Sinonasal Adenocarcinomas: Our Experience

José Luis Llorente, Faustino Núñez, Juan Pablo Rodrigo, Ramón Fernández León, César Álvarez, Mario Hermsen, and Carlos Suárez
Servicio de Otorrinolaringología y Unidad de Base de Cráneo, Instituto Universitario de Oncología del Principado de Asturias, Hospital Central Universitario de Asturias, Oviedo, Asturias, Spain

Introduction and objectives: Sinonasal adenocarcinoma is a rare epithelial cancer of the nasal cavities and paranasal sinuses and exposure to sawdust particles is a strong aetiological factor.
Material and method: Seventy-nine patients (78 men and 1 woman) operated on between 1986 and 2002 were studied.
Results: In 62 patients (78.5%) there was a history of exposure to wood dust. The clinical factors presenting statistical significance in the multivariate analysis with prognosis were: the exclusive invasion of the middle concha (as good prognosis), recurrence, and invasion of the dura mater (as bad prognosis). The actuarial survival rate was 36% at 5 years falling to 28% at 10 years.
Conclusions: Exposure to wood dust, even over a short period of time, must be considered as a high risk factor for the development of a sinonasal adenocarcinoma. This tumour must be ruled out in all patients suffering any type of sinonasal pathology.

Key words: Sinonasal adenocarcinoma. Paranasal tumours. Head and neck. Wood dust.

Adenocarcinomas nasosinusales: nuestra experiencia

Introducción y objetivos: Los adenocarcinomas nasosinusales (ADNS) son tumores epiteliales malignos de las fosas nasales y los senos paranasales cuya etiología está muy relacionada con la exposición al polvo de madera.
Material y método: Se estudió a 79 pacientes operados entre los años 1986 y 2002 de los que 78 eran varones y 1 mujer.
Resultados: En total, 62 (78,5%) pacientes tenían el antecedente de trabajar en contacto con polvo de madera. Los 3 factores clínicos que presentaron significación estadística con el pronóstico en el análisis multivariable fueron: la invasión exclusiva del cornete medio (buen pronóstico), que se tratase de una recidiva o la invasión de la duramadre (como mal pronóstico). La supervivencia fue de un 36% a los 5 años, que disminuyó a un 28% a los 10 años.
Conclusiones: El antecedente de haber trabajado en contacto con la madera, aunque sea por corto tiempo, se debe considerar como un factor de riesgo elevado para desarrollar un ACNS, en estos casos es necesario descartarlo ante todo paciente que presente cualquier tipo de afección nasosinusal.

Palabras clave: Adenocarcinomas nasosinusales. Tumores paranasales. Cabeza y cuello. Polvo de madera.

INTRODUCTION

Sinonasal adenocarcinomas (SNAC) are malignant epithelial tumours of the nasal fossae and paranasal sinuses, characterized by glandular structures.[1]

The overall incidence of sinonasal tumours is less than 1 case per 100 000 inhabitants/year, of which between 4% and 20% are adenocarcinomas. In Europe, the incidence of SNAC is 0.19 cases per 100 000 inhabitants/year.[1,2] There are also regions with greater prevalence, such as Spain and northern Europe.

The most frequent location (85%) is in the ethmoid and the upper part of the nasal fossae (superior and middle conchae and middle meatus), followed by the maxillar sinus (10%), and is exceptional in the rest of the sinusal cavities.[3-5]

The mean age on presentation is 50-60 years. The distribution by gender is 4:1 in favour of males.[4,5]

SNACs are related to professional exposure to wood dust. It is estimated that these workers' risk of developing this tumour is 500 times greater than that of the unexposed male population and almost 900 times more than that of the general population. Exposure to other chemicals commonly used in this industry is excluded as a risk factor, such as polishes, varnishes, preservatives, and others.[4-8]

Correspondence: Dr. J.L. Llorente Pendás.
J.M. Caso, 14. 33006. Oviedo. Asturias. España.
E-mail: llorentependas@telefonica.net

Received February 14, 2008.
Accepted for publication February 20, 2008.

Table 1. Anatomical Areas Affected by the Tumour[a]

Involvement	*Cases, No. (%)*
Bilateral	7 (9%)
Solely the middle concha	10 (13%)
Orbit	17 (21%)
Lamina cribosa	42 (53%)
Dura mater	19 (24%)
Brain	18 (22%)

[a]Some cases showed more than one area involved.

Table 2. Types of Surgical Approaches

Craniofacial	32 (1 with maxillectomy)
Paralateronasal	31
Sub-cranial	10
Infratemporal maxillectomy	2
Palliative treatment	4 (2 radiation therapy, 2 palliative)

The mean time of exposure to wood dust is generally prolonged, from years to decades.[3-7] wood dust particles larger than 5 µm are transported by the nasal airflow and deposited on the mucosa in the target areas, whereas smaller sized particles enter the lower airways. The first produce a reduction in the ciliary function of the nasal cells, and persistent contact encourages the carcinogenic effect. No mutagenic effect has yet been found in wood dust so other oncogenic factors, such as chronic inflammation, have been implicated.

These tumours represent a considerable work-related health problem with serious consequences in terms of morbidity and mortality; therefore, its early diagnosis and appropriate treatment are required.

According to the WHO's histological classification, there are 2 main types of adenocarcinomas: intestinal adenocarcinoma (ITAC) and non-intestinal. Non-intestinal adenocarcinomas are not connected with wood dust and behave differently.

The classifications by Barnes[9] and by Kleinsasser et al[5] distinguish 5 histopathological types of intestinal adenocarcinoma: papillary tubular cylinder cell I (PTCC-I), colonic (PTCC-II), solid (PTCC-III), mucinous, and mixed or transitional. The most frequent type is colonic (40%), followed by solid (20%), papillary (18%), and the mucinous and mixed varieties (both 22%).

MATERIAL AND METHOD

A total of 79 patients operated on between 1986 and 2002 were studied. Of these, 78 were male and 1 was female. The tumours were staged according to the latest revision of the TNM classification (2002). In total, 69 patients (88%) did not receive any kind of pre-operative treatment and 10 (12%) did (surgery or radiation therapy).

The pathological clinical variables were statistically analyzed using SPSS software, version 12.0 for Windows (SPSS® Inc. Illinois, United States). The association of qualitative characteristics was performed using Pearson's χ^2 correlation test or Fisher's exact test. The differences in qualitative characteristics were calculated by comparison of means, applying the *t* test for independent samples and McNemar's test of change and Yates's correction for Pearson's χ^2 with a level of significance at $P \leq .05$. To estimate survival, Kaplan-Meier curves were used to compare the survival distributions with the log-rank test. A *P* value less than .05 was considered significant.

RESULTS

The mean age of the 79 patients was 61 years, with a range spanning from 40 to 82 years; 62 patients (78.5%) had a history of working in contact with wood dust, all of them with over 10 years' exposure.

Extension of the Tumour

The anatomical involvement of various structures by the tumour is shown in Table 1. Classified by the TNM methodology on diagnosis, they were all M0, all N0 except for one and T stages were: T1, 12 (15%); T2, 12 (15%); T3, 20 (25%); T4a, 11 (14%); and T4b, 24 (31%).

Treatment

The surgical approaches used are given in Table 2. In 3 patients, it was necessary to associate exenteration of the orbit. The mean stay in hospital was 14 days (range, 7-67). In 4 patients, it was considered to be residual disease (3 R2 and 1 R1).

Post-surgical complications arose in 20 patients (25%) (Table 3); 52 patients (65%) received post-operative radiation therapy; and 27 (35%) did not.

Follow-up

During follow-up, 7 patients (9%) presented metastasis and 32 (41%), loco-regional relapse; 38 (48%) died as a result of the tumour and 6 (7%) by other causes.

Specific survival was 36% at 5 years and 28% at 10 years (Figure 1), and global survival was 31% at 5 years and 20% at 10 years.

Survival by stage is shown in Figure 2.

There was no statistical significance (P=.55) in survival when comparing patients who had had contact with wood with those who had not.

As for prognostic factors, the patients with bilateral involvement presented a worse course, particularly post-operatively, perhaps also as a consequence of more aggressive surgical approaches, but without statistically significant differences in terms of survival (P=.36).

When solely the middle concha (the habitual area for the start of these tumours) was affected, the prognosis was excellent, with a statistically significant difference (P=.016), as both a single variable and multivariable.

The involvement of the lamina cribosa (P=.001) and the orbit (P=.0160) appeared as a factor for poor prognosis albeit only in the univariate analysis.

Table 3. Post-Surgical Complications and Their Treatment[a]

Type of Complication	*Patients, No. (%)*	*Treatment*
Abscess in surgical wound	3 (4%)	Drainage + 1 withdrawal of miniplate
Rhinoliquorrhea	7 (9%)	Spontaneous closure in all cases except in one closed by NES
Meningitis	4 (5%)	Resolution with medical treatment
Intra-hospital pneumonia	2 (2.5%)	Resolution with medical treatment
Frontal osteomyelitis	3 (4%)	2 surgical debriding procedures and resolution with antibiotics
Myelitis secondary to radiation therapy	1 (1.5%)	Palliative treatment
Intracranial haemorrhage + cerebral oedema + behavioural alterations	3 (4%)	2 deaths within one month; 1 still alive

[a]NES indicates nasal endoscopic surgery.

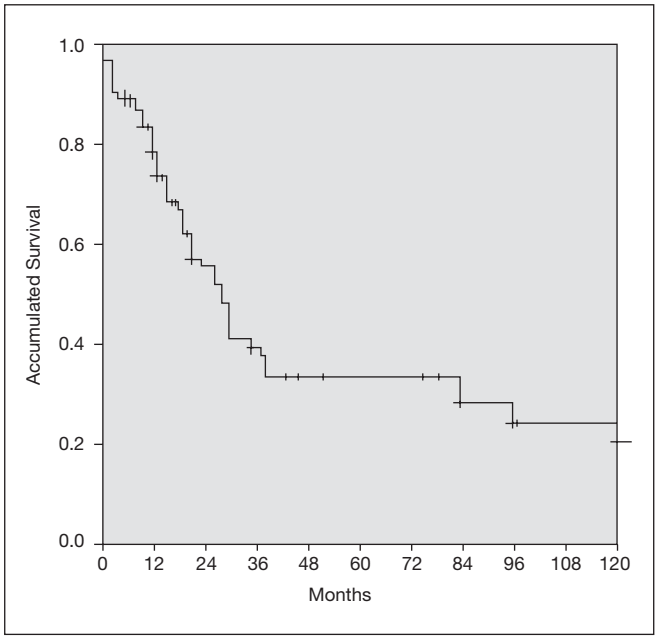

Figure 1. Kaplan-Meier curve for specific survival in sinonasal adenocarcinomas.

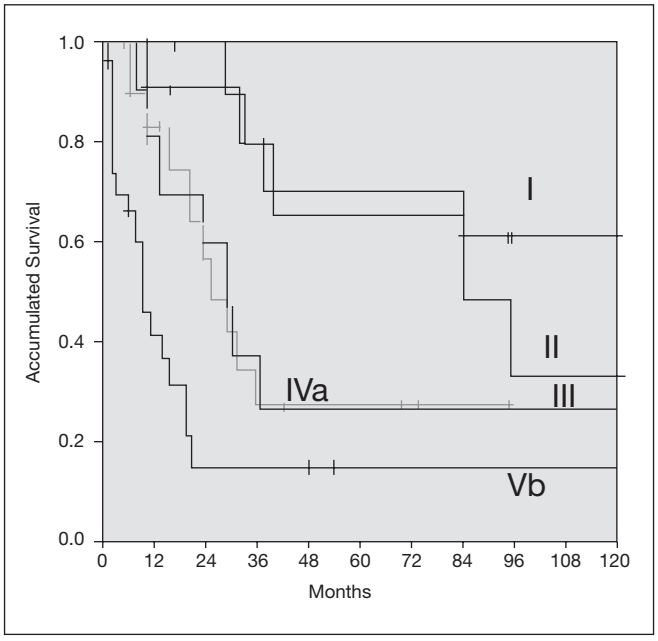

Figure 2. Kaplan-Meier curves for survival by stages.

Involvement of the dura mater was also a factor for poor prognosis (*P*=.0001) in both the univariate and multivariate analysis.

Survival in the event of relapse (even if salvage treatment was applied) was a factor for poor prognosis (*P*=.0001) in both the univariate and multivariate analysis.

The 3 factors with statistical significance in the multivariate analysis were: exclusive invasion of the middle concha (good prognosis), relapse, or invasion of the dura mater (poor prognosis).

DISCUSSION

Among the epidemiological characteristics of our SNAC series, the virtual absence of women is striking.

For other authors, albeit with smaller series, females represent between 5% and 47%; a proportion of 45:1 is the most cited.[10]

Patients exposed to wood dust numbered 62 (78.5%), although all of the members of the group had been exposed on occasions. As with other authors,[11] the predominance of patients exposed to wood dust in our series might partly explain the absence of women, as it is not common in our setting for women to be engaged in jobs with this kind of exposure. The mean age of our patients coincides with that cited in the literature (50-60 years of age), although there is disagreement with the school of thought that says that exposure to wood dust reduces the age of onset of the disease. We have not observed this trend, indeed rather the contrary.

Other clinical characteristics studied, such as histology, symptomatology, and diagnosis, coincide with those described in the bibliography.[3,12] It is only worth noting that all the cases of SNAC originated in the ethmoid, the upper part of the nasal fossae and the middle concha, with no tumours observed in the maxillary sinus.[13]

Staging was performed using the latest revision of the TNM classification (2002).[14] Our results conform to those

observed by other authors where the most advanced stages (III and IV) account for 70%. In fact, at the moment of diagnosis, in 53% of cases there was already involvement of the lamina cribosa; in 24%, of the dura mater; and in 22%, the brain. This undoubtedly constrains the choice of treatment and approach to be used. Extensive infiltration of the brain, although allowing complete extirpation of the tumour, constrains a poor survival rate and a mucho higher level of morbidity, especially in terms of mood alterations and behaviour.

It should be highlighted that the discrimination made by the TNM classification (2002) in our cases for survival in stages III and IVa is not appropriate, as can be noted in Figure 2. Perhaps identifying involvement of the dura mater as a risk factor (univariate and multivariate) may, together with the orbit, be useful as the cornerstone of a clinically more useful and discriminating classification.

Although paralateronasal approaches predominated in the early years, craniofacial approaches were used when the lamina cribosa or the base of the skull was involved. Sub-cranial approaches were indicated when the involvement was bilateral. In 3 patients, it was necessary to associate exenteration of the orbit due to tumoral involvement of the eye socket. It was recently proposed to perform endoscopic approaches (not included in this series) to treat early stages.

The introduction of craniofacial approaches has implied the treatment of more advanced stages of SNAC, previously considered inoperable, and even the consideration of salvage surgery in relapses. When the anterior fossa is involved, the results in terms of complications and survival are considerably worse.

Nonetheless, 75% of patients in the whole series had no complication of any kind and minimal sequelae.

Complementary radiation therapy is advisable in all cases, except in small, well-defined tumours, where surgical treatment seems to be sufficient. In our series, there were 27 patients who did not receive this treatment and although the difference in terms of survival was not statistically significant, it is difficult to draw conclusions and establish comparisons by stages. The justification of the application of radiation therapy in stages T1 or T2, where resection margins are adequate, would be to minimize the possibility of the appearance of subsequent primary tumours. In adenocarcinomas, there is histological evidence about the existence of tumoral nests in healthy mucosa of areas far from the tumour.[15] Complementary radiation therapy would be intended to treat these areas. During surgery, it is also recommended to proceed with an extensive extirpation of the mucosa, beyond the edges of the tumour, in order to include those possible tumoral nests, for example by including both ethmoids.

At the end of our study, the specific survival was 36% at 5 years and 28% at 10 years. From this figure, it can be inferred that the risk of relapse continues and lifelong follow-up must be effected. The complications observed are related to the surgery performed and the infiltration of the brain; the most serious are in cranial approaches due to haemorrhage, oedemas, and meningitis.[16,17]

The most frequent causes of mortality were local relapse and the invasion of the base of the skull (32 patients, 41%), 7 patients presented remote metastases. Other far from negligible causes of death are those secondary to treatment for haemorrhage and/or oedema in the brain (2 cases, 2.5%). Another 2 patients, one with cerebral haemorrhage and oedema and the other with myelitis following radiation therapy, presented major sequelae.

Another finding that may alter survival is the salvage surgery performed in 13 cases with local relapse. Nowadays, thanks to nasal endoscopy and imaging studies (computerized tomography or magnetic resonance), it is possible to detect early relapses. Craniofacial approaches allow recovery of relapses that previously had no kind of effective treatment.

In short, a history of having worked in contact with wood, even if for only a short time, must be considered as a high-risk factor for developing an SNAC and in these cases it must be considered and excluded whenever faced with any patient presenting sinonasal involvement.

REFERENCES

1. Hyrams VJ, Batsakis JG, Michaels LM. Nonepidermoid epithelial neoplasms of the upper respiratory tract. In: Tumors of the upper respiratory tract and ear. Washington: AFIP; 1988. p. 83-111.
2. Alessi DM, Trapp TK, Fu YS, Calcaterra TC. Non salivary sinonasal adenocarcinoma. Arch Otolaryngol Head Neck Surg. 1998;114:996-9.
3. Núñez F, Suárez C, Álvarez I, Losa JL, Barthe P, Fresno M. Sino-nasal adenocarcinoma: epidemiological and clinicopathological study of 34 cases. J Otolaryngol. 1993;22:86-90.
4. Muir CS, Nectoux J. Descriptive epidemiology of malignant neoplasm of nose, nasal cavities, middle ear and accessory sinuses. Clin Otolaryngol. 1980;5:195-211.
5. Kleinsasser O, Schroeder HG. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behaviour in 79 cases. Arch Otorhinolaryngol. 1998;245:1-15.
6. Hayes RB, Gerin M, Raatgever JW, de Bruyn A. Wood related ocupations, wood dust exposure, and sinonasal cancer. Am J Epidemiol. 1986;124: 569-77.
7. Ironside P, Matthews J. Adenocarcinoma of the nose and paranasal sinuses in woodworkers in the state of Victoria, Australia. Cancer. 1975;36:1115-21.
8. Klintenberg C, Olofsson J, Hellquist H, Sökjer H. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer. 1984;54:482-8.
9. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Pathol. 1986;10:192-202.
10. Engzell U, Englund A, Westerholm P. Nasal cancer associated with occupational exposure to organic dust. Acta Otolaryngol (Stockh). 1987;86:4 37-42.
11. Bimbi G, Squadrelli M, Riccio S, Gatta G, Licitra L, Cantu G. Adenocarcinoma of ethmoid sinus: an occupational disease. Acta Otorhinolaryngol Ital. 2004;24:199-203.
12. Sanz JJ, Martínez P, Aguilar F, Bernal Sprekelsen M, Nadal A. Adenocarcinoma nasosinusal tipo intestinal. A propósito de 7 casos. Acta Otorrinolaringol Esp. 2000;51:599-602.
13. Morales Angulo C, Megía López R, Valle Zapico A, Acinas O, Rama J. Adenocarcinoma nasosinusal en pacientes expuestos a polvo de madera en la Comunidad de Cantabria. Acta Otorrinolaringol Esp. 1997;48:620-4.
14. Sobin LH, Wittekind C. UICC. TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss; 2002.
15. Bussi M, Gervasio CF, Riontino E, et al. Study of ethmoidal mucosa in a population at occupational high risk of sinonasal adenocarcinoma. Acta Otolaryngol. 2002;122:197-201.
16. Suarez C, Llorente JL, Fernandez León R, Maseda E, Lopez A. Prognostic factors in sinonasal tumors involving the anterior skull base. Head Neck. 2004;26:136-44.
17. Lund VJ, Howard DJ, Wei WI, Cheesman AD. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses. A 17-year experience. Head Neck. 1998;20:97-105.