

ORIGINAL ARTICLE

Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995–2004

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Abstract

Objective. To evaluate the treatment outcome for sino-nasal carcinomas in Denmark from 1995–2004 and compare the results to the previous Danish survey covering 1982–1991. **Design.** Retrospective follow-up. **Materials and methods.** In the five Danish head and neck oncology centres, charts of all consecutive patients with sino-nasal carcinomas were reviewed and data extracted to a common database. Altogether 242 patients from the period 1995–2004 were identified. Of these 162 (67%) were male and 80 (33%) female. Histologies included squamous cell carcinoma (55%), adenocarcinoma (28.5%), adenoid-cystic carcinoma (5.0%), undifferentiated carcinoma (4.5%), transitiocellular carcinoma (1.7%), mucoepidermoid carcinoma (0.8%), neuroendocrine carcinoma (2.5%), small cell carcinomas (1.2%) and carcinomas not otherwise specified (0.8%). Treatments included radiotherapy alone 79 (33%), surgery alone 29 (12%), combined surgery and radiotherapy 96 (40%), palliative/no treatment 38 (16%). A total of 204 (86%) patients were treated with curative intent. **Results.** Of the 204 patients treated with curative intent, 94 (46%) relapsed. Most failures were in T-site (63, 30%). N-site failures were 10 (5%) and M-site failures six (3%). Failure occurring in T+N-site, T+M-site, N+M-site and T+N+M-site were seven (3%), two (1%), one (0.5%) and five (3%) respectively. The 5-year actuarial local, nodal and loco-regional control rates were 55±4%, 86±3%, 49±4%, respectively. The overall 5-year actuarial survival rate for the entire cohort was 47±3%, and the corresponding cancer-specific 5-year actuarial survival rate was 57±3%. Female gender, nasal cavity tumour, adenocarcinoma and low clinical stage were significant positive prognostic factors in univariate analysis. A Cox multivariate analysis showed that only tumour site and clinical stage were independent significant prognostic factors. **Conclusion.** The current series has confirmed stage and tumour site as independent prognostic factors. Compared to the previous Danish survey covering the period 1982–1991, the overall survival and cancer-specific survival rates have improved significantly.

Carcinomas of the nasal cavity and the paranasal sinuses are rare. The many different histologies and subsites, with proximity of sensitive organs, further add to the complexity of management of this disease. Outcome research is thus difficult, as institutional series often include too few patients to establish the prognostic value of the various parameters. This calls for studies

on a larger scale, facilitating a more valid analysis of the treatment outcome in a multivariate setting.

In Denmark, patients with sino-nasal cancer are treated and followed within one of the five head and neck oncology centres.

The Danish Society for Head and Neck Oncology (DSHHO) has previously published treatment

outcome for sino-nasal cancer patients treated in the period 1982–1991 [1]. Since then, DSHHO and the Danish Head and Neck Cancer Group, DAHANCA, have published a set of national guidelines for the diagnostics, treatment and rehabilitation of these patients (2007). In this context, an update of the nationwide experience, covering the patients treated 1995–2004 was done. The present study is an evaluation of the treatment outcome from the five Danish centres treating sino-nasal cancer, and the results are compared to the 1982–1991 study.

Material and methods

In the five Danish head and neck oncology centres, patient charts, radiology reports and pathology reports, of patients with malignant disease of the nasal cavity, maxillary sinus, ethmoid sinus, sphenoid sinus and frontal sinus diagnosed from 1995 to 2004 were reviewed. Results were entered into a common DAHANCA database.

Patients were identified by searching local registries for cases of malignancy in the nasal cavity (excl. the nasal vestibule), the maxillary sinus, the ethmoid sinus, the frontal sinus, the sphenoid sinus and paranasal sinuses not otherwise specified, corresponding to ICD-10 codes C 30.0, C 31.0–C31.3, C 31.8 and C31.9. After reviewing the charts of these patients, relevant patients were included in the study.

A total of 242 patients were included (Copenhagen: 68, Herlev: 57, Odense: 34, Aarhus: 59, Aalborg: 24); 162 (67%) were male and 80 (33%) were female (Table I). The median age was 65 years (20–91).

Tumour origin and involvement was determined by the description of the clinical examination supported by imaging techniques, mainly CT scans, as well as by the surgical findings. One hundred and sixty patients (66%) had tumours originating in the nasal cavity. In 62 cases (26%) the tumour originated in the maxillary sinus. Tumours of the remaining paranasal sinuses were rare: Ethmoid sinus: 15 (6%), sphenoid sinus: four (2%) and frontal sinus: one case. The majority of the patients presented with squamous cell carcinomas, 133 cases (55%). The other major group was adenocarcinomas, 69 cases (29%). Remaining cases presented adenoid-cystic carcinoma 12 (5%), undifferentiated carcinoma 11 (5%), transitiocellular carcinoma four (2%), neuro-endocrine carcinoma six (2%), small cell carcinoma three (1%), muco-epidermoid carcinoma two (1%) and carcinoma Not Otherwise Specified (NOS) two (1%). Pathology reviews specific for this study were not performed.

The patients were retrospectively staged according to the UICC 2002 based on the description of the clinical examination as well as radiological and

pathological findings. The retrospective staging proved possible in most cases; in only three cases staging was not possible.

The tumours were often presented at a late stage. Stage distribution was: Stage 1: 28 (12%), Stage 2: 32 (13%), Stage 3: 63 (26%), and Stage 4: 116 (47%). Thus 179 patients (74%) presented Stage 3–4 disease.

Thirty-eight patients (16%) received palliative treatment or no treatment. Two hundred and four patients (84%) were treated with curative intent. Of these patients, 96 (47%) were treated with combined radiotherapy and surgery, 29 (14%) with surgery alone, and the remaining 79 (39%) received radiotherapy alone. Elective neck treatment was only performed in cases where neck lymph node metastases were clinically present.

Of the 96 patients treated with the combined approach of both surgery and radiotherapy, 83 patients (87%) had primary surgery and postoperative radiotherapy. The type of surgery most widely used for radical treatment was lateral rhinotomy, cases, consistent with the high number of nasal cav-

Table I. Demographic distribution.

Parameter	Total	Patients treated with curative intent
N	242	204
Gender		
Male	162	143
Female	80	61
Histology		
Squamous cell carcinoma	133	112
Adenocarcinoma	69	63
Adenoid-cystic carcinoma	12	10
Undifferentiated carcinoma	11	8
Transitiocellular carcinoma	4	3
Neuro-endocrine carcinoma	6	4
Small cell carcinoma	3	2
Muco-epidermoid carcinoma	2	2
Carcinomas not otherwise specified	2	0
Primary Tumour Site		
Maxillary sinus	62	51
Nasal cavity	160	136
Frontal sinus	1	1
Sphenoid sinus	4	1
Ethmoid sinus	15	15
Age		
–65	150	112
66+	92	92
Stage (UICC 2002)		
1	28	28
2	32	32
3	63	56
4	116	85
1+2	60	60
3+4 (advanced)	179	141
Staging not possible	3	3

ity tumours. Endoscopic skull base surgery was used increasingly in the latter half of the period.

Statistical methods

Treatment outcome was analysed actuarially using the Kaplan-Maier method and Cox multivariate analysis. Endpoints were loco-regional control defined as complete absence of recurrence in T-site and N-site, cancer-specific and overall survival. All time estimates were calculated from the date of the first consultation at the oncology centre, either the ENT departments or the oncologic departments. The vital statuses of all living patients were cross-checked with the centralised Danish Civil Registration System per April 1st, 2008. The data were analysed using SPSS for Windows, version 13.0, statistical software. For comparison with the previous Danish study [1], the original data from this study regarding carcinomas treated with curative intent were obtained.

Results

The failure pattern is shown in Figure 1. A total of 204 patients were treated with curative intent. Of these, treatment failure occurred in 94 patients (46%), and 110 (54%) remained disease-free after the primary treatment. Failure most frequently involved the T-site (81%), either isolated or together with N-site and/or M-site. Sites of failure were: T-site: 63 (31%), N-site: 10 (5%), M-site: six (3%), T+N: seven (3%), T+M: two (1%), N+M: one (.5%) and T+N+M: five (3%) (percentage of patients treated with curative intent).

For all patients (palliative and curative) the 5-year loco-regional control, disease specific and overall survival were 41%, 57%, and 47%, respectively. For patients treated with curative intent only, the similar values were 49%, 66%, and 55%, respectively. The 5-year actuarial analysis of prognostic factors for outcome is shown in Table II. Age did not influence the cancer-specific survival or loco-regional control. Histology was not a major significant factor apart from adenocarcinoma patients (compared to the other major group of squamous cell carcinomas) having a relatively better prognosis. There was no significant difference in treatment outcome between the five centres in loco-regional control and cancer-specific survival. When tested in a univariate analysis there was a significant difference in loco-regional control for the following factors: Treatment modality ($p=0.001$), tumour localisation ($p=0.000$) and tumour stage ($p=0.001$). This effect was also the case in cancer-specific survival ($p=0.023$, $p=0.000$

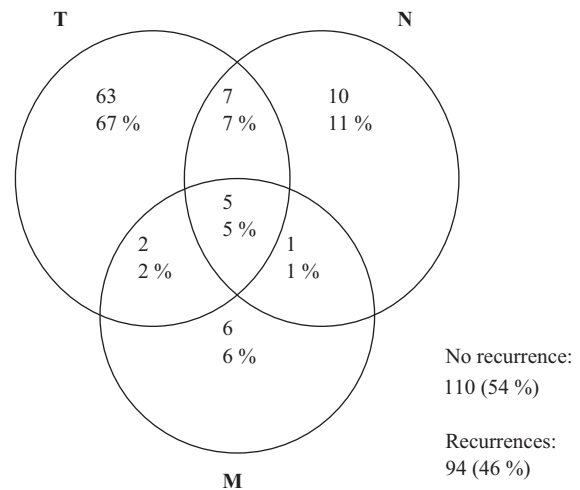


Figure 1. Failure pattern: N=204 (all patients treated with curative intent) Numbers in circles represent: Recurrences in each site

and $p=0.000$, respectively) and overall survival ($p=0.000$, $p=0.000$ and $p=0.000$, respectively).

When tested in a Cox multivariate analysis, tumour localisation in the nasal cavity and having received combined surgery and radiotherapy were independent prognostic factors for loco-regional disease control. For cancer-specific survival, tumour stage and localisation were independently significant whereas the treatment was not.

The results found in this study were compared to the results of the previous Danish study [1]. (Figure 3) The results showed a significant improvement in cancer-specific 5-year survival from 42 to 66% ($p=0.000$), and correspondingly in overall survival from 34 to 55% ($p=0.000$). The 5-year loco-regional disease control was 41% in 1982–1991 and 49% in 1995–2004 ($p=0.069$).

The improved survival was significant also when stratifying for localisation, histology, and treatment, respectively. Also, the treatment of recurrences has improved. The cancer-specific survival from the time of first recurrence has improved significantly from $15\% \pm 3\%$ to $24\% \pm 5\%$ ($p=0.016$).

Discussion

The current nationwide outcomes analysis of sinonasal cancer 1995–2004 shows encouraging improvements compared to our earlier series. Survival has improved by more than 20 percentage-points. Several factors contribute to this positive development. Most importantly, there has been a shift to more tumours in the nasal cavity, a location with better prognosis than other sites. The reason for this shift is unknown, but it is possible that more of the larger carcinomas that also involve the sinuses have been

Table II. Data in Table I represent the 5-year actuarial estimate \pm standard error, using the Kaplan-Meier method. The significance level is 5% for all tests. Estimates were carried out for patients treated with curative intent.

	No. of patients	Loco-regional control		Cancer-specific survival		Overall survival	
		(%) \pm s.e.	p-value	(%) \pm s.e.	p-value	(%) \pm s.e.	p-value
Patients treated with curative intent	204	49 \pm 4		66 \pm 4		55 \pm 4	
Gender							
Male	143 (70%)	42 \pm 5		63 \pm 4		53 \pm 4	
Female	61 (30%)	66 \pm 7		72 \pm 6		60 \pm 6	
			0.019		0.069		0.112
Age							
\leq 65	112 (55%)	52 \pm 5		67 \pm 5		64 \pm 5	
$>$ 65	92 (45%)	44 \pm 7		64 \pm 5		45 \pm 5	
			0.739		0.698		0.000
Histology							
Squamous cell carcinomas	112 (55%)	49 \pm 6		59 \pm 5		48 \pm 5	
Adenocarcinomas	63 (31%)	55 \pm 7		72 \pm 6		61 \pm 6	
Other Carcinomas	29 (14%)	43 \pm 11		78 \pm 8		69 \pm 9	
			0.177		0.177		0.162
Localisation							
Maxillary sinus	51 (25%)	26 \pm 9		45 \pm 8		33 \pm 7	
Nasal cavity	136 (67%)	61 \pm 5		74 \pm 4		66 \pm 4	
Ethmoid sinus	15 (7%)	22 \pm 13		62 \pm 14		47 \pm 13	
			0.002		0.000		0.000
Nasal cavity	136 (67%)	61 \pm 5		74 \pm 4		66 \pm 4	
Other localisations	68 (33%)	24 \pm 7		49 \pm 7		35 \pm 6	
			0.000		0.000		0.000
UICC 2002 stage							
1	28 (14%)	85 \pm 7		100		93 \pm 5	
2	32 (16%)	42 \pm 13		78 \pm 8		65 \pm 9	
3	56 (27%)	51 \pm 8		69 \pm 7		57 \pm 7	
4	85 (42%)	37 \pm 6		47 \pm 6		38 \pm 5	
			0.001		0.000		0.000
1+2	60 (29%)	62 \pm 8		87 \pm 4		77 \pm 5	
3+4	141 (69%)	42 \pm 5		56 \pm 4		46 \pm 4	
			0.009		0.000		0.000
Treatment							
Surgery	29 (14%)	32 \pm 12		74 \pm 9		65 \pm 9	
Radiotherapy	79 (39%)	34 \pm 7		55 \pm 6		40 \pm 6	
Surgery and radiotherapy	96 (47%)	64 \pm 6		72 \pm 5		65 \pm 5	
			0.001		0.023		0.000

counted as nasal cavity in the current series compared to the previous series. Secondly, the loco-regional control has improved. It may be speculated, that this is due to improved surgical procedures with more tumours being primarily resected in a combined treatment approach, but this could not be substantiated by the present data. Introduction of skull base teams and endoscopic techniques are the most

important changes in the surgical approach. Finally, it is encouraging that the survival after first recurrence has improved almost 10 percentage point.

Despite the positive development, there is still a significant proportion of patients who die from the disease. The main problem remains to obtain tumour control in the primary site, an issue that has been pointed out in various studies [1–3]. The present study shows

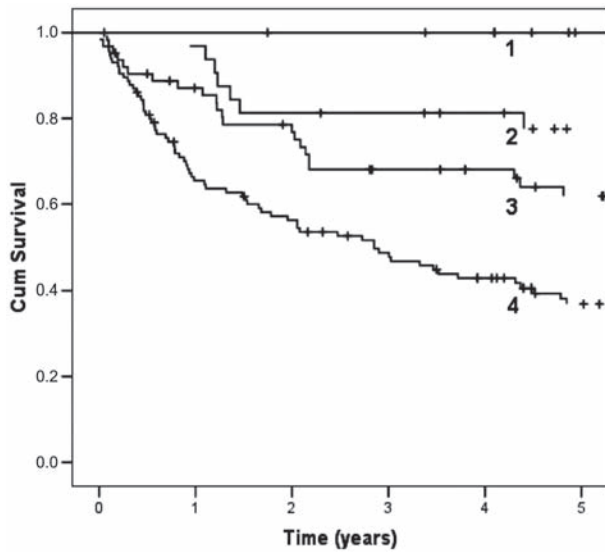


Figure 2. Cancer-specific 5-year actuarial survival, UICC 2002 stages 1–4.

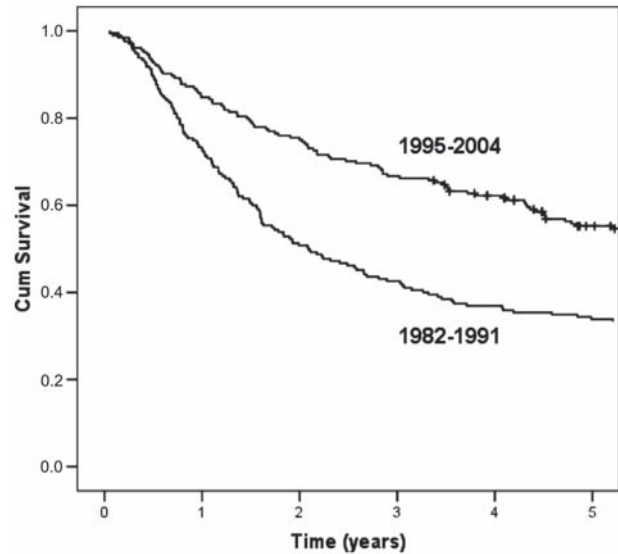


Figure 3. Overall 5-year actuarial survival 1982–1991 and 1995–2004.

that the combined therapy approach has a clear advantage in achieving T-site control, and thus the accessibility of the tumour for surgical resection is crucial.

The identification of tumour location, stage and treatment modality as prognostic factors in respect to loco-regional control as well as cancer-specific and overall survival is demonstrated in various earlier studies [1,3–8].

It has been suggested that stage 4 patients should be treated with elective neck irradiation [6,9]. Based on the present study, the approach of restricting neck irradiation to cases with verified neck lymph node metastases seems reasonable since isolated N-site recurrences were rare. Of 85 stage 4 patients, 15 had N-site recurrence and of these, only four were isolated N-site recurrences. This low number does not justify treating the neck in all patients since it would require bilateral neck dissection or bilateral irradiation, procedures which are associated with significant morbidity for the patients.

This is one of the first larger series to confirm the usefulness of the new AJC/UICC staging system for

all subsites of sinonasal cancer. Previous versions only included the maxillary and ethmoid sinuses. It is our experience that the classification system is easy to use, also for retrospective classification. The data in Figure 2 confirm that this classification is indeed able to separate patients in different risk groups, with cancer specific survival rates going from 100% for Stage I patients to 37% for stage 4. Similar results have been found in other studies [3,5,7–9].

In conclusion, the current series has confirmed stage and tumour site as independent prognostic factors (Table III). Compared to the previous Danish survey covering the period 1982–1991 the overall survival and cancer-specific survival rates have improved significantly.

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Table III. Cox multivariate analysis of prognostic factors for cancer-specific death in patients with adenocarcinoma or squamous cell carcinoma

Parameter	Relative risk	95% confidence interval	Significance
Combined therapy vs. monotherapy	N.s.	-	0.212
Advanced disease (stage 3–4) vs. Stage 1–2	3.4	1.63–6.96	0.001
Adenocarcinoma vs. SCC	N.s.	-	0.196
Nasal cavity vs. Other localisations	0.48	0.29–0.80	0.005
Male vs. Female	N.s.	-	0.196

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Grau C, Jakobsen MH, Harbo G, Svane-Knudsen V, Wedervang K, Larsen SK, et al. Sino-nasal cancer in Denmark 1982–1991—a nationwide survey. *Acta Oncol* 2001;40:19–23.
- [2] Dulgerov P, Allal AS. Nasal and paranasal sinus carcinoma: How can we continue to make progress? *Curr Opin Otolaryngol Head Neck Surg* 2006;14:67–72.
- [3] Hicsonmez A, Andrieu MN, Karaca M, Kurtman C. Treatment outcome of nasal and paranasal sinus carcinoma. *J Otolaryngol* 2005;34:379–83.
- [4] Bhattacharyya N. Cancer of the nasal cavity: Survival and factors influencing prognosis. *Arch Otolaryngol Head Neck Surg* 2002;128:1079–83.
- [5] Dulgerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: Are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001;92:3012–29.
- [6] Katz TS, Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Villaret DB. Malignant tumors of the nasal cavity and paranasal sinuses. *Head Neck* 2002;24:821–9.
- [7] Harbo G, Grau C, Bundgaard T, Overgaard M, Elbrond O, Sogaard H, Overgaard J. Cancer of the nasal cavity and paranasal sinuses. A clinico-pathological study of 277 patients. *Acta Oncol* 1997;36:45–50.
- [8] Carrillo JF, Guemes A, Ramirez-Ortega MC, Onate-Ocana LF. Prognostic factors in maxillary sinus and nasal cavity carcinoma. *Eur J Surg Oncol* 2005;31:1206–12.
- [9] Myers LL, Nussenbaum B, Bradford CR, Teknos TN, Esclamado RM, Wolf GT. Paranasal sinus malignancies: An 18-year single institution experience. *Laryngoscope* 2002;112:1964–9.