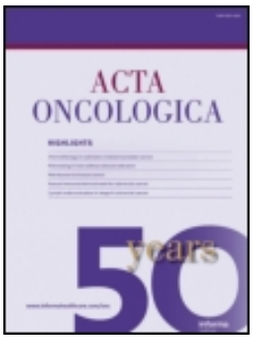

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ORIGINAL ARTICLE

Survival for ethmoid sinus adenocarcinoma in European populations

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Abstract

Background. Adenocarcinoma of the ethmoid sinus is rare. EUROCARE data provide a good opportunity to study the survival of this rare disease in a population of continental size. *Patients and methods*. A total of 204 cases, age 15 to 99 years, diagnosed with primary ethmoid sinus adenocarcinoma between 1983 and 1994, were analyzed. The data were contributed by 22 population-based cancer registries from the nine countries participating in EUROCARE. Relative survival by sex, age, period

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of diagnosis, region and stage, and adjusted relative excess risk (RER) of death, were estimated. *Results.* Survival was 83%, 58% and 46%, 1, 3 and 5 years, respectively after diagnosis. Five-year survival was best (60%) in patients of 55 – 64 years and worst (33%) in the oldest age group (≥65 years). Five-year survival differ between European population: in Norway (55%, 95% confidence interval 26.4–80.9) and western Europe that includes populations from Eindhoven, Saarland, Geneva, Italy and France (56%, 95%CI 41.3–68.9) was higher than in the UK (41%, 95% CI 30.8 – 51.8) and eastern Europe which includes Slovakia and Slovenia, (22%, 95% CI 3.5–54.4). Five-year survival did not improve over time. Due to the rarity of the disease, all the survival differences did not reach the statistical significance. *Conclusions*. Since no survival improvement with time was evident from this study, efforts should be made to improve early diagnosis. GPs and ENT specialists should be alerted to the disease and encouraged to take occupational histories in people with persistent nasal symptoms, which may lead to a reasonable suspicion of malignancy. Monitoring of exposed workers may also improve early diagnosis. Patients with suspected ethmoid cancer should be referred immediately a specialized diagnosis and treatment centre.

Adenocarcinoma of the ethmoid sinus is rare. Incidence and survival at the population level are known from Cancer Incidence in Five Continents [1] and from EUROCARE publications [2] on all cancers of the nasal cavities (International Classification of Diseases codes 160 for ICD-9 [3]; or C31 and C30 for ICD-10 [4]). The annual European incidence of nasal cavity cancers is no more than 2 per 100 000 in men and less than 1 per 100 000 in women [1]; while 5-year relative survival in 1990–1994 was 45% [2]. Ethmoid sinus cancers account for about 10% of paranasal sinus cancers and 1% of all malignant head and neck tumours [5].

It is important to study this rare disease because (a) it is strongly associated with exposure to wood dust especially the intestinal-type (ITAC) [6]; (b) it has a tendency to spread insidiously to an advanced stage before producing symptoms and signs leading to diagnosis; and (c) the ethmoid region is anatomically complex being close to eyes, brain and cranial nerves, so that radical surgery and irradiation must be performed with care, and frequently result in complications.

One way to study rare cancers is to assemble very large databases. The EUROCARE studies [7] – based on 67 population-based cancer registries in 22 European countries – provided the opportunity to study the epidemiology of rare cancers in a population of continental size. Studies from this dataset on the survival of patients with nasopharyngeal cancer [8] and different head and neck subsites [9] have been published.

In the present study we report survival in adult European patients with ethmoid adenocarcinoma, in relation to major demographic and clinical variables. We also analyze variations in survival over time and in different parts of Europe. No similar large-scale analysis of ethmoid adenocarcinoma has previously been attempted.

Patients and methods

Data on 204 patients, age 15 to 99 years, diagnosed with primary ethmoid sinus adenocarcinoma between 1983 and 1994 were analyzed. These cases were selected from 515 cases with cancer of the ethmoid sinus in turn forming part of the 4 988 nasal cavity cancer cases registered. Eligible cases were primary malignant cancer of the ethmoid sinus as defined by the 9th [3] and 10th revisions of the International Classification of Diseases [4] (ICD-9: 160.3; ICD-10: C31.1). Adenocarcinoma morphology defined by the International Classification of Diseases for Oncology (ICD-O) [10], forming group Ib of Berg's histology group [11].

The cases were contributed by 22 adult cancer registries from eleven European countries (England, Scotland, Wales, France, Switzerland, Italy, Germany, The Netherlands, Slovakia, Slovenia and Norway) participating in EUROCARE and able to provide data on ethmoid cancers over the period 1983–1994 (12 years). The combined population of these countries is 59 million, and the 22 registries cover about 58% of this total. The registries of Wales, Norway, Scotland, Slovakia and Slovenia cover their entire populations. Other countries are represented by one or more local or regional registries covering variable proportions of the national population as shown in Table I.

Because of the rarity of ethmoid adenocarcinoma, we considered survival in four geographic groupings within which survival rates are known to be broadly similar based on previous EUROCARE survival studies [2,12]. England, Wales and Scotland were grouped as the UK (group 1); France, Germany, Italy, the Netherlands, and Switzerland were western Europe (group 2); Slovakia and Slovenia represented eastern Europe (group 3); and Norway represented northern Europe (group 4).

Table I also shows sample size and case characteristics by country. From the table it is evident that ethmoid sinus adenocarcinoma was very much more common in men than women (86% overall) in all countries except Scotland where a minority of cases (45%) were male. All cases were microscopically verified in all countries except England, which had 92% microscopic verification.

To provide an indication as to whether geographic differences in registration completeness may have influenced survival figures, we calculated the ratio of the incidence all nasal cavity tumours to the incidence of all ethmoid sinus tumours, for

Table I. Number of cases of ethmoid sinus adenocarcinoma in adults during 1983–1994 in 11 European countries. Proportions of population coverage (%coverage), microscopically verified (MV), male (male), unspecified cancer sub-site by country. Numbers of morphologic groups and incidence rates by country.

Country/Registry	No of cases	%coverage	%MV	%male	% unspecified site codes (ICD9 1609)	Unspecified morphology, number	Squamous cell carcinoma, number	Other specified morphlogy, number	Incidence of all cancers of nasal cavities / 100 000/year*	Incidence of all ethmoid cancers / 100 000/year*	**Ratio
UK, group 1											
ENGLAND*	96	62.5	92	85	2	63	88	32	0.91	0.089	10.17
SCOTLAND	11	100	100	45	3	3	9	4	0.76	0.062	12.24
WALES	5	100	100	60	3	11	7	3	1.35	0.098	13.76
Western Europe, group 2											
FRANCE*	39	2.9	100	92	1	3	18	11	1.35	0.493	2.74
SWITZERLAND, Geneva	1	5.6	100	100	11	1	1	2	0.99	0.13	7.62
ITALY*	13	6.1	100	100	5	4	6	2	0.83	0.083	10.00
GERMANY, Saarland	4	1.3	100	75	13	3	1	0	0.73	0.083	8.75
THE NETHERLANDS, Eindhoven	5	6.3	100	100	0	0	2	0	0.67	0.076	8.86
Eastern Europe, group 3											
SLOVAKIA	4	100	100	100	4	2	10	2	0.72	0.038	19.05
SLOVENIA	8	100	100	84	1	5	10	7	0.87	0.13	6.90
Northern Europe, group 4											
NORWAY	18	100	100	89	10	8	18	4	1.11	0.132	8.39
Total	204	58	96	86	3	103	170	67	0.91	0.1	9.10

*Regional cancer registries represented are East Anglia, Merseyside and Cheshire, Oxford, South Thames, Wessex, West Midlands, and Yorkshire (England); Calvados and Bas Rhin (France); and Florence, Latina, Turin, and Varese (Italy).

*Crude incidence rates; source: EUROCARE data set.

**Ratio between ethmoid (ICD9 1603) and all nasal cavities (ICD9 160) crude incidence rates.

each country. These ratios are shown in Table I: most fall within a reasonably narrow range (between 7 and 19); however the ratio for France was an outlier. Table I also shows the percentages of cases with nasal cavity cancers of unspecified subsite (ICD9 1609), and the numbers of ethmoid cancers of non-adenocarcinoma morphology (squamous cell carcinoma, unspecified morphologies, and other specified morphologies). Norway, Geneva and Wales had rather high numbers of unspecified carcinoma cases.

No cases were known by death certificate only (DCO), diagnosed only at autopsy, or lost to follow-up.

All registries provided follow-up information up to December 31, 1999. Descriptions of the cancer registries, data collection methods and procedures for ensuring data comparability and quality have been published in EUROCARE monographs [2,7,12].

For 45 (22%) cases, information on stage at diagnosis was available. Stage was classified into four categories: lesion confined to site of origin, spread to immediately adjacent tissues, spread to distant organs, and stage not available.

The influence of age, sex, geographic area, period of diagnosis and stage on relative survival at one, three and five years after diagnosis was investigated by univariate analyses. Relative survival is the ratio of the observed survival to the expected survival in the general population from which the cases were drawn and was calculated using the Hakulinen method [13] from estimates of expected survival determined from regional or national life tables [14].

Multiple regression analysis for grouped life table data [15] was then performed to examine the individual impact of sex, age, period of diagnosis and geographic grouping on survival, by estimating the relative excess risk (RER), with youngest age group, men, 1983–1985 diagnosis period, and the UK geographic grouping as reference categories. We used the SEERstat program to perform the univariate analyses of relative survival [16]. The multiple regression analysis was done with Stata software [17].

Results

The results of the univariate analyses of the influence of sex, age, diagnosis period, geographic

Table II. Relative survival (%) and relative excess risk of death (RER) with 95% confidence intervals (CI) of European patients diagnosed with ethmoid sinous adenocarcinoma in 1983–1994 by sex, age, diagnosis period, geographic grouping and stage.

	No. of patients	One-year survival (95% CI)	Three-year survival (95% CI)	Five-year survival (95% CI)	RER** (95% CI)
All	204	**83.2** (76.9–88.1)	**57.7** (49.9–64.9)	**46.1** (38.1–53.9)	
Sex					
Male	174	**82.3** (75.4–87.7)	**56.9** (48.5–64.7)	**46.4** (37.8–54.9)	**1**
Female	30	**87.9** (68.7–96.5)	**62.4** (41.3–78.8)	**44.0** (24.2–63.7)	**0.95** (0.53–1.72)
Age group (years)					
<55	56	**82.5** (69.7–90.4)	**56.2** (42.1–68.3)	**46.7** (32.9–59.7)	**1**
55–64	62	**83.5** (71.3–91.1)	**65.9** (52.0–77.1)	**59.5** (45.1–71.9)	**0.69** (0.40–1.21)
65+	86	**83.3** (72.4–91.0)	**52.0** (39.2–64.1)	**33.0** (21.3–46.1)	**1.26** (0.77–2.09)
Diagnosis period					
1983–85	43	**85.8** (70.6–94.2)	**57.9** (40.7–72.5)	**48.2** (31.2–64.3)	**1**
1986–88	58	**80.1** (66.7–89.2)	**55.3** (40.5–68.6)	**41.1** (27.0–55.6)	**1.29** (0.71–2.35)
1989–91	54	**84.1** (70.5 – 92.5)	**53.1** (37.9–66.8)	**46.9** (31.4–62.2)	**1.15** (0.63–2.12)
1992–94	49	**83.3** (68.8 – 92.1)	**65.4** (49.0–78.6)	**49.1** (32.7–64.7)	**1.06** (0.55–2.02)
Geographic grouping					
UK (group 1)	112	**80.2** (71.1–87.1)	**57.4** (46.7–67.1)	**41.2** (30.8–51.8)	**1**
Western Europe (group 2)	62	**83.7** (71.5–91.3)	**61.3** (47.3–73.0)	**55.8** (41.3–68.9)	**0.90** (0.54–1.51)
Slovenia and Slovakia (group 3)	12	**85.2** (46.6–99.0)	**41.1** (12.6–70.9)	**22.4** (3.5–54.4)	**1.62** (0.71–3.72)
Norway (group 4)	18	**98.3** (69.4–100.0)	**56.7** (29.4–79.4)	**55.0** (26.4–80.9)	**0.74** (0.32–1.71)
Stage					
Localized	23	**99.1** (74.6–100.0)	**81.6** (55.1–97.3)	**77.3** (48.7–97.3)	
Regional	19	**93.0** (66.6–100.0)	**53.5** (27.6–76.1)	**26.0** (8.1–50.7)	
Metastatic	4	**50.3** (5.8 – 85.0)	**25.5** (0.9–67.8)	**0.0** (0.0–0.0)	
Unknown	158	**80.6** (73.2 – 86.4)	**56.5** (47.7–64.6)	**45.5** (36.6–54.3)	

*Variable not included in the multiple regression analisys; for stage definition see text.
**RER at 5 years from the multiple regression analysis.

grouping and stage on the survival of European patients with ethmoid sinus adenocarcinoma are shown in Table II. Survival was 83%, 58% and 46% at 1, 3 and 5 years, respectively, after diagnosis, without differences between sexes. One-year survival was similar in all age groups. Five-year survival was best (60%) in patients of the middle age group (55–64 years) and worst (33%) in the oldest age group ($\geq$65 years). One and 5-year survival remained stable, while three-year survival improved especially in the last period 1992 – 1994. Among patients diagnosed in 1983 – 1985, survival was 86% one year, 58% three years and 48% five years after diagnosis; the corresponding figures for patients diagnosed in 1992 – 1994 were 83%, 65% and 49%. The improvement in 5-year survival with time was greatest for youngest patients ($<$55 years) (from 37 to 71%) (not shown in Table II).

Five-year survival in Norway (55%) and western (56%) European countries was higher than in the UK (41%) and in Slovenia and Slovakia (22%). In the UK, western Europe and Slovenia and Slovakia, survival declined steadily after diagnosis, from around 80% at one year to below 56% at five years. By contrast, in Norway, survival was good at one year (98%), but fell markedly at three years (57%) and little more after five years (55%).

Information on tumour stage was available for 45 (22%) cases only. In this sub-group, 5-year survival was clearly dependent on disease stage at diagnosis: 77% for localized cancers, 26% for locally advanced, and no patients with distant metastasis at presentation were alive 5 years after diagnosis. Cases with no information on stage (78% of total) had, as expected, 5-year survival similar to the overall average (46%). The impact of stage on survival could not be modelled because information was available for so few patients.

RERs of death five years after diagnosis, as estimated by the multiple regression analysis, are shown in last column of Table II. No variable included in the model (sex, age, period of diagnosis, geographic grouping) had a significant influence on relative survival. The small number of cases investigated probably limited the power of the multiple regression analysis to reveal any such influence. In general, the results of the multiple regression analysis are concordant with the results of the univariate analyses.

Discussion

Table III shows 5-year survival in our European patients with ethmoid adenocarcinoma in relation to survival data from published clinical series [18–21] and a study on the SEER population database [22]. In all these studies, survival was net survival, calculated by the Kaplan Meyer or actuarial methods; in addition diagnosis periods were longer and sometimes less recent than the 1983–1994 period of the present study [18–20]; while average ages were similar. European survival rates were lower than both the clinical series and the SEER study. Survival was highest (80%) in the French series [18], with the lowest proportion of T4 cases (21%). Furthermore, cases with distant metastasis (M+) at diagnosis and cases with unassessed T (TX) were excluded from all the clinical and SEER analyses; the UTDMACC study [22] also excluded T4 cases.

In the clinical series, [18–20] patients were treated at one or sometimes two specialised centres. Combined surgery and radiotherapy, or surgery alone for small localised lesions, were reported to provide better local control and cure rates than radiotherapy alone [18–21]; chemotherapy was seldom given [19,20]. Patients were reported to develop disease recurrence at a steady rate for up to 10 years after treatment [20]. The multivariate analyses reported by these studies indicated that tumour stage had a significant influence on survival and that T4 lesions had a much worse prognosis than T1–T3 tumours [22]. Intracranial involvement in T4 lesions notably

Table III. Comparison of 5-year survival for ethmoid sinous cancer in clinical series, SEER data and in Europe.

	No. of cases	Survival	Mean age
University Hospital of Bordeaux, 1975–2000	76	80	61
University of California-Los Angeles and Geneva University hospitals, 1975–1994*	47	48	57#
Danish Society for Head and Neck Oncology, 1982–1991 §	41	53	66#
SEER database, 1988–1998	23	55	60
UTMDACC, USA, 1969–1993	13	50	57
Present study,1983–1994	204	46	61

na: information not available.
*All ethmoid sinus cancer.
§Adenocarcinoma of all sino-nasal cancers.
#Mean age of all sino-nasal cancers.

complicates surgical management and probably contributes to poorer outcomes.

In agreement with the findings of the present study, the clinical studies reported no improvement in survival from the 1980s to the 1990s [20,21].

Age, sex and region were the only other prognostic factors considered in our study, since population-based cancer registries do not routinely collect standardised information on treatment and stage. Both the univariate and the multiple regression analyses found that age (worse in oldest age group) and region (worse in the UK and Slovenia and Slovakia) influenced survival. Although the present study is the largest yet published, the number of cases analysed was relatively small, and variable-related survival differences were never significant at the $p < 0.05$ level.

With regard to age, both the univariate and multiple regression analyses found that survival was better in middle-aged patients (55–64 years), although as noted differences were never significant. It is unusual to find better survival in this age range than in younger patients. A possible reason is that diagnosis was delayed in the younger age group because malignant disease is unexpected, and the malignancy under consideration is rare and typically presents only generic symptoms. However there are no data to support this suggestion, as information on stage was lacking. Age was not investigated in the Jiang et al. study [19]; no age-related survival differences were found by Dulguerov et al. [20]; while decreased survival with increasing age was noted in the other studies [21,22].

Stage is a crucial prognostic factor to be considered in explaining cancer survival differences. Unfortunately, stage was not available for all cases collected by the European cancer registries and it was not always possible to compare directly the available data. A major goal for future studies is to obtain comparable information on stage from cancer patients in each of the contributing cancer registries: this will pinpoint remediable causes of international cancer survival differences and to quantify the impact of removing them.

Since incomplete incidence data can bias survival estimates and confound inter-registry comparisons, it is important to assess completeness. To provide an indication of completeness we calculated the ratio of all ethmoid sinus cancers to all cancers of the nasal cavities, by country. Most ratios fell within a reasonably narrow range (between 7 and 19); however the ratio for France was an outlier with a low ratio. France had a very high incidence of all cancers of the ethmoid sinus (ICD-9 1603) and also a high absolute number (39) of cases of ethmoid sinus adenocarcinoma (Table I). Since most nasal cavity cancers are diagnosed at fairly advanced stage, it is often difficult to determine their exact site of origin, and this is probably the main reason why some countries had high ratios of ethmoid to nasal cavity cancers (Table I). Completeness of ascertainment of ethmoid sinus cancer would be difficult to assess without pathological review of all registered nasal cavity cases.

In our study we did not performed analysis by type of adenocarcinoma. The term "adenocarcinoma" is a heterogeneous group of tumours with evidence of glandular differentiation, such as papillary adenocarcinoma, intestinal-type adenocarcinoma, polymorphous adenocarcinoma, etc. with different prognosis. Also survival is different from an oncotype to another. As our data was codified according to the ICD-O the characterisation by oncotype was not possible. Furthermore, the proportion of cases codified as "adenocarcinoma not otherwise specified" was 58%, therefore the analysis by histotype was not possible.

Advanced stage at diagnosis could be also the reason for the high proportion of cases with unspecified morphology (ICD9 80003 and 80103): advanced stage may have discouraged complete pathological definition. Thus, for Wales, with high numbers of unspecified morphology cases (with low survival (35%) in our study), survival for ethmoid adenocarcinoma may have been slightly overestimated.

Note that no cases were lost to follow-up, there were no DCO cases and the overwhelming majority of cases were microscopically verified. These findings suggest that the quality of diagnosis and follow-up for cases included in the analysis is high.

The proportion of all nasal cavity tumours with unspecified subsite was also acceptably low ($\leq 10\%$) in most registries, the exceptions being except Norway, Geneva (Switzerland) and Saarland (Germany) (Table I). Again the reason for this could be the difficulty of determining the exact site of origin of these cancers. Actually, even if the individual clinical records are available the information on subsite of origin is not reliable and misclassification may be relative common. We have repeated the analysis including all the adenocarcinoma of nasal cavities (ICD-O 1600-1609). Based on the 1 091 cases studied, 5-year relative survival was slightly higher (55%) than those found for the ethmoid. We found the same trend, with no differences among age groups, sex, period of diagnosis and regions. Because of their location ethmoid tumours can probably grow for long periods – expanding to fill the sinus – without producing noticeable symptoms. Early symptoms of these cancers are unspecific and resemble those of many common nasal complaints

[21]; in addition symptoms often regress following antibiotic treatment, falsely reassuring both patient and physician. If more alarming symptoms become apparent, outcomes tend to be less favourable [23]. For this reason it is important to alert GPs and ear nose and throat specialists to these diseases and encourage the taking of occupational histories in people with persistent nasal symptoms, which may lead to a reasonable suspicion of malignancy. There is an established association between exposure to wood dust and ethmoid sinus adenocarcinoma [24]; furthermore increased risks of these diseases are associated with shoemaking, and exposure to nickel, mustard gas, isopropanol and other chemicals [25]. Monitoring of exposed workers may improve the early diagnosis of these cancers. Patients with suspected ethmoid cancer should be referred immediately a specialized diagnosis and treatment centre.

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