumor control and survival are controversial. Due to the rarity of the disease most published case series did not allow powerful univariate and multivariate analysis. In most multivariate analyses, advanced T stage, regional, and distant metastasis were the most predictive of poor survival.[1,7–12] The effect of combined modality treatment has less frequently been elucidated, and is not clear. In some studies the type of therapy was not prognostic,[7,11,13] whereas others identified treatment modalities as an important prognostic factor.[1,10,12]

We retrospectively analyzed our 37-year experience in a series of 229 patients with nasal and paranasal carcinoma treated with a relatively standardized treatment approach. We analyzed the treatment results and calculated potential prognostic factors in order to assess their validity with regard to local control, overall survival, disease-specific survival, and disease-free survival.

Methods

Patient selection, inclusions and exclusions

A retrospective study was conducted. We reviewed the case records of all patients with the diagnosis of a carcinoma of the nose or of the paranasal sinuses admitted to a single centre (Clinic of Otolaryngology, Head and Neck Surgery, University of Cologne, Germany) from January 1967 to August 2003. Patients with lymphoma were not included into the study. This time frame was selected to provide adequate follow-up. Patients with primary skin tumors with secondary invasion of the sinuses and nose were excluded. We identified 236 cases admitted during the selected time frame. A complete chart review was possible for 229 of the 236 patients. Demographic and follow-up clinical information was obtained from the review of the patients' medical histories and pathology reports.

Tumor classification and diagnostic workup

The tumor site was determined from the epicenter of the disease at the time of diagnosis. Each case was classified according to TNM stage proposed by the according to the 2002 International Union Against Cancer (UICC) guidelines.[14] Patients who were not classified at the time of diagnosis according to these UICC guidelines were reclassified retrospectively by reevaluating the clinical and radiologic data. As part of the staging workup, 149 patients underwent CT, MRI, or both. In 80 patients, there was no record of CT or MRI being performed, especially in cases before the 1990s. Since the 1990s, diagnostic management included ultrasonography of the neck and abdomen, chest X-ray, and CT and/or MRI of the neck. Non-squamous cell primary tumors and tumors completely outside maxillary and the ethmoid sinus were assigned a T classification by analogy to a similar squamous cell carcinoma of maxillary sinus and the ethmoid sinus.

Treatment strategies

During the long time of the study several treatment strategies were applied. Treatment consisted of surgery, radiation, chemotherapy, or various combinations of these modalities. In general, limited disease was treated by surgery alone. Locally advanced and resectable disease was treated by a combination of surgery and radiotherapy. Radiotherapy or radiochemotherapy was reserved for unresectable advanced cases. In the absence of clinical and radiologic evidence of cervical lymph node involvement, a neck dissection was not performed. Resection methods included medial or total maxillectomy, ethmoidectomy, orbital exenteration, and craniofacial resection. Depending on the extent of disease, a combination of these different surgeries was used. Postoperative Radiotherapy was administered with daily doses of 1.8–2.0 grays (Gy) 5 days per week for a total dose of 60–65 Gy. The technique used most often combined one anterior field and two lateral fields of ^{60}Co beams or 6 MeV photons. Until 1991, conventional treatment planning and simulator localization was used, since than three dimensional conformal radiotherapy techniques were used facilitating preservation of surrounding normal tissues. Definitive radiotherapy and preoperative radiotherapy were applied in similar techniques. The chemotherapy regimen used for most patients was carboplatin.

Statistical methods

Statistical analysis of the data was performed using SPSS software for medical statistics, version 11.0.1. The Kaplan–Meier method was used for the estimation of overall survival, cancer-specific survival, and disease-free survival. Univariate comparisons were performed by the log-rank test. Multivariate survival analysis was performed with the Cox proportional hazards method. Nominal two-sided p values are reported. The significance level was set at $p < 0.05$.

Results

Study population

The study group consisted of the 229 patients with newly diagnosed carcinoma of the nose or of the paranasal sinuses. There were 74 female patients and 155 male patients with a mean age of 62 years (age range 14–100). Fifty-eight patients were smokers, 11 had a history of daily alcohol consumption, and 31 patients smoked and consumed alcohol. 105 patients did neither smoke nor drunk alcohol. Smoking and drinking behavior was unknown for 24 patients. 123 patients presented with relevant cardiovascular comorbidity, 45 patients with pulmonal comorbidity. The most common presenting symptom was nasal obstruction, followed by facial swelling and epistaxis (Table 1). The diagnosis of a carcinoma was obtained in average 2.6 ± 2.4 months after onset of the first symptoms. Fourteen male patients showed an occupational history of exposure to wood dust. All of whom but one had an adenocarcinoma. Overall, histologic diagnosis showed squamous cell carcinoma in 87 patients, sarcoma in 20 patients, undifferentiated carcinoma in 16 patients, adenocarcinoma in 15 patients, malignant melanoma in 15 patients, adenoid-cystic carcinoma in 12 patients, and various other seldom (<10 patients, respectively) histological subtypes in 64 patients.

Staging

The distribution by T classification was 18 patients with T1 tumors, 25 patients with T2 tumors, 35 patients with T3 tumors, and 151 patients with T4 tumors. Tumor was detected in the maxillary sinus in 163 patients, in the ethmoid sinus in 114 patients, the nasal cavity in 105 patients; the sphenoid sinus in 57 patients and the frontal sinus in 36 patients. The orbita was infiltrated in 76 patients, the nasal septum in 34 patients, the skull base in 34 patients, the hard palate in 30 patients, the pterygpalatine fossa in 29 patients, intracranial extension in 18 patients, the nasal vestibulum in 16 patients, the nasal floor in 15 patients, the nasopharynx in 14 patients, and the infratemporal fossa in 8 patients. 184 patients did not show cervical lymph node metastasis (cN0). Thirty-four patients had cervical lymph node metastasis at time of admission. In addition, 11 patients were depicted to have cervical metastasis by the diagnostic work-up. Hence, 45 patients had cervical metastasis at the start of treatment: Eighteen patients were classified with cN1 status, 16 patients with cN2 status, and 11 patients with cN3 status. Within the cN+ subgroup the lymph node metastases were distributed through the whole neck: The lymph node metastases were localized in 7 patients in level IA (submental), in 18 patients in level IB (submandibular), in 16 patients in level II/III (upper and middle jugular), in 6 patients in level IV (lower jugular), and in 4 patients elsewhere (perifacial, parotid). The relation between T status and N status is given in Table 2. Advanced N status was predominately seen in patients with advanced T status. 214 patients did not have distant metastasis. Fifteen patients already had distant metastasis at time of diagnosis: 10 patients in the lung, 4 patients in the skeleton, 2 in the major salivary glands, and 1 patient in the heart. Overall, 15 patients were classified as stage I, 22 patients as stage II, 34 patients as stage III, and 158 patients as stage IV.

Table 1
Symptoms at presentation*

Symptom	No. patients
Nasal obstruction	108
Facial swelling	97
Epistaxis	94
Pain	81
Vision loss	49
Headache	46
Rhinorrhea	39
Hyposmia/Anosmia	26
Diplopia	25
Chronic sinusitis	22
Weight loss	12
Proptosis	12
Facial sensible deficits	11
Lymph node swelling	9
Paresis of caudal brainstem nerves	9
No symptoms	7

*Some patients presented with more than one symptom.

Treatment

Surgery was performed in 182 patients either as the sole treatment modality (74 patients) or combined with radiation therapy (108 patients). Hence, multimodal therapy was the most frequent treatment. Three different modalities were used: Preoperative radiation therapy before surgery in 16 patients, postoperative radiation therapy after surgery in 74 patients, and preoperative and postoperative radiation therapy (sandwich therapy) in 18 patients. Radiation therapy was used alone in 25 patients, and combined with concurrent chemotherapy in 17 patients. Chemotherapy was administered as single treatment to 5 patients because they denied surgery or radiation therapy (2 patients) or as palliative treatment because of advanced distant metastasis (3 patients). The chemotherapeutic drugs used for most patients were cisplatin, carboplatin, 5-fluoruracil, and since some years paclitaxel. Fourteen of the 45 cN+ patients

Table 2
Relation between T and N classification

	T1	T2	T3	T4	Total
N0	16	23	29	116	184
N1	2	1	2	13	18
N2	0	1	4	11	16
N3	0	0	0	11	11
Total	18	25	35	151	229

were treated by neck dissection, 20 patients received a radiation therapy of the neck. Five patients only received chemotherapy, and the treatment of the neck was unknown in 6 patients. Surgery as single treatment was more often used for limited disease, whereas a combined modality was chosen more often for advanced disease. The histology did not seem to have an influence on the treatment modality. Only for melanoma, surgery as single treatment was predominately used (Table 3).

Oncological results

The median follow-up period for all patients was 33 months (range, 1–462 months). The median follow-up period for survivors was 126 months (range, 1–419 months). In all, 68 patients developed a recurrence and 171 patients died in the follow-up time. For the entire population, the local control rate was 79% at 2 years, 64% at 5 years, and 57% at 10 years. The disease-free survival rate was 53%, 34%, and 23% at 2 years, 5 years, and 10 years, respectively (Table 4). Operated patients had higher disease-free survival rates than non-operated patients. Using a multimodal approach, especially postoperative radio-(chemo)-therapy increased significantly the survival rates. Disease-free survival was higher in the non-operated patients if radiochemotherapy was used in comparison to radiotherapy alone. At all, the overall survival rate was 59%, 41%, 27%, and the carcinoma specific survival rate was 64%, 51%, and 45% at 2 years, 5 years, and 10 years, respectively (Table 5). Operated patients had higher overall survival rates and cancer-specific survival rates than non-operated patients. Patients that were treated by surgery alone showed the highest overall survival rates and disease-specific survival rates, but it has to be noticed that many patients in this subgroup had limited disease (T1/T2). Using a multimodal approach, patients with surgery and postoperative radiotherapy showed the highest overall and disease-specific survival rates. Tables 4 and 5 give detailed information about the survival rates related to T classification, tumor stage, and type of therapy.

Univariate survival analysis

The factors influencing local control on univariate analysis, in order of significance, were: age ($p < 0.001$), histology ($p < 0.001$), and use of radiotherapy as a part of the treatment concept ($p = 0.036$). Disease-free survival was influenced by N classification ($p < 0.001$), type of therapy ($p < 0.001$), use of surgery as part of the treatment concept ($p < 0.001$), age ($p = 0.007$), UICC stage ($p = 0.0116$), M classification ($p = 0.028$), and T classification ($p = 0.033$). Prognostic factors for overall survival were: age ($p < 0.001$); N classification ($p < 0.001$), UICC stage ($p < 0.001$), surgery ($p < 0.001$), type of therapy in general ($p = 0.001$), M classification ($p = 0.003$), T classification ($p = 0.008$), radiation therapy ($p = 0.032$), intracranial tumor infiltration ($p = 0.041$), histology ($p = 0.047$), and tumor infiltration into the orbita ($p = 0.05$). Disease-specific survival was influenced by: M classification ($p < 0.001$), UICC stage ($p < 0.001$), type of therapy ($p < 0.001$), surgery ($p < 0.001$), T classification ($p = 0.001$), N classification ($p = 0.002$), intracranial tumor infiltration ($p = 0.008$), radiation therapy ($p = 0.009$), tumor infiltration of the pterygopalatine fossa ($p = 0.02$), infiltration of the skull base ($p = 0.021$), and infiltration of the orbita ($p = 0.041$).

Multivariate survival analysis

The multivariate analysis for overall survival revealed that therapy was an independent risk factor ($p = 0.025$). Especially surgery as single treatment had a positive influence on overall survival in comparison to radio-(chemo)-therapy ($p = 0.003$), combined with radio(chemo)-therapy in comparison to radio-(chemo)-therapy alone ($p = 0.023$), or combined with preoperative and postoperative

Table 3
Cross tabulation of treatment modality by histology, and T classification

Characteristic	Surgery	Surgery and radio(chemo)therapy	Radio(chemo)therapy	Chemotherapy	Total
Global	74	108	42	5	229
Histology					
Squamous cell carcinoma	20	51	14	2	87
Sarcoma	4	9	7	0	20
Undifferentiated carcinoma	4	7	5	0	16
Adenocarcinoma	6	8	1	0	15
Melanoma	10	4	0	1	15
Adenoidcystic carcinoma	6	4	2	0	12
Miscellaneous	24	25	13	2	64
T stage					
T1	12	4	2	0	18
T2	10	15	0	0	25
T3	14	17	4	0	35
T4	38	72	36	5	151

Table 4
Local control rates and disease-free survival rates

Parameter	No.	Local control		Disease-free survival	
		5 years	10 years	5 years	10 years
All patients	229	63.7%	56.7%	33.8%	22.8%
T1	18	NA	NA	38.3%	26.4%
T2	25	76.1%	69.2%	13.2%	0%
T3	35	65.3%	NA	7.5%	0%
T4	151	67.8%	59.7%	0%	0%
Stage I	15	NA	NA	46.4%	29.0%
Stage II	22	78.0%	70.2%	55.0%	44.0%
Stage III	24	62.7%	NA	39.4%	25.7%
Stage IV	158	68.0%	NA	26.9%	16.8%
Surgery only	74	60.8%	52.5%	36.9%	23.4%
Preoperative radio(chemo)therapy and surgery	16	76.1%	NA	35.7%	23.8%
Surgery and postoperative radiotherapy	74	74.0%	66.1%	41.4%	25.5%
Surgery and pre-/postoperative radiotherapy	18	71.4%	NA	28.4%	NA
Radiotherapy only	25	NA	NA	6.5%	NA
Radiochemotherapy only	17	NA	NA	13.8%	NA
Radiotherapy ± chemotherapy	42	NA	NA	11.8%	NA

NA = not applicable.

radio-(chemo)-therapy in comparison to radio-(chemo)-therapy alone ($p = 0.013$). Advanced T classification (T2 vs T4; $p = 0.014$), advanced UICC stage (stage II vs IV; $p = 0.005$), N+ ($p = 0.005$), and distant metastasis ($p = 0.015$) were independent negative prognostic factors for overall survival. Multivariate analysis for cancer-specific survival demonstrated that T classification ($p = 0.042$), N classification ($p = 0.035$), M classification ($p = 0.007$), UICC stage ($p = 0.038$), and type of therapy ($p = 0.038$) were independent prognostic factors.

Discussion

Sinonasal carcinomas have a low incidence, a wide histologic variability, and a high variety of treatment concepts. A uniform staging system for tumors of all different sinuses is lacking. Therefore, the literature of carcinoma of the sinonasal tract is difficult to interpret. Taking into account these typical problems of a rare disease, it was valuable to analyze our large series of 229 patients treated for nasal and paranasal cancer. Of course, although large, the series suffered from the usual shortcomings of any retrospective study: mainly, a retrospective staging in some patients and non-randomized treatment selection.

Patient characteristics and problems of tumor classification

Overall, the characteristics of patients were not different to the data reported in the literature: Male patients are dominating (about two thirds), and the mean age is about 60 years.[15,16] This explains the high comorbidity which

Table 5
Overall survival rates and disease-specific survival rates

Parameter	No.	Overall survival		Disease-specific survival	
		5 years	10 years	5 years	10 years
All patients	229	40.8%	27.2%	50.5%	45.3%
T1	18	46.7%	33.3%	54.6%	51.0%
T2	25	62.5%	51.3%	27.8%	NA
T3	35	44.1%	31.9%	NA	NA
T4	151	33.7%	18.6%	24.4%	0%
Stage I	15	50.0%	41.7%	63.6%	NA
Stage II	22	66.7%	53.5%	NA	NA
Stage III	24	45.9%	30.8%	58.8%	NA
Stage IV	158	33.4%	18.7%	42.1%	34.5%
Surgery only	74	51.5%	36.3%	62.5%	NA
Preoperative radiotherapy and surgery	16	35.7%	23.8%	52.6%	NA
Surgery and postoperative radiotherapy	74	49.3%	29.4%	54.3%	47.0%
Surgery and pre-/postoperative radiotherapy	18	30.3%	NA	38.5%	38.5%
Radiotherapy only	25	12.0%	NA	21.7%	NA
Radiochemotherapy only	17	13.8%	NA	18.3%	NA
Radiotherapy ± chemotherapy	42	12.7%	NA	20.8%	NA

NA = not applicable.

frequently has to be taken into consideration for treatment planning. Similar to our results, the most commonly encountered histology is squamous cell carcinoma with 30 to 50% of the cases.[16] According to the literature and also in our study, the maxillary and ethmoid sinuses with two thirds of the cases are the most frequent primary sites. But these data might be biased by the fact that the current TNM staging system does not allow staging for frontal and sphenoid carcinomas, and often these tumors are classified as T4 ethmoid tumors.[2] Moreover, because of the non-specific symptoms in the beginning, patients are frequently diagnosed at advances stages making the localization of the primary site difficult. In the present study, the diagnosis was obtained in average two and a half months after onset of the first symptoms. In consequence, about 80% of the patients presented with advanced disease. Due to the urban background of the patients, wood dust exposure was a relevant risk factor in only 6%. It was striking that about 40% of the patients had a smoking history, confirming the evidence that smoking should be considered as a risk factor.[16,17]

Neck metastasis: diagnostics and treatment

In comparison to other types of head and neck cancer the metastasis rate is low. The literature reports of about 14% neck metastasis at the time of diagnosis.[1,18,19] This may seduce to neglect the discussion of the optimal treatment of the neck as it was even done in a recent detailed review,[2,16] although N stage is one of the most important prognostic factors. We found a higher metastasis rate of about 20% after termination of the diagnostic work-up. We believe that the higher detection rate is the consequence of the better imaging techniques that are available nowadays. Therefore, we recommend a careful neck staging, and in any N+ neck a neck dissection and postoperative radiotherapy to improve the outcome.

Outcome of single modality and multimodality treatment for sinonasal cancer

Overall, we found a local control rate of 64%, a disease-free survival rate of 34%, an overall survival rate of 41%, and the carcinoma specific survival rate of 51% 5 years after treatment. Of course, a wide range of results has to be taken into account. For instance, patients treated by surgery (predominately early stages) showed a 5-year overall survival of 52%, whereas in contrast patients treated by radiotherapy (predominately advanced and non-resectable cases) alone had an overall survival of only 13%. Nevertheless, in comparison to recent reports from other centers the oncological results are lying in the upper range of the reachable results. This might be explained by the fact that 80% of the patients were treated by a multimodal approach applying surgery and radiochemotherapy. Despite the inherent patient selection bias of either ours or other retrospective studies, it is commonly accepted that that the local control and cure rates in advanced sinonasal cancer are better with surgery and combined surgery and radiation than radiotherapy alone.[2,16] Of course, our series like others are biased in patient selection: Patients with limited disease are often selected for surgery alone. But especially the results of our multivariate analysis have clearly confirmed our interpretation. The sequence of surgery and radiotherapy in the management has remained open to debate since we and also others showed no clear difference between preoperative and postoperative radiotherapy,[15,20] but our analysis showed a trend of better results when radiotherapy was applied after surgery.

Perspectives: better radiation protocols and adjuvant chemotherapy

Newer methods of conformal radiation delivery like intensity-modulated radiation therapy may allow higher doses of radiation to the tumor while avoiding exposure to adjacent critical structures. Hence, theses methods probably will optimize the combined therapy of sinonasal carcinoma in the future.[21] However, as local disease recurrence still remains the main cause of treatment failure and death, and as we found a 5-year DSS rate of only 43% even by a combined treatment of surgery and radiotherapy for advanced sinonasal cancer, adjuvant chemotherapy appears to be a promising approach. There is increasing evidence that adjuvant chemotherapy concurrent to radiotherapy can improve survival in advanced resectable head and neck cancer.[22] Unfortunately, due to their rare incidence, sinonasal cancer is underrepresented in the large controlled studies. In the present study adjuvant chemotherapy was not applied in patients with resectable cancer. In same small studies, especially neoadjuvant chemotherapy or radiochemotherapy showed excellent local control and survival rates compared to surgery alone or of surgery combined with radiotherapy: Neoadjuvant cisplatin und 5-fluorouracil, surgery, followed by radiochemotherapy with hydroxyurea and 5-fluorouracil in 15 patients with advanced sinonasal cancer led to a 5-year overall survival rate of 73%.[23] Also primary chemotherapy with leucovorin, 5-fluorouracil, and cisplatin followed by anterior craniofacial resection and postoperative radiotherapy showed an overall survival of 69% at 3 years in 49 patients with sinonasal cancer.[24] Neoadjuvant selective intra-arterial cisplatin with concurrent radiation therapy followed by a conservative craniofacial resection is another interesting option giving overall survival rates of about 60 to 80% in small series.[25] Of course, larger controlled studies are needed to definitely evaluate these new approaches.

Additionally, more information is needed to identify precisely which patients are most suitable for such intense treatment as multimodal treatment. For this, the results of the multivariate analysis concerning the independent prognostic factors are very helpful: Advanced T stage, N+, M+,

advanced UICC stage are significant negative prognostic factors in patients with nasal and paranasal cancer. Therefore, we recommend a multimodal treatment for all patients fulfilling one of these parameters. Although subject to caveats of the non-randomized treatment selection, the analysis has also shown that patients with limited disease (T1-T2 stage, UICC stage I-II) seem to be ideally treated with surgery alone as this unimodal approach led at minimum to a 10% better 5-year OS or DSS than any multimodal approach in patients with advanced sinonasal malignancy.

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