Rhinology, 37, 117–121, 1999

Squamous cell carcinoma of the nasal vestibule*

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SUMMARY

From 1978 to 1992, 66 patients (32 women and 34 men) were treated for carcinoma of the nasal vestibule at Odense University Hospital. The treatment was radiotherapy (41 patients), surgery (13 patients) or a combination of the two modalities (12 patients). Twenty-one patients (32%) developed recurrence. Of these, 17 (81%) were diagnosed within the first two years of follow up. The recurrence rate was found to be correlated to the anatomic site of the tumour-origin; septal site of origin meant higher risk of recurrence. Five-year disease specific and crude survival of all patients were 87.0% and 58.5%, respectively. Several variables (sex, age, anatomic site of origin, Wang-classification, tumour volume and regional lymphnode metastases at time of diagnosis) were evaluated as possible prognostic indicators. In univariate analysis, regional lymph node metastases at the time of diagnosis and anatomic site of origin of the tumour showed a significant influence on survival. In multivariate analysis, septal origin of primary tumour was a significant, independent predictive factor of recurrence and the presence of lymph node metastases at the time of diagnosis showed to be a highly significant prognosticator of both disease specific and crude survival ($p<0.0001$).
We conclude that patients with primary lymph node metastases and septal location of primary tumour need intensive primary treatment and close follow up.

Key words: cancer of the nasal vestibule, squamous cell carcinoma, survival, results of treatment

INTRODUCTION

Squamous cell carcinoma (SCC) of the nasal vestibule is a rare condition. Surgery and radiotherapy are the most used therapy entities, but no golden standard has been defined[1,2,3]. Several papers describe the disease. However, the relatively small number of patients in the studies makes it hard to draw firm conclusions[1,3,4,5]. An international classification has never been accepted. Therefore, comparisons among different series are difficult. The purposes of this study were to contribute further clinical information about carcinomas of the nasal vestibule and to identify possible prognostic indicators, which might be useful in the planning of treatment.

MATERIAL AND METHODS

Patients with histologically verified SCC of the nasal vestibule, treated at the Head and Neck Oncology Center, Odense University Hospital from 1978 to 1992 were included in the study. Histological revision of the material was not performed. As UICC has no T-classification for cancers of the nasale vestibule, the extension of the tumours were classified according to Wang (14; Table 1). For the N- and M-classification the general rules of the UICC (1992) were applied[6].

Treatment consisted of surgery or radiotherapy or a combination of these two modalities. No guidelines or reference programs were followed. Radiotherapy to the T-site was administered as external beams of electrons.

Registration of data concerning symptoms, signs, tumourvolume and treatment was done retrospectively by review of patients records. The tumour volume was assessed with the measurement of three tumour diameters, which were put into the formula for an ellipse:

Tumour volume (cm^3) = 22/42 * d.1 * d.2 * d.3., where d is the diameter.

The database and analysis system "Medlog" was used for the statistical analysis. For analysis of categorical data including two groups, a x^2-test with correction or a Fisher's exact test was used[8]. Fisher's exact test was used when the overall total was between 20 and 40 and the smallest expected numbers was less than five. Survival curves were calculated by the Kaplan-Meier method [7], and compared by the Mantel-Haenzel test[8]. For mul-

* Received for publication September 30, 1998; accepted May 10, 1999

Table 1. T-clasifidication for cancers of the nasale vestibule proposed by Wang.

DEFINITION	STAGE
The lesion is limited to the nasal vestibule, relatively superficial, involving one or more sites within.	T1
The lesion has extended from the nasal vestibule to its adjacent structures, such as the upper nasal septum, upper lip, philtrum, skin of the nose and/or the nasolabial fold, but not fixed to the underlying bone.	T2
The lesion has become massive with extension to the hard palate, buccogingivale sulcus, large portion of the upper lip, upper nasal septum, turbinate and/or adjacent paranasal sinuses, fixed with deep muscle and bone involvement.	T3

tivariate analysis the Cox regression model was used[9]. The assumption of proportionality between mortality rates was confirmed by graphical methods. Backward selection procedures were performed.

RESULTS

Sixty-six patients were included in the study. Age and sex distribution is shown in Figure 1. The median age at the time of diagnosis of the overall series was 68 years (range: 34-85). The primary symptom was a growing tumour (49%), ulceration (28%), other symptoms (17%) and no information (6%). The anatomic site of origin involved the septum in 29 patients (44%), the floor of the vestibule in 19 patients (29%), and the ala in 16 patients (24%). Two patients (3%) had their lesions located to the roof of the vestibule. The extension of the primary tumours is described and categorised according to the Wang classification (Table 2). The median volume of the primary tumours was estimated to 0.52 cm^3 (range: 0.01-33.5).

Regional lymph node metastases were found in five cases (6%). One of these was classified N1 (20%) and four were classified N2 (80%). In all of the five N-positive patients the submandibular region was involved. Only one patient (1%) had primary distant metastases (pulmonary).

As primary treatment 13 patients (20%) received only surgery (11 patients had extirpation of the tumour and two ablation of the nose) (Table 3). In 12 of these cases (92%) the surgical intervention was considered radical by the surgeon, and in one case (8%) no comments concerning radicality was registered in the patient records. By evaluation of the histo-pathological records it was found that 11 of the patients (85%) had no microscopical signs of residual tumour. In one case no histological evaluation of the surgical radicality was done, and in another the microscopy was suspicious for residual tumour. However, this patient did not receive adjuvant therapy. Forty-one patients received primary external radiotherapy with a median dose of 60 Gy (range: 16-71 Gy) in 30 fractions (range: 8-35). The treatment was given as 5 fractions per week. The field area depended on the size of the tumour, but was in average 36 cm^2. A combination of surgery and radiotherapy was given to 12 patients (18%).

To evaluate if one or more factors were influencing the choice of the treatment, the use of primary surgery was correlated to patient age at diagnosis, T-status (Wang), N-status and tumour-site (Table 1). No such correlation was found. As a part of the primary treatment four had a radical neck dissection. Three of these showed regional lymph node metastases.

The median follow-up time for patients alive at last control was 6.0 years (range: 0.3-17.1 years). Twenty-one patients (including three never free of tumour) had recurrent disease within the time of follow-up. Seventeen of these (81%) had their recurrence diagnosed within the first two years after primary treatment. The localisations of the recurrences are shown in Table 4. The five-year recurrence free survival rate (RFS) was 69% (Table 5). The recurrence frequency for females and males was equal. Figure 2 shows the recurrence free survival (RFS) for the overall material. Twelve patients received salvage surgery,

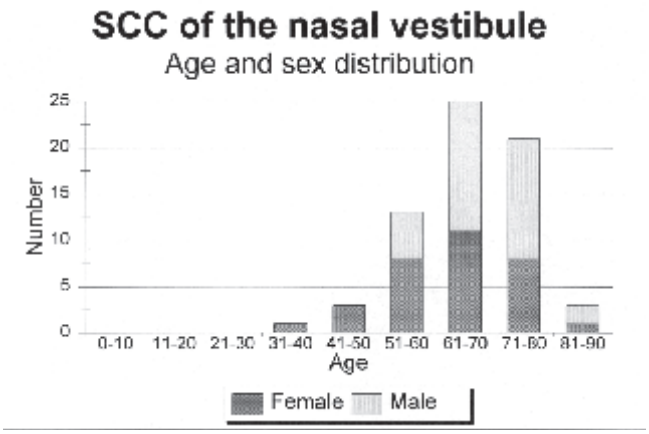

Figure 1. Age and sex distribution for 66 patients with cancer of the nasale vestibule.

Table 2. Distribution according to the classification of Wang (14) in a series of 66 patients with squamous cell carcinoma of the nasal vestibule.

T-Status (Wang)	Number	Percent
T1	36	55
T2	23	35
T3	7	11
Total	**66**	**101**

Table 3. Distribution of primary treatment according to T-stadium (Wang) in a series of 66 patients with squamous cell carcinoma of the nasal vestsibule.

	Number	Percent	T1	T2	T3
Surgery	13	20	8	5	0
Radiotherapy	41	62	23	15	3
Surgery and radiotherapy	6	9	4	1	1
Radiotherapy and surgery	6	9	1	2	3
Total	**66**	**100**	**36**	**23**	**7**

Table 4. Distribution of recurrence positions of 21 patients with squamous cell carcinoma of the nasale vestibule (three patients never free of tumour are included).

	Number	Percent
T-position	16	76
N-postion	3	14
N- and M-position	1	5
M-position	1	5
Total	**21**	**100**

which was tumour extirpation (9 patients: recurrence in T-position) and neck dissection (3 patients: recurrence in N-position). All were treated with a curative intention. Salvage radiotherapy was given to two patients. Six patients had no salvage treatment because of advanced disease or bad general condition. Reconstructive surgery as part of the treatment of the first recurrence, was performed in 10 patients. Split skin graft and nasolabial transposition flap were the most used operations. A bone transplantation to the nose was performed in 3 patients.

All of the primary N-positive patients had recurrent disease and a significantly poorer RFS-rate than those without regional spread ($p<0.0001$). By univariate analysis sex, age, T-status (Wang), tumour-localisation, tumour-volume (dichotomized by the median), histopathological radicality, and primary treatment were found without any significant influence on the 5-year RFS (Table 5). However, comparing RFS for patients with a septal origin of tumour to a group composed by those with alternative primary sites with a log rank test (using all of the observation time) a significantly poorer result ($p<0.001$) was found for the "septal" group. In a multivariate Cox regression analysis (based on RFS)

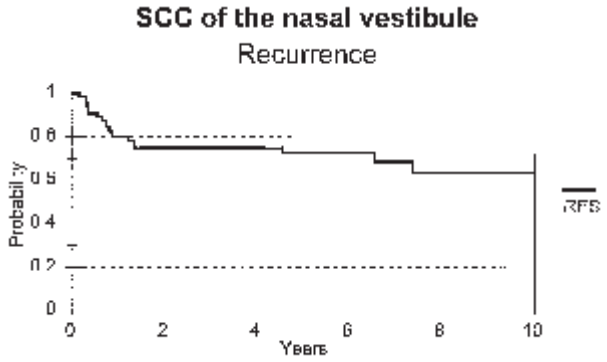

Figure 2. Recurrence free survival (RFS) for 66 patients with cancer of the nasale vestibule.

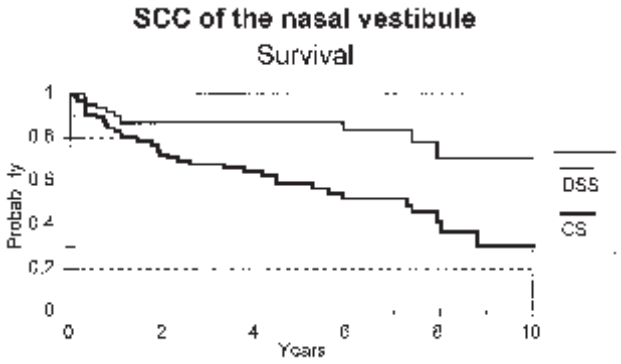

Figure 3. Disease specific and crude survival for 66 patients with cancer of the nasale vestibule.

Table 5. Five-year recurrence free survival (RFS), disease specific survival (DSS), and crude survival (CS) correlated to clinical and histological variables for 66 patients with cancer of the nasale vestibulum.

	N	5 years (%)	RFS C.I.*	5 years (%)	DSS C.I.*	5 years (%)	CS C.I.*
All pat.	66	69	57-81	87	79-95	59	47-71
Female	32	74	58-89	86	74-99	67	49-84
Male	34	65	47-82	88	76-100	52	35-69
<67,8 years of age	33	74	58-89	94	85-100	75	60-90
>67,8 years of age	33	64	46-82	80	66-94	43	25-61
T1 (Wang)	36	76	61-91	91	82-100	67	51-83
T2 (Wang)	23	58	37-79	80	63-98	42	21-61
T3 (Wang)	7	71	38-100	83	53-100	57	20-94
N-negative	61	75	64-87	93	86-100	62	49-75
N-positive	5	0	0-0	0	0-0	0	0-0
Located septum	29	57	39-76	79	63-94	61	42-79
Located ala	16	86	67-100	89	68-100	54	29-79
Located floor	19	76	54-97	88	72-100	57	34-80
Located roof	2	–	0-100	100	100-100	50	0-100
<0.52 cm^3	32	76	60-90	86	74-99	67	50-84
>0.52 cm^3	34	63	46-80	87	76-99	52	34-69
Primary surgery	13	75	51-100	92	78-100	69	44-94
Primary irradiation	41	66	51-81	86	75-97	48	32-64
Combined	12	83	62-100	83	62-100	83	62-100

* C.I.: Confidence Intervals

including gender, tumour volume, age, primary radiotherapy and anatomic site of origin the septal site of primary tumour appeared to be a significant and independent prognostic factor.

The 5-year disease specific survival (DSS) and crude survival rates (CS) were 85% and 59%, respectively. Kaplan-Meier plots illustrating DSS and CS of the overall material are shown in Figure 3. To identify possible prognostic indicators the patients were categorized according to sex, localisation of primary tumour (septum, alae, floor, roof), tumour volume, T-status (Wang) and N-status. Univariate survival analyses were performed (Table 5). RFS, DSS and CS were used as endpoints. Patients with neck metastases at the time of diagnosis were found to have significant lower values for both DSS and CS (Table 5). To evaluate if the choice of primary treatment (external irradiation, surgery, or a combination) was of prognostic importance, the patients were allocated to the relevant groups and univariate survival analysis performed (Table 5). The results showed no significant differences between groups. To correct for prognostic influence from the patient age, tumour volume, and gender a Cox regression analysis including these variables was performed. The age and the tumour volume were included as continuous variables in the multivariate analysis. "Death from all causes" was chosen as endpoint. The multivariate analysis showed that the presence of regional lymph node metastases was a highly significant prognostic factor ($p<0.0001$). The relative risk (RR) was 10.2 (95% confidence interval: 3.5-30.5). Also the age at diagnosis showed significant prognostic influence ($p=0.002$) in this analysis.

DISCUSSION

In no study the incidence of squamous cell carcinomas of the nasal vestibule is discussed. Therefore, a comparison of the frequency in different geographical regions is not possible. The patients in our study came from the county of Funen and the 2 southern counties of Jutland in Denmark, containing 1 million inhabitants. Sixty-six patients were admitted to the Head and Neck Cancer Centre at the University Hospital of Odense during a period of 16 years. Hence the annual incidence of squamous cell carcinoma of the nasal vestibule is 0.41 per 100.000 inhabitants. It is likely that the real incidence might be higher, because of patients treated by their own ENT-specialist without reference to the Centre.

In contrast to other studies, where more males than females are affected [2, 3, 4, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19], our material shows a nearly equal distribution between sexes.

As mentioned before, there is no international tumour-classification for the nasal vestibule. Comparing of different studies is therefore very difficult, but essential for further investigation and improvement in treatment and knowledge. We can not recommend Wang's classification as it didn't show any prognostic value in our study. We hoped that tumour volume was a prognostic indicator and a possible parameter of classification. However, in this relatively small material the tumour volume was not a significant prognostic indicator. Further investigation, including a larger number of patients and more precise methods of volume estimation, may show that tumour volume might contain significant prognostic information.

In literature, the choice of treatment for early staged disease seems to be a controversial issue [2, 3, 4, 5, 10, 12, 14, 15, 17, 22]. Supporters of radiotherapy recommend this modality especially for the excellent cosmetic results [1, 3, 10, 14, 19, 20, 22].

There is no agreement concerning the advanced lesions. Vendelbo et al.[13], and Patel et al.[10], prefer surgery in spite of the risk of cosmetic complications. Other authors support radiotherapy [2, 12, 14]. In our study no significant differences in survival or recurrence were found comparing primary surgery to primary external irradiation. However because of of the size of our material and the design of the study we are not able to conclude on this subject. A randomized prospective study is missing.

The septum is the most involved anatomic site of the tumour [2, 11, 17, 19, 20, 21]. Mak et al., stated in their study that the tumours located to the nasal septum or with extension to the septum have an unfavourable prognosis. In fact 50% developed local recurrences, whereas no recurrence was seen if the septum was not involved[20]. We also found that tumours originating from the septum had a significantly higher risk of recurrence. Possibly, it is the most difficult area of the nasal vestibule to treat curatively. Perhaps a more aggressive treatment should be considered for tumours involving the septum.

Approximately eight percent of the patients had regional lymph node metastases at the time of presentation. Other studies have shown rates between 0 and 14 percent [1, 2, 4, 5, 11, 12, 13, 14, 17, 18, 19, 20, 21, 22, 23, 24]. In accordance with other investigations [3, 10, 12, 18, 21, 25] our results show that the presence of lymph node metastases is correlated to a very poor prognosis. In fact, our results showed that all patients with primary lymph node metastases died of the disease. The presence of primary lymph node metastases in head and neck tumours generally means a poor prognosis [27, 28], but far from the astonishing bad situation when dealing with carcinoma of the vestibule. However, most authors agree that elective treatment of clinically uninvolved regional lymph nodes is not preferable because of a low benefit and a low incidence [5, 10, 12, 14].

Six percent developed a recurrence in the regional lymph nodes. Other studies have shown rates between 0 and 11 percent [1, 10, 11, 12, 14, 15, 19, 20, 23, 24]. Because the nodal failure rate is low most authors conclude that elective lymph node resections of the neck are not necessary[5, 10, 12, 14, 15, 16, 23,25]. We found in agreement with Vendelbo et al., that most local and regional recurrences are diagnosed during the early period of follow-up[13].

Squamous cell carcinoma of the nasal vestibule has a relative good prognosis. Most studies indicate a 5 years disease specific survival rate between 64 and 97 percent (some studies investigated only smaller tumours). This is in agreement with our study; 87% 5-years disease specific survival. Early presentation and low incidence of nodal spread may be the reasons.

Other studies have found that radiotherapy dose[12,20], tumour size[13,15,20], "Wang classification"[13], histological graduation[15,20], sex[13,15] and bone involvement[5] are significant prognostic factors. We conclude that presence of regional lymph node metastases at first presentation is a highly significant prognostic factor indi-

cating the need for intensive treatment. Septal location of primary tumour is a significant factor for local recurrence also indicating the need for more aggressive treatment.

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