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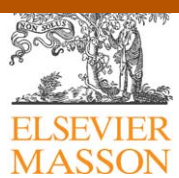

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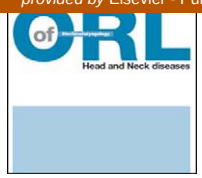

ORIGINAL ARTICLE

Adenocarcinoma of the ethmoid sinus: Retrospective study of 42 cases

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KEYWORDS
Adenocarcinoma of the ethmoid sinus;
Paranasal sinus neoplasms;
Sinus surgery;
Skull base reconstruction

Summary
Objectives: Retrospective analysis of the oncological results and morbidity of ethmoid sinus adenocarcinoma surgery, and identification of survival factors.
Material and methods: Forty-two patients were treated from 1990 to 2009. The study covered clinical presentation, medical imaging, histologic data, TNM grade, treatment, morbidity and overall recurrence-free survival.
Results: Forty-one men and one woman, with mean age at diagnosis of 61.5 years, were included. 85.7% had been exposed to wood dust. Twenty patients (47.6%) were graded T4 at diagnosis. Thirty-three (78.5%) were treated by surgery followed by radiation therapy; nearly half of these showed recurrence. Overall specific 5-year survival was 44.2% at 5 years and recurrence-free 5-year survival 46.4%. The factors of poor prognosis found were cerebromeningeal or orbital invasion and local recurrence.
Conclusion: This series confirms the epidemiological literature on ethmoid adenocarcinoma and the influence of poor prognosis factors. Survival depended directly on local tumor control and seemed to be enhanced on an isolated transfacial approach.

Introduction

In France, the incidence of facial sinus cancer is less than 1/100,000 per year [1] and 70% to 80% of malignant ethmoid tumors are adenocarcinomas [2]. Clinical signs are poorly specific and appear only at an advanced stage, whence the high rate of grades T3 and T4. Surgery followed by external radiation therapy is the current attitude of choice. The present study retrospectively assessed oncologic results and morbidity for various treatments and on various surgical approaches. The secondary objective was to identify survival factors.

Patients and methods

This retrospective study systematically reviewed the records of ethmoid adenocarcinoma patients treated and followed up in the ENT department of Angers University Hospital (France) between 1990 and 2009. Patients presenting with non-adenocarcinoma ethmoid tumor or

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adenocarcinoma of other paranasal sinuses were excluded. The data collected concerned symptomatology, radiological lesion characteristics (TNM grade on the 1997 UICC classification) and management. The WHO histological classification [3] was used. Evolution and recurrence characteristics and treatment were recorded.

Data were analyzed on SPSS 13.0 software. Qualitative variables were compared on Khi^2. Survivorship was calculated on the Kaplan-Meyer method (end of study: March 1st, 2010). Survival was compared between two groups by log rank and between more than two groups by Cox models. Nonspecific overall survivorship was based on date of death from whatever causes or date of last consultation. Specific overall survivorship was based exclusively on disease-related death. Results were expressed as hazard ratios (HR) with 95% confidence intervals, with an asymptotic significance threshold of $p = 5\%$.

Results

Study population

The study population comprised 42 patients, including one female. Median age at diagnosis was 61.5 years (range, 35—81 years). Median FU was 2 years 5 months (range, 10 days to 19 years 10 months).

Occupation was known for 41 patients, 36 of whom (85.7%) had had occupational exposure to wood dust, and none to leather. When specified, exposure time was a mean 30.4 ± 14 years. The mean interval between end of exposure and diagnosis of ethmoid adenocarcinoma was 10.9 years. The remaining patients had exposure to no known risk factors, except for one who worked in metallurgy, although nickel exposure was not specified. Initial American Society of Anesthesiologists score (ASA: predictive of perioperative morbidity-mortality) was 1 for 83% of patients, 2 for 12% and 3 for 5%.

Diagnosis

At initial diagnosis, evolution was for a mean 5.6 ± 4 months. Initial symptoms, in order of frequency, were epistaxis (71%), nasal obstruction (64%), rhinorrhea (33%) and anosmia (26%).

CT and MRI were performed in all but one patient (CT only). 11.9% of tumors were T1 (5/42), 31% T2 (13/42), 9.5% T3 (4/42) and 47.6% T4 (20/42). There were no cases of lymph-node invasion or diagnostic-stage metastasis. There was no correlation between tumor grade and time of evolution ($p = 0.73$) or of wood dust exposure ($p = 0.19$). All tumors were intestinal type adenocarcinomas (ITAC): 40.5% mucinous, 26% colonic, 7.1% papillary and 2.4% solid; histologic subtype was unspecified in 24% of patients.

Treatment

The surgical approaches were: mixed (sub-frontal and paralateronasal [PLN]), isolated PLN, Labayle's enlarged PLN as modified by Vaneecloo [4,5] and nasal endoscopic. In case of skull base resection, reconstruction used one of two techniques: temporal aponeurosis with an inferior-hinged pediculated galea aponeurotica flap or rectus abdominis muscle aponeurosis with abdominal fat graft.

Thirty-five of the patients (83%) were operated on, with the following approaches: 14 PLN, 11 enlarged PLN including seven with skull base resection, eight mixed, one isolated sub-frontal and one associating nasal endoscopic and sub-frontal. Mean hospital stay was 11.3 ± 10 days. Mean diagnosis-to-surgery time was 6.4 ± 3 weeks. Table 1 presents the postoperative complications. Apart from one case of meningitis and one convulsive attack, both following surgery on a PLN approach, all neurosurgical complications were secondary to a mixed approach. Apart from the convulsive attack, all were secondary to skull base reconstruction by galea aponeurotica flap with temporal aponeurosis. There were no late complications. Two patients operated on using a mixed approach did not undergo postoperative radiation therapy, due to death: one on day 10 following coma related to hydrocephalus and frontotemporal ischemia, and one at 9 weeks following unexplained deterioration in general health status. Preoperative neoadjuvant chemotherapy was performed in four of the 35 operated patients (5-fluorouracil associated to cisplatin, by general route). In the 33 patients receiving postoperative radiation therapy, the mean surgery-to-radiation interval was 6.12 ± 2 weeks, with a mean dose of 60 Gy. Seven patients could not be operated on due to poor general health status or tumor extension. All operated patients were considered as treated. None of the seven non-operated patients were considered as in remission: one died after admission for coma, without receiving treatment; two died during induction chemotherapy; one died after radiochemotherapy; and three were in evolution after radiochemotherapy at end of follow-up. These patients were not included in the analysis of recurrence.

Evolution

Eleven of the 35 patients operated on (31.4%) showed local recurrence, two (5.7%) metastasis, and three (8.6%) local and metastatic recurrence. Mean recurrence interval was 13 months (range, 8.7—28.5 months). There was no cervical lymph-node invasion associated with recurrence. Metastasis was intracerebral in two patients, hepatic in one, osseous in one and cutaneous in one. The recurrence rate was 100% (eight patients) with a mixed approach, and 18.8% (11 patients) with an enlarged PLN approach ($p = 0.02$). There was no significant difference in T-stage or tumoral invasion between the two approaches. Thirteen of the 16 patients with recurrence died (including one from intercurrent causes) at a mean 3.7 years. Two patients were in remission after surgical revision for focal recurrence, at respectively 18 and 6 years' FU, and one was in local evolution at end of follow-up. No recurrence risk factors emerged from the study variables: age at diagnosis ($p = 0.42$), T-stage ($p = 0.55$), orbital invasion ($p = 0.2$), dura-mater invasion ($p = 0.2$), cerebral invasion ($p = 0.55$), sphenoid invasion ($p = 0.58$), histologic subtype ($p = 0.86$), or surgery-to-radiation therapy time ($p = 0.75$). At end of follow-up, 21 patients had died (including three from

Table 1 Immediate postoperative complications (less than 2 weeks).

Complications ($n = 35$)	%	(n)	Approach	Skull base reconstruction (specified for neurosurgical complications)
No complications	60	(21)		
Meningitis	2.8	(1)	PLN	No skull base resection
Rhinoliquorrhea	5.7	(2)	Mixed	Temporal aponeurosis and pediculated galea aponeurotica
Intracerebral hematoma	2.8	(1)	Mixed	Temporal aponeurosis and pediculated galea aponeurotica
Non-regressive diplopia at 2 weeks	11.4	(4)	2 PLN, 2 mixed	—
Epilepsy	2.8	(1)	Enlarged PLN	Rectus abdominis aponeurosis and fat patch
Extradural abscess	2.8	(1)	Mixed	Temporal aponeurosis and pediculated galea aponeurotica
Dacryocystitis	5.7	(2)	PLN	—
Local infection	2.8	(1)	PLN	—
Death from frontal ischemia	2.8	(1)	Mixed	Temporal aponeurosis and pediculated galea aponeurotica
Total complications	40	(14)		

unrelated causes), 21 were alive (including three with evolution). Mean time to death was 3 years 2 months (median survival, 29 months).

Survival

Table 2 shows survival and recurrence rates. Specific and non-specific overall 1-, 3- and 5-year survival was respectively 82% and 83%, 64% and 60%, and 44% and 41%. Exophthalmia, reduced visual acuity, headache and anosmia at diagnosis emerged as factors for poor prognosis. Figure 1 shows the specific survival curve according to recurrence.

Figure 2 shows the survival curve according to T-grade. Overall 5-year survival was 100% in T1, 49.1% in T2, 50% in T3 and 21% in T4. Orbital and cerebromeningeal invasion emerged as factors for poor prognosis ($p < 0.01$). The hazard ratio for orbital involvement was 1.62 (95% CI, [1.06;3.18]); for dura-mater involvement, 5.27 (95% CI, [1.93;14.41]); and for cerebral involvement, 6.42 (95% CI, [2.34;17.6]). Maxillary or sphenoid sinus involvement did not affect survival ($p = 0.72$ and $p = 0.59$, respectively).

Survival was significantly lower in non-operated patients than in those undergoing surgery and radiation therapy (overall 3-year survival, 28.6% vs. 71.6%; $p < 0.05$).

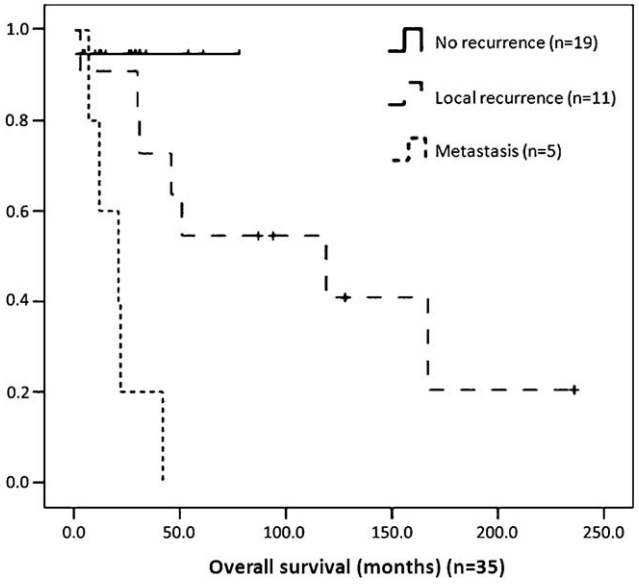

Figure 1 Overall specific survivorship according to recurrence ($p < 0.01$).

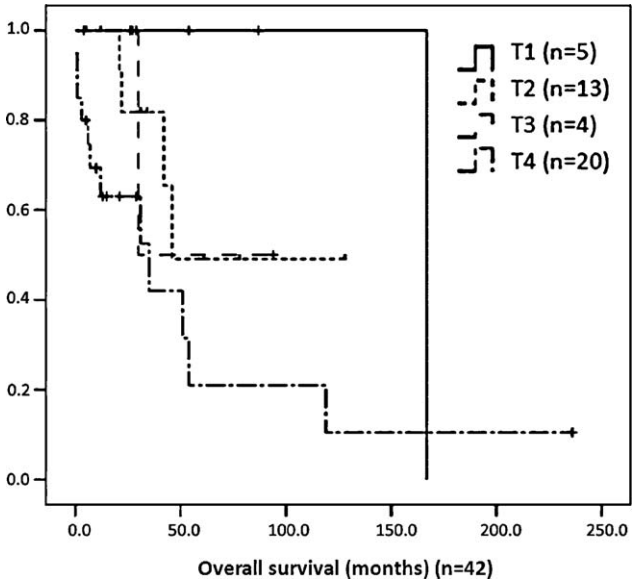

Figure 2 Overall specific survivorship according to T grade ($p = 0.08$).

Table 2 Overall specific survival and recurrence.

	n	Recurrence rate (% patients operated)	*p*	5-year survival	*p*
Age					
< 61.5 years	21	50	0.42	48.5	0.62
> 61.5 years	21	41		37.9	
Wood-dust exposure					
Yes	36	43.3	0.6	37.8	0.88
No	5	50		60	
T grade					
1	5	40	0.55	100	0.083
2	13	38.4		49.1	
3	4	50		50	
4	20	54		21	
Orbital invasion					
No	25	37.5	0.2	59.4	< 0.01
Muscles intact	10	62.5		36.5	
Muscles invaded	7	66.6		16.7	
Sphenoid invasion					
Yes	3	33.3	0.58	0	0.59
No	39	46.8		45.1	
Maxillary invasion					
Yes	7	42.8	0.6	45.7	0.72
No	35	46.4		43.2	
Meningeal invasion					
Yes	18	63.6	0.2	9.2	< 0.01
No	24	37.5		69.1	
Cerebral invasion					
Yes	11	60	0.55	0	< 0.01
No	31	43.3		59	
Treatment					
Surgery and radiation	33	43.7	—	53.7	< 0.01
PLN approach	14	35.7	0.02	75	< 0.01
Mixed approach	8	100	0.02	12.5	< 0.01
Enlarged PLN	11	18.8	0.02	100	< 0.01
Surgery only	2	Postoperative death	—	0	< 0.01
Other	7	—	—	0	< 0.01
Recurrence (*n* = 35)					
No recurrence	19	—		94.7	< 0.01
Locoregional recurrence	11	—		54.5	
Recurrence with metastasis	5	—		0	

Survival according to surgery, calculated for enlarged PLN and mixed approaches, showed a significant difference in favor of the enlarged PLN approach ($p < 0.01$). The distribution of poor prognosis factors was similar in the two approach groups.

Discussion

The low incidence of adenocarcinoma of the ethmoid has so far prevented any prospective randomized study. All the published series were retrospective, and comparison is hindered by disparities: variable histology, inclusion of adenocarcinoma of other paranasal sinuses, and varying surgical approaches. Table 3 presents the series published in the last 10 years, non-exhaustively.

The present epidemiological data (sex ratio, age at diagnosis and wood-dust exposure) were in agreement with the literature. They show the importance of wood-dust exposure (85.7% of cases) and of long exposure in particular (30.4 years in the present series; 22—31.5 years in the literature). Risk, however, seems to exist as of the first years of exposure: 2 years, in the case of one of the present patients.

Table 3 Review of retrospective ethmoid adenocarcinoma series since 2000.

Author, place, date	*n* (m/f)	Age (years)	Wood-dust exposure (%)	T grade (%)				5-yr survival (%)	Recurrence (%)
				T1	T2	T3	T4		
De Gabory, Bordeaux [15] 2010	87/8	64	73	2	22	37	39	78	31
Mayr, Erlangen [16] 2009	31	–	32	–	–	–	–	–	–
Choussy, GETTEC study [1] 2008	418	63	28	3	32	23	42	64	51
Liétin, Clermont-Ferrand [17] 2005	59/1	62	26	–	–	–	–	47	–
Jegoux, Nantes [9] 2004	78/2	63	67	5	23	31	41	63	44
Michel, Amiens [18] 2003	10	–	–	–	–	–	–	53	60
Guillotte, Reims [19] 2003	17	–	–	0	12	0	88	41	58
Claus, Bruges [20] 2002	47	–	81	4	36	23	36	60	–
Dulguerov, Los Angeles [21] 2001	25	–	–	–	–	–	–	63	–
Choussy, Rouen [22] 2001	19	57	–	0	37	50	13	69	–
Stoll, Bordeaux [23] 2001	71/5	61	26	3	18	58	20	80	23
Breheret, Angers 2010	41/1	61	85	12	31	9	48	44.2	46

Clinical presentation was poorly specific. Hemorrhagic rhinorrhea and nasal obstruction were prime features. The very ordinariness of these symptoms explains why diagnosis is often delayed and why most series include few small tumors.

There is now consensus as to the reference attitude in adenocarcinoma of the ethmoid, based on surgery associated to postoperative adjuvant radiation therapy, as in 78.5% of the present series. This association improves local control and overall and recurrence-free survival [6]. The approach depends on oncologic requirements, notably as concerns skull base resection and the team's particular habits. Certain authors [7] distinguish four groups of tumors, according to Roux's TNM classification [8]. In the first (T1 and T2), the skull based is unaffected, and the approach should be lateral rhinotomy. In the second (T3), the tumor touches without invading the cribiform plate; classically, the approach is paralateronasal without skull base resection, while trimming the cribiform plate to ensure against invasion; the authors, however, recommend systematic skull base resection here, as non-invasion is difficult to confirm on radiography or histology. In the third group (T4a), the tumor invades only the cribiform plate, and systematic skull base and meningeal resection is recommended. In the last group (T4b), the dura mater or even the frontal lobes show clear invasion: surgery is not an obvious option, due to deficient local control.

In the present series, cribiform plate invasion was initially dealt with on a mixed approach, reserving a PLN approach for lesions without skull base extension. The enlarged PLN approach has nowadays largely replaced the mixed approach, with indications being progressively extended to cribiform plate resection. By simplifying the procedure, this approach may have extended indications for skull base resection, thereby improving local control.

This variant PLN approach was introduced by Moure and Sebilleau then modified by Labayle in 1957 and again by Vaneecloo [5], who recommended extending incision outward above the eyebrow so as to be able to control the entire cribiform plate and ethmoid roofs. In agreement with several authors [7,9], we find that it provides a satisfactory approach to the skull base and sinonasal cavities while reducing esthetic blemish and morbidity-mortality as compared to a mixed approach. Most neurosurgical complications in the present series were associated with a mixed approach, which in the literature is associated with a higher rate of postoperative neurological and infectious complication than a transfacial approach, and with mortality ranging from 0 to 11% [7]. A mixed approach does, however, allow exeresis of tumors that could not be removed on an enlarged PLN approach (cerebral or pterygomaxillary fossa involvement), although this has not been demonstrated to improve survival rates. Finally, overall and recurrence-free survival were enhanced using an enlarged transfacial approach in the present series (overall 5-year survival 100% vs. 12.5%, respectively). Although there were no significant differences in prognostic factors between the mixed and enlarged PLN groups, these results should still be interpreted with caution: a mixed approach was probably indicated for more extensive tumors with more difficult local control. The lower morbidity associated with the enlarged PLN approach may have enabled indications for skull base resection to be extended, particularly in elderly patients (who would not have been operated on with a mixed approach) or in tumors with simple cribiform plate contact.

Endoscopy has recently been suggested as an alternative to lateral rhinotomy [10,11], providing easy access to the olfactory cleft, which is probably the starting point of adenocarcinoma of the ethmoid [12]. Certain authors [12,13] consider that this approach, thanks to the development of image-guided sinus surgery, can now meet the same oncologic requirements as open ethmoid adenocarcinoma exeresis. The endoscopic approach should begin by reducing tumor volume, followed by total bilateral ethmoidectomy, before dissecting the olfactory clefts. The contribution of this technique remains hard to assess, as series have been relatively small (18 and 12 patients, respectively [10,11]) and follow-up short (25 and 34 months).

Although complications are rare on an enlarged PLN approach, postoperative morbidity very much depends on skull base reconstruction quality. Several methods have been recommended for dural plane reconstruction. A

dura-mater patch should be created using, say, rectus abdominis aponeurosis graft [7] or an inferior-hinged pediculated epicranial flap. Temporal fascia, fascia lata or Neuro-Patch® (polyester-urethane) have been suggested as alternatives.

The technique used in the present series was based on that of Reyt [14] as modified by the team from Nantes [7]. Dural reconstruction uses a rectus abdominis aponeurosis graft. An abdominal fat patch is then applied, kept in place by a silicone arch. This simple reconstruction technique seems to be an excellent compromise between reliability and rapidity. In the present series, it was associated with a lower neurologic complications rate than for epicranial flap and temporal aponeurosis graft reconstruction.

In the present series, 45.7% of patients showed recurrence at a mean 26 months, in line with literature reports (51% recurrence at a mean 28 months in the GETTEC study [1]). The recurrence risk factors classically described (T4 grade and skull base invasion) were not observed.

The 5-year survival rate was 44.2%, lower than in most reports. Orbital and skull base invasion emerged as factors of poor prognosis. There was a significant difference in survival between absence of skull base invasion and meningeal or cerebral invasion. These findings confirm the importance of distinguishing between tumors invading, exceeding or not invading or the cribiform plate, and thus the prognostic value of Roux's TNM classification TNM [8] and the 2002 UICC classification. The survival impact of presenting symptomatology (reduced visual acuity, exophthalmia, anosmia and headache) confirms their relevance as prognostic factors.

As in the literature, grade T4 directly impacted survival (hazard ratio, 3.7; 95% CI, [1.29;10.6]). Local recurrence and metastatic evolution emerged as major risk factors for poor prognosis.

Given these findings, the present relatively low survival rate was probably due to the presence of risk factors for poor prognosis: 40% orbital invasion, 42.9% dura-mater invasion, 26.2% cerebral invasion, and 47.6% grade-T4 cases, versus respectively 23%, 15%, 15% and 42% in the GETTEC study [1].

Conclusion

Adenocarcinoma of the ethmoid is a rare tumor, often diagnosed only at an advanced stage due to prolonged clinical latency. In these aggressive tumors, local control is the determining prognostic factor. The priority is thus primary complete exeresis, with the approach determined according to presence or absence of skull base invasion.

The present results argue for systematic skull base resection in case of cribiform plate contact. The enlarged paralateronasal approach is more reliable than a mixed approach, in terms of both postoperative morbidity and oncologic result: survival and recurrence rates were both considerably improved on this isolated transfacial approach.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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