

# Adenocarcinoma of the Ethmoid Sinuses. A Review of 46 Cases

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## ABSTRACT

**Objective:** To describe the clinical and radiological presentation, management, and outcomes of adenocarcinoma of the ethmoid sinuses

**Materials and methods:** We retrospectively reviewed the medical charts of the 46 patients managed for adenocarcinoma of the ethmoid sinuses at a teaching hospital in Toulouse, France, over an 11-year period (1992-2002). Of the 38 patients with operable tumors, 36 were treated with surgery followed by radiation therapy and 2 were also given neoadjuvant chemotherapy. The 8 remaining patients received palliative therapy.

**Results:** Mean follow-up was 3.7 years. Actuarial survival rates were 70.8% after 3 years and 62.2% after 5 years.

**Discussion:** As part of the pretreatment work-up, computed tomography and magnetic resonance imaging used in combination provide 98.5% agreement with histology.

The management of adenocarcinoma of the ethmoid sinuses is not standardized. We recommend radiation therapy and surgery when curative therapy is feasible. Radiation therapy plus chemotherapy can be used for inoperable tumors. Nasal endoscopy is useful for diagnosing and monitoring the tumor; its contribution to the treatment is being evaluated.

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Cancer of the ethmoid sinuses contributes only 0.2 to 0.8% [1] of all malignancies and 2.5 to 3% of head and neck cancers [2-3].

Presenting symptoms are dominated by nasal manifestations including nasal obstruction, epistaxis, rhinorrhea, and pain. Because these symptoms lack specificity, the initial examination may show evidence of local spread, such as hypoesthesia in the distribution of V2, a facial lump, epiphora, or diplopia.

The treatment is incompletely standardized and the prognosis often unfavorable. New treatment methods include excision surgery performed simultaneously by head-and-neck surgeons and neurosurgeons. Radiation therapy is now combined with surgery in the overwhelming majority of patients. Concomitant administration of chemotherapy and radiation therapy is appropriate in some cases. Imaging methods have improved, and accurate maps of the tumor can be obtained using computed tomography (CT) and magnetic resonance imaging (MRI).

We conducted a retrospective study of patients with adenocarcinoma of the ethmoid sinuses to obtain information on the clinical and radiological presentation, the management, and the oncological outcomes.

### PATIENTS AND METHODS

We retrospectively reviewed the medical charts of the 46 patients managed at the Rangueil Teaching Hospital, Toulouse, France between January 1992 and December 2002 for adenocarcinoma of the ethmoid sinuses. Patients managed before January 1992 (n=15) did not undergo MRI and were managed using a variety of strategies; consequently, we started the study period in January 1992. We excluded 8 patients with adenocarcinoma arising initially from the maxillary sinus, as this condition raises specific issues, and 6 patients with incomplete data. For each of the 46 study patients, we abstracted the following from the medical chart: age, gender, and occupation; symptoms at presentation including nasal symptoms (nasal obstruction, epistaxis, rhinorrhea, or pain), ophthalmologic symptoms (exophthalmos, diplopia, vision loss, or extraocular muscle palsy), and neurological symptoms (hypo-

esthesia, dysesthesia, anesthesia, or neuralgia); findings from routine investigations including nasal endoscopy with biopsies collected under visual guidance, full ENT evaluation, chest radiograph, abdominal ultrasound scan, high-resolution CT (HRCT), and MRI. HRCT consisted in acquisition of contiguous 1-mm slices in the transverse and coronal planes, with contrast medium injection. For MRI, spin-echo T1- and T2-weighted sequences were used, as well as T1 weighted sequences after gadolinium injection. Reformations were obtained in all three planes.

Based on the results of the initial work-up, patients were classified according to the TNM UICC 1992 system [4]. Treatment decisions were based on the TNM stage. Contraindications to surgery were severe debilitation, inoperable tumor, and patient's unwillingness to undergo surgery. Patients with contraindications to surgery were either given external-beam radiation therapy with or without chemotherapy or left untreated. Surgically treated patients received postoperative radiation therapy to the surgical site. Lymph node sites were not irradiated in patients with N0 disease. The clinicopathological target volume was determined based on tumor size before surgery and on the risk of microscopic extensions evaluated according to tumor size and location. High-risk regions for microscopic extensions were the cribriform plate and olfactory grooves, nasal cavities, sphenoid, and papyraceous lamina. Conformal radiation therapy is now used, with an anterior interorbital beam, lateral oblique beams, and if needed a noncoplanar vertical beam or a posterior beam. High-energy photons (6-8 MV) produced by a linear accelerator were used. The postoperative dose was 60-65 Gy, in daily dosages of 1.8-2 Gy, often with a reduction in the target volume after the delivery of 50 Gy. When surgery was not performed or excision was incomplete, the dose to the tumor or tumor remnant was 65-70 Gy. Neoadjuvant chemotherapy was added to the treatment regimen in patients with major local spread; cisplatin and 5-fluorouracil were used.

The surgical approaches were selected according to tumor spread. Changes in approaches occurred over the study period, most notably regarding the endoscopic endonasal approach. Paralateronasal rhinotomy was the most widely

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used approach early in the study period. If needed, this approach was combined with hemimaxillectomy (in patients with spread to the maxillary), exenteration (in patients with intraconal orbital spread), or a bicoronal approach (to treat intracranial spread). The endonasal endoscopic approach was used late in the study period in patients with very small tumors. Lymph node dissection was not performed routinely. In patients with clinically enlarged nodes, the jugulocarotid chains were removed and radiation was delivered to the cervical lymph node sites in addition to the tumor site.

All study data were entered in a computer via File Maker Pro (Microsoft, Santa Clara, CA). The data were then processed using the conversational survey data processing software DM 90 (Medical Informatics Department, school of Medicine, Toulouse, France). The Kaplan-Meier method was used to compute actuarial survival rates.

### RESULTS

The 46 study patients, 40 men and 6 women (M/F ratio, 6.6/1), had a mean age of 61 years with a range of 43 to 92 years. Occupational exposure to wood dust was reported by 32 (69.5%) patients. Table I lists the presenting symptoms and Table II shows tumor extent as assessed by CT and MRI.

In 15 patients, the tumor was confined to the ethmoid.

TNM stages are given in Table III.

At presentation, a single patient had lymph node involvement (N2b) and none of the patients had metastases.

Of the 38 patients treated with curative intent:

- 36 received surgery and postoperative radiation therapy,

- two received neoadjuvant chemotherapy; a greater than 50% response was achieved in both patients, who subsequently underwent surgery via the paralateronasal approach, followed by radiation therapy. Ethmoidectomy was performed:

- via endonasal endoscopy in 1 patient and,

- via the paralateronasal approach in 37 patients; of these 37 patients, 2 underwent exenteration, 1 hemimaxillectomy, and 2 intracranial surgery via the bicoronal approach.

Of the 14 patients with upward tumor spread, 6 had

contraindications to surgery, 6 were initially treated via the paralateronasal approach either without chemotherapy (upward extension confined to the cribriform plate, n=4) or with neoadjuvant chemotherapy (n=2), and 2 were treated via a combined paralateronasal and bicoronal approach.

**Table I: Presenting manifestations**

	Adénocarcinomes (46 patients)
<b>Nasal manifestations</b>	45 cas (97.8%)
Nasal obstruction	41 (89.1%)
Epistaxis	23 (50%)
Rhinorrhea	12 (26%)
Pain	10 (21.7%)
<b>Ophthalmologic manifestations</b>	8 cas (17.3%)
Exophthalmos	7 (15.2%)
Extraocular palsy	1 (2.1%)
Blindness	1 (2.1%)
<b>Neurological manifestations</b>	3 cas (6.5%)

**Table II: Tumor spread**

<b>Lateral spread</b>	<b>12</b>
Isolated lysis of the papyraceous lamina	4
Orbit	8
<b>Superior spread</b>	<b>14</b>
Skull base only	9
Brain	5
<b>Medial spread</b>	<b>25</b>
Nasal cavity	7
Contralateral ethmoid	7
Septum	16
<b>Posterior spread</b>	<b>3</b>
Cavernous sinus, optic chiasm	2
Pterygomaxillary fossa	2
<b>Inferior spread</b>	<b>1</b>
Bony palate	1
<b>Spread to other sinuses</b>	<b>21</b>
Maxillary	15
Sphenoid	13
Frontal	5

*Some patients had spread in more than one direction (medial and/or posterior and/or to other sinuses).*

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**Table III: TNM UICC 1992 classification [5]**

Tumor stage	Number of patients	Percentages
T1	3	6.5
T2	12	26.0
T3	12	26.0
T4	19	41.5

**TNM UICC 1992 Classification:**

T1: tumor confined to the ethmoid sinus  
 T2: spread to the nasal cavity  
 T3: spread to the anterior orbit or maxillary sinus  
 T4: spread to the intracranial cavity, orbital apex, sphenoidal sinus, frontal sinus, or skin over the nose

N1 : homolateral node no greater than 3 cm in diameter  
 N2a : homolateral node 3 to 6 cm in diameter  
 N2b : multiple homolateral nodes no greater than 6 cm in diameter  
 N2c : contralateral or bilateral nodes no greater than – cm in diameter  
 N3: node greater than – cm in diameter

M0 : no metastases at remote sites  
 M1 : metastases at remote sites

**Table IV: Recurrence rate estimated using the Kaplan-Meier method**

	No recurrence	Recurrence
14 months	88.4%	11.6%
32 months	68.3%	31.7%

Of the 8 patients who did not undergo surgery, 5 had contraindications to surgery independent from the tumor; 2 of these 5 patients had inoperable tumors and 1 refused surgery. The 3 remaining patients had inoperable tumors. Of these 8 patients, 5 were given radiation therapy alone and 2 were given chemotherapy and radiation therapy; the remaining patient refused treatment.

Mean follow-up was 44 months with a range of 1 to

117 months. The patient with a follow-up of 1 month declined treatment and died 1 month after the diagnosis.

Of the 7 other patients who did not undergo surgery:

- five experienced continuous local disease progression and 2 a local recurrence. In all, local recurrence was noted,

- in 13 (28.2%) patients, after a mean of 28.3 months (range, 5-78 months),

- lymph node recurrence was recorded in 2 (4.3%) patients, after 2 and 16 months, respectively.

Metastatic disease developed in 5 (10.8%) patients, - after a mean of 34.8 months (range, 2-72 months); the bone was involved in 3 patients, the lung in 3 patients, and the brain in 1 patient. Recurrence rates are reported in Table IV.

Of the 5 nonoperated patients who experienced continuous disease progression, 2 received further palliative chemotherapy and 3 were not given additional treatment.

The 3 nonoperated patients who were alive with no disease progression at the end of treatment were given no further treatment.

Local recurrences (n=13)

- were treated with surgery only (n=4),

- surgery and radiation therapy (n=4),

- surgery and chemotherapy (n=1), or

- radiation therapy only (n=1);

in the 3 remaining patients, the local recurrence was not treated.

In the 2 patients with lymph node recurrences, the jugulocarotid chains were removed and radiation was delivered to the cervical lymph node sites. Of the 5 patients with metastatic disease:

- two received chemotherapy and

- three radiation therapy.

At last follow-up, 26 patients were alive, including 25 with no evidence of disease progression. In the 20 patients who died, the cause of death was tumor progression (n=16), postoperative complications (n=2), or a condition unrelated to the tumor (n=2). Overall actuarial survival rates were 70.8% after 3 years (95% confidence interval [95%CI], 55.4-82.5) and 62.2% after 5 years (95%CI, 46.5-75.8). Estimated median survival was 61.7 months. Five-year actuarial survival was 82% in patients with T1/T2 tumors and 51% in those with T3/T4 tumors.

### DISCUSSION

#### Comparison to previous data

The epidemiological data from our study are consistent with earlier findings.

A study in the Nord Pas-de-Calais region of France found that sinonasal cancer accounted for 2.5% of all upper aerodigestive tumors, with a male-to-female ratio of 2.4 and a mean age of 60 years [5]. In a population with adenocarcinoma of the ethmoid sinus, Wax et al. found that mean age was 50 years (range, 26 to 73 years) and that males and females were equally affected [6]. Myers et al. reported a mean age of 60 years in patients with paranasal sinus malignancies [7].

As early as 1923, Portmann et al. suggested a carcinogenic effect of wood dust in furniture workers [8]. The first epidemiological studies were conducted in 1965 by Mac Beth et al. [9] and in 1967 by Acheson et al. [1]. Substances that can cause sinonasal cancer include alkaloids, saponins, stilbene, aldehydes, phenol compounds (quinines and flavones), resins, and oils [10]. Tannins, which are phenol compounds, are the chemicals most likely to contribute to the development of adenocarcinoma of the ethmoid sinus. High risk populations include furniture workers and carpenters; leather, shoe, and textile workers; and workers exposed to nickel, chromium, paint, varnish, and glue [10]. In France, adenocarcinoma of the ethmoid sinus is an occupational disease, and patients are entitled to workers' compensation [11-12].

The main presenting symptom in our study was nasal obstruction, followed by other nasal symptoms (epistaxis, rhinorrhea, and pain) [13]. Kraus et al. [14] reported nasal obstruction in 78.9% of cases and epistaxis in 36.8%. In a study by Myers et al. [7], only 34% of patients presented with nasal obstruction; 34% had pain, 29% a growing mass, 23% epistaxis, 14% hypoesthesia in the distribution of V2, 11% epiphora, and 11% diplopia.

Because symptoms are nonspecific and delayed, the disease is often advanced at diagnosis [7]. Thus, in our study, 67.5% of patients had T3/T4 diseases, compared to only 32.5% with T1/T2 disease. Lymph node involvement is uncommon. A

single patient in our study had lymph node involvement at diagnosis. In earlier studies, the proportion of patients with lymph node involvement ranged from 1 to 26% [7, 15-16].

Comparing outcomes across studies is difficult given the heterogeneity of patient populations and management strategies. Some studies included patients with a variety of tumors that differ markedly in terms of prognosis. In our study, actuarial survival rates computed using the Kaplan-Meier method were 70.8% after 3 years and 62.2% after 5 years. Table V shows that these results are consistent with the literature [3, 7, 12, 17-19]. For instance, in a study by Claus et al. of 47 patients with adenocarcinoma of the ethmoid, after exclusion of 4 patients with inoperable or metastatic disease, overall survival was 71% after 3 years, 60% after 5 years, and 38% after 7 years [18]. Until the 1970s, 5-year survival did not exceed 30-35% [20].

#### Contribution of imaging studies

CT and MRI of the facial structures are now performed routinely in patients with adenocarcinoma of the ethmoid sinus. When used in combination, these two imaging studies provide an accurate map of the tumor that serves as a guide to the surgeon. Tumor spread must be recorded in detail, as involvement of each site carries specific therapeutic consequences [21].

- Upward spread may result in contact between the tumor and skull base without osteolysis, in osteolysis of the cribriform plate or upper labyrinth surface, in meningeal involvement, or in intracranial spread.

- Lateral spread may be seen as isolated lysis of the papyraceous lamina without orbital involvement, as extraconal orbital involvement, or as invasion of the orbital fat.

**Table V: Five-year survival rates in previous studies**

Bhattacharya et al [3]	40.3 %
Myers et al [7]	52.0 %
Marandas et al [12]	48.0 %
Stoll et al [17]	80.0 %
Claus et al [18]	60.0 %
Roux et al [19]	42.5 %

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- Inferiorly, the tumor may be in contact with, or cause lysis of, the bony palate.
- Posterior spread may result in isolated lysis of the posterior wall of the maxillary sinus, involvement of the pterygomaxillary fossa, involvement of the optic nerve or optic chiasm, or spread to the cavernous sinus.
- Finally, the other sinuses may be involved. The rate of agreement between imaging finding and operative specimen histology is 98.5% with CT and MRI in combination [21], 85.2% with CT only, and 94.1% with MRI only. CT is extremely useful for evaluating osteolysis. MRI provides accurate information on soft tissues and differentiates tumor tissue from inflammatory tissue and retained material. The main drawback of MRI is its low performance for evaluating bony structures.

### Management

The management of adenocarcinoma of the ethmoid sinus is not standardized. Because the condition is rare, obtaining enough cases for a valid comparison treatment strategies is difficult [7]. Most authors recommend combining surgery and radiation therapy [6-7, 17-18, 23-25], although whether radiation or surgery should be done first remains controversial.

Advances in endonasal endoscopic surgery have led some groups to use this approach in patients with small tumors. The indications for endonasal endoscopic surgery are not standardized, however. Patients with small tumors confined to the ethmoid labyrinth may be good candidates for endonasal endoscopic surgery alone. Limitations of this approach are related not only to tumor size and location, but also to availability of appropriate technical equipment and experienced surgeons.

Advantages of the endonasal endoscopic approach include [2]:

- absence of visible scars,
- a shorter operating time,
- a shorter hospital stay, and
- lower morbidity.

However, the need to achieve complete tumor removal in order to ensure an optimal oncological outcome should guide the choice of the surgical approach.

Endoscopy is useful [22] as part of the preoperative workup to obtain accurate information on the endonasal status and to collect biopsies under visual guidance.

- When used in combination with an external approach, endoscopy helps to achieve complete tumor excision in hard-to-access regions such as the skull base, sphenoidal sinus, and parasinus region.

- Endonasal endoscopy is a valuable method for monitoring operative sites in order to achieve early detection of recurrences. Small recurrences may be treatable by the endoscopic route used alone.

Ethmoidectomy via the paralateral approach is the most widely used surgical technique. The indications for combining an ENT approach with a neurosurgical approach vary across groups. The combined approach is usually recommended for T3/T4 tumors and for tumors extending posteriorly or superiorly [25-26]. It has been advocated for all tumors contacting or invading the skull base. Sisson et al. [28] use the combined approach for T3/T4 tumors and consider that contraindications consist of spread to the frontal lobes, involvement of both optic nerves, or lateral spread to the region of the orbital fissure and cavernous sinus. Although surgery is technically possible in these situations, it does not improve survival. Myers et al. recommended similar contraindications related to local spread [7].

In our series, the combined approach was used in patients with osteolysis of the cribriform plate or upper labyrinth surface and in those with spread to the meninges or brain. Contraindications to the combined approach were spread to the posterior wall of the sphenoid, jugum, or cavernous sinus, as well as massive invasion of the frontal lobes. In this retrospective study, the Cairns-Unterberger neurosurgical exposure was used for all combined approaches. However, the value of the subfronto-orbitonasal approach should be pointed out.

The management of ocular involvement varies across groups. Kraus et al. stated that lysis of the papyraceous lamina without spread to the orbital cone does not contraindicate preservation of the orbital contents [14]. This recommendation was followed in our case-series: exenteration was reser-

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ved for patients with involvement of the orbital cone (orbital fat or extraocular muscles). Brasnu et al. advocated exenteration in patients with tumor spread confined to the anterior part of the orbit [27]. Posterior spread contraindicates exenteration, as complete excision of optic canal is not feasible. When exenteration is not performed in a patient with osteolysis of the papyraceous lamina, no spread to the orbital cone, and complete tumor excision by gross examination, an additional dose of radiation can be delivered to the orbital contents in order to improve the cosmetic, psychological, and functional outcomes. This treatment does not ensure preservation of visual acuity, given the high risk of optic nerve atrophy or purulent destruction of orbital contents (which may require exenteration). Kraus et al. reported blindness in 33% of patients, including 8% with bilateral blindness, after radiation therapy [14].

Radiation therapy also lacks standardization. Routine external-beam radiation therapy combined with surgery is usually advocated [3, 7, 13, 18]. Myers et al. underscored the feasibility of preoperative radiation therapy [7], and Lavertu et al. [24] showed that preoperative radiation therapy was associated with improved survival rates, as compared to postoperative radiation therapy. Several groups reserve radiation therapy for the postoperative treatment of patients with positive excision margins [6, 28] or histological involvement of the dura mater or cribriform plate [6]. A few groups use radiation therapy without surgery in patients with T1/T2 tumors [22, 28-29], delivering 55 to 65 Gy over 5 to 6 weeks. This strategy provided local control in 79.5% of patients; 5-year survival rates were 85.9% and 81.7% in patients with T1 and T2 tumors, respectively [29]. In our case-series, surgery was performed whenever possible and was routinely followed by radiation therapy. In patients with inoperable tumors, radiation therapy provided a 32% local control rate after 3 years [30].

Few data are available on neoadjuvant chemotherapy followed by combined-approach surgery then by external-beam radiation therapy has been advocated [19]. In our series, 2 patients received neoadjuvant chemotherapy with the goal of shrinking the tumor in order to facilitate surgery.

Few data are available on the use of concomitant chemotherapy and radiation therapy for the

management of large inoperable tumors. In some series, cases of advanced sinus tumors were studied together with head and neck tumors at other sites [31]. All histological types of advanced sinonasal cancer were lumped together in these studies, and radiotherapy-chemotherapy regimens varied in terms of both the medications used and the administration modalities. Survival rates were about 65%-70% [32-33]. Intraarterial chemotherapy has been used [32], as well as postoperative chemotherapy combined with radiation therapy (multimodality therapy) [33-34]. Higher survival rates have been reported with the chemotherapy-surgery-radiation therapy+chemotherapy sequence, compared to surgery followed by radiation therapy [33]. Roux et al. reported that neoadjuvant chemotherapy produced no response in 59% of patients, a partial response in 19%, and a complete response in 22% [19].

Based on the present case-series, a review of the literature, and recent advances in surgical techniques, we recommend the following management strategy.

- Small tumors (T1/T2) should be treated surgically via the paralateronasal approach then given external-beam radiation therapy delivered to the tumor site.

- Small tumors strictly confined to the labyrinth, without lysis of the bony walls can be removed via the endonasal endoscopic route.

- In patients with T3/T4 tumors, the treatment strategy should be determined based on local spread:

- when CT shows only osteolysis of the papyraceous lamina or upper labyrinth surface and MRI shows no evidence of spread to the orbit or dura mater, conventional tumor removal via the paralateronasal approach is in order; in patients who have intraconal orbital extension with involvement of orbital fat, exenteration should be considered. Spread to the dura mater or frontal cerebral parenchyma requires surgery via the combined approach,

- maxillectomy should be performed in patients who have inferior spread with osteolysis of the bony palate,

- in patients with advanced tumors involving the skull base or orbit, neoadjuvant chemotherapy should be given, followed by surgery then by radiation therapy,

- if the tumor is inoperable, chemotherapy and

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radiation therapy are given concomitantly.

- at our institution, contraindications to surgery are major tumor spread with involvement of the body and posterior wall of the sphenoid, cavernous sinus, or orbital apex; extensive involvement of the cerebral parenchyma is also a contraindication,

- local recurrences are usually treated by surgical removal whenever possible. When surgery is contraindicated, either further radiation therapy is given, in doses calculated according to the initial dose, or palliative chemotherapy is used. Lymph node recurrences are treated by removal of the jugulocarotid chains followed by additional radiation therapy,

- the treatment of metastatic disease depends on the number and location of the metastases.

### CONCLUSION

Because the symptoms of adenocarcinoma of the ethmoid sinus are delayed and nonspecific, the diagnosis is usually established only at an advanced stage. CT and MRI supply invaluable information on tumor spread, most notably to the skull base and orbit. The detailed map provided by these imaging studies guides treatment decisions. Surgery and radiation therapy in combination is the most widely used treatment strategy. Radiation therapy combined with chemotherapy may be a valid alternative in patients with inoperable tumors. Nasal endoscopy provides useful diagnostic information and helps to monitor the course. Endoscopic surgery may be used as a complement to open surgery. In patients with very small tumors, complete excision may be feasible via the endonasal endoscopic approach used alone.

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