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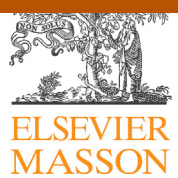

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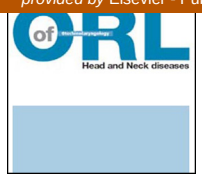

REVIEW

Paranasal sinus cancer

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Anterior skull base surgery;
Endoscopic sinus surgery;
Radiotherapy;
IMRT

Summary Paranasal sinus cancers are rare, aggressive tumours that are usually diagnosed at an advanced stage. They differ from other upper aerodigestive tract tumours in terms of risk factors (wood dust exposure) and premalignant lesions (inverted papillomas). The diagnosis should be suspected in the presence of unilateral and continuous nasal sinus symptoms or bone lysis or a heterogeneous opacity on imaging. The definitive positive diagnosis is based on histological examination. Staging must comprise face, brain, neck and chest CT as well as face and brain MRI. Tumours are stage T3-T4 in two-thirds of cases and are associated with cervical lymph node involvement in 10% of squamous cell carcinomas and 4% of adenocarcinomas. These tumours must be managed in reference centres experienced in all of the various treatment modalities. Treatment decisions must be based on a multidisciplinary approach comprising local, regional and national REFCOR expertise (French rare head and neck cancer network). Optimal treatment is surgical resection with clear margins associated with adjuvant intensity-modulated radiotherapy (IMRT). Although it has been improved over recent decades, the prognosis remains poor with local recurrences occurring in 38% of cases and a five-year overall survival of about 63%.

Introduction

Paranasal sinus cancers are rare, aggressive tumours. Due to their rarity, the diagnostic modalities must be effectively mastered to avoid further delaying the classically late diagnosis of these tumours. This delayed diagnosis is related to the late onset of the relatively commonplace symptoms that are often neglected by the patient. The majority of tumours are therefore diagnosed at an advanced stage, requiring invasive and mutilating surgery.

The rarity of these tumours also explains the limited scientific rationale and the low level of proof of treatment guidelines in this field. Modifications of the gold standard represented by a combination of surgery and radiotherapy have been recently introduced: endonasal surgery, IMRT radiotherapy, induction or concomitant chemotherapy, complex reconstructions, etc. The prognosis of these tumours has been improved and the functional results of these innovative treatments are also the subject of close scrutiny.

This article is designed to present a didactic review of the current knowledge concerning the diagnosis, treatment and prognosis of paranasal sinus cancers.

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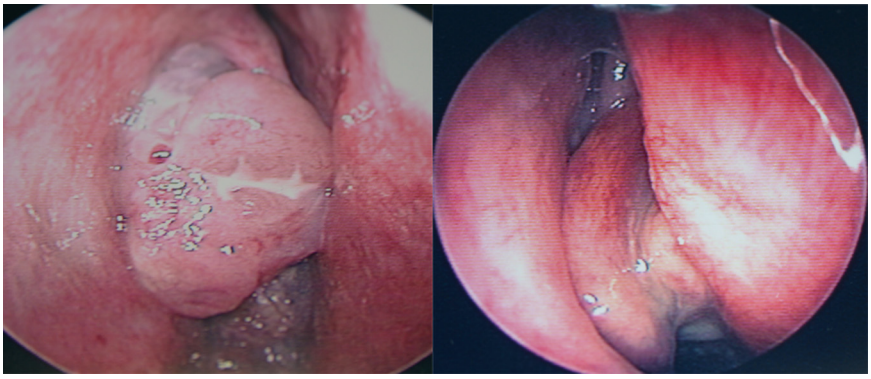

Figure 1 Nasal endoscopy: granulating tumour arising from the right ethmoid sinus. The tumour may be visualized either in the region of the middle meatus (left image) or in the olfactory groove (right image).

Diagnosis

Mode of presentation

In the vast majority of cases, these tumours are diagnosed at the stage of symptoms.

When the tumour has only invaded the paranasal sinuses, symptoms are non-specific: unilateral blocked nose, mucopurulent rhinorrhoea, and epistaxis. These symptoms are neglected for a long time by patients, who are usually chronically exposed to wood dust and who have experienced these symptoms for very many years. In a study that we conducted on 934 wood dust exposed workers in Brittany between 2007 and 2009, 25% of subjects reported blocked nose, 18% reported rhinorrhoea, 18% reported sneezing, 9.9% reported epistaxis and 7.5% reported dysosmia. However, these symptoms were bilateral or alternating in 92.6% of cases (in press).

The unilateral and continuous nature of these symptoms must raise the suspicion of paranasal sinus cancer.

Extension beyond the sinuses, in addition to sinus symptoms, also causes neurological (headache, anaesthesia in the territory of the trigeminal nerve), ophthalmological (exophthalmos, recurrent conjunctivitis, diplopia) or dental symptoms (pain or mobility of maxillary teeth).

Paranasal sinus cancers are rarely diagnosed or suspected before the onset of symptoms, but may be an incidental finding on imaging or histology or can rarely be discovered systematically in the context of early screening programmes in exposed occupations. However, since 28 February 1995, Article D461-25 of the French Social Security Code has proposed ''ENT examination, chest X-ray, sinus X-rays, possibly completed by five or six frontal CT sections'' every 2 years for workers exposed to wood dust under certain exposure conditions. The French Société de Médecine de Travail (French Society of Occupational Medicine) guidelines published in 2011 and validated by iNCA (French Cancer Institut) and the HAS (High Authority of Health) propose nasal endoscopy every 2 years in subjects with cumulative exposure greater than 12 months over a period of more than 30 years.

Clinical examination

The nasal fossae must be examined with a bivalve rhinoscope or nasal speculum using a suction system to eliminate the often abundant secretions from the nasal fossae and cotton buds soaked in Xylocaine® with 5% naphazoline. This examination allows direct visualization of the tumour, which presents the characteristics of a malignant tumour: irregular and granulating, contact bleeding, painless. It can be visualized at various levels: underneath the middle turbinate, arising directly from the ethmoid sinus, in the olfactory groove (Fig. 1), anywhere in the nasal fossa as far as the floor or even in the nostril. More rarely, polyps with a benign appearance may mask the tumour itself, therefore resulting in a false-negative diagnosis.

Clinical examination then comprises the use of a flexible or rigid 0° and/or 30° optic nasal endoscope in order to visualize the tumour and try to delineate its contours.

Examination of the oral cavity must look for vaulting of the palate, soft palate, cheek, superior gingivolabial sulcus, or mobility of the maxillary teeth. Posterior rhinoscopy using a mirror may visualize the posterior part of the tumour which protrudes into the nasopharynx. This visual inspection must be systematically combined with endobuccal palpation, which is sometimes the only way to induce suspicious contact bleeding or reveal submucosal induration not detected by inspection. The rest of the upper aerodigestive tract mucosa must be systematically examined looking for a possible second tumour, especially in patients with associated alcohol and smoking risk factors. Otoscopic examination may reveal seromucous otitis which, in this context, is suggestive of auditory tube obstruction. All cervical lymph node areas must be palpated looking for lymphadenopathy.

Neurological examination must test all cranial nerves, particularly the three divisions of the trigeminal nerve. Ophthalmological examination looks for exophthalmos and determines whether or not it is reducible, the presence of defective eye tracking or loss of visual acuity.

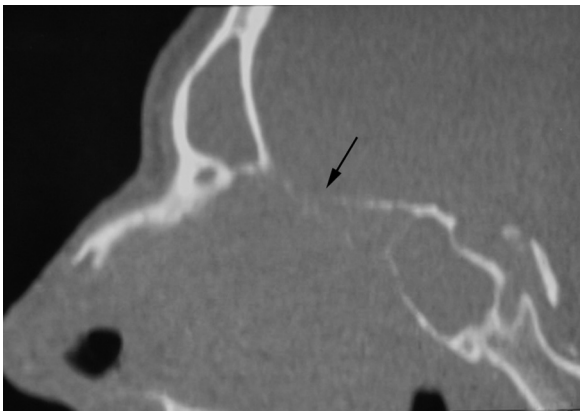

Figure 2 CT scan of the sinuses, bone window setting, sagittal section. The arrow indicates osteolysis of the roof of the anterior part of the ethmoid sinus.

Diagnostic imaging

When clinical examination demonstrates the typical features of a malignant tumour and in the absence of contraindications, biopsy can be performed immediately. In this case, imaging is essentially performed for staging purposes.

In the other cases, imaging can confirm the suspicion of malignant tumour, ensure the absence of contraindication to biopsy (intensely contrast-enhanced lesion) and is useful for staging (Figs. 2, 3). The first-line examination is computed tomography of the sinuses with bone and soft tissue windows and contrast injection. Examination must focus on the sinus walls and contents. Signs suggestive of malignant tumour are osteolysis of the sinus walls, unilateral and/or heterogeneous opacity of the nasal cavity or sinus with heterogeneous enhancement. MRI can also suggest the diagnosis in the presence of a heterogeneous unilateral opacity.

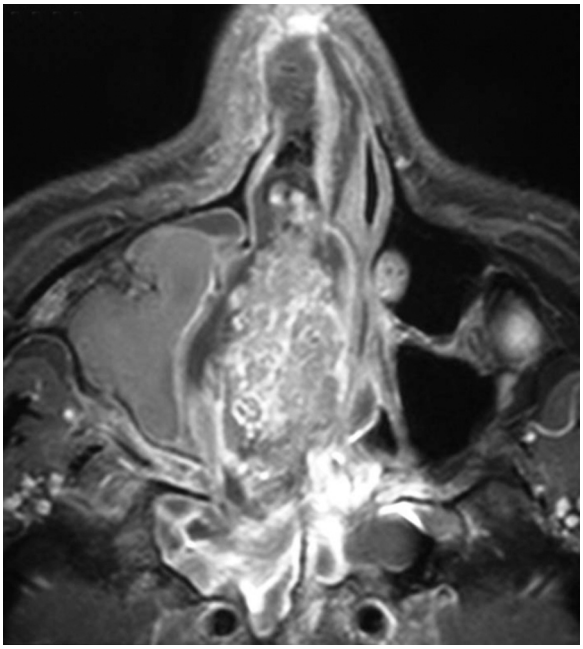

Figure 3 MRI, gadolinium-enhanced T2-weighted sequence, axial scan. The ethmoid sinus presents an exuberant heterogeneous opacity extending onto the anterior wall of the sphenoidal sinus which is lysed. The maxillary sinus presents a homogeneous mucosal opacity.

Differential diagnosis

Unilateral nasal sinus polyposis and inverted papilloma can present the clinical features of paranasal sinus cancer. However, this diagnosis must always be confirmed by biopsy.

The presence of unilateral but homogeneous opacity of the sinus with intact bony walls may indicate a diagnosis of Kilian's polyp. The definitive diagnosis is based on histological examination. Opacity of the sinus associated with osteolysis may correspond to mucocele or odontogenic cyst. In both of these cases, the mass remains very regular and is often surrounded by a fine layer of bone, reflecting the slow and noninvasive growth of the lesion.

Heterogeneous unilateral sinus opacity sinus with intact bony walls may correspond to a diagnosis of sinus aspergillosis. Treatment is surgical and all operative specimens must be submitted to histological examination. The presence of lysis of the bony walls may indicate fibrous dysplasia or benign tumours (ossifying fibroma, cemento-ossifying fibroma).

Histology

Only biopsy and histological examination can provide the definitive diagnosis. A tumour fragment must be frozen for storage in a tumour bank, when available. As these tumours are rare, the slides must be reviewed when there is any doubt about the diagnosis or in the case of doubtful histology. The distribution of histological types varies from one country to another with, globally, squamous cell carcinoma accounting for 50% of all sinus tumours, adenocarcinoma: 22%, adenoid cystic carcinoma: 10%, non-Hodgkin's lymphoma: 11%, olfactory esthesioneuroblastoma: 3%, sarcoma: 3% and mucosal melanoma: 2% [1]. This list is not exhaustive and the WHO classification comprises a very large range of tumours in this site.

A correlation between tumour site and histology is typically observed. Ethmoid tumours are adenocarcinomas in 75% of cases and maxillary sinus tumours are squamous cell carcinomas in 75% of cases. The nasal fossae are mainly the primary site of squamous cell carcinoma, malignant melanoma and olfactory esthesioneuroblastoma.

Staging assessment

Assessment of a cancer comprises a general assessment of the patient and staging of the tumour. Assessment of the patient must comprise a diagnosis disclosure consultation, an anaesthetic consultation, nutritional assessment (BMI, serum albumin), pain assessment (VAS), evaluation and management of risk factors (occupational medicine, smoking and alcohol withdrawal, when associated). Staging comprises CT and MRI of the facial bones and contrast-enhanced CT of the neck and chest.

CT of the facial bones (Fig. 2) is designed to determine the limits of the tumour, identify zones of osteolysis and any anatomical variants (optic nerve, internal carotid vessels).

MRI (Fig. 3) is performed systematically and must comprise at least two T1-weighted sequences before and after injection, a T2-weighted sequence in at least two different planes, and a diffusion sequence. MRI is able to distinguish zones of fluid retention from zones of tumour invasion (T2-weighted and FLAIR sequences), and can identify invasion of the periorbital fat (FAT-SAT and STIR sequences) and invasion of the dura mater (gadolinium-enhanced T2 and T1 sequences) and cerebral cortex. MRI also has a higher sensitivity than computed tomography for the diagnosis of invasion of the infratemporal fossa and pterygopalatine fossa [2].

The place of PET-CT (Fig. 4) has not yet been clearly defined and no formal consensus has been reached concerning this indication. According to the 2003 Standards-Options-Recommendations of the Fédération de Lutte Contre le Cancer (French cancer centre federation), this examination can be performed as part of the standard initial staging assessment (level of proof B2) [3]. Wild reported the results of PET for initial staging and restaging in a series of 21 patients with paranasal sinus cancer [4]. PET demonstrated distant metastases in five patients, resulting in treatment modification for nine patients. However, it remains to be demonstrated whether these treatment modifications result in a benefit for the patient.

Classifications

The official classification of paranasal sinus tumours is the UICC TNM 2006 classification [1]. It essentially has a prognostic value, but also allows homogeneous classification, facilitating communication and publication.

Sixty seven percent of squamous cell carcinomas of the maxillary sinus are stage T3-T4 [5], while the majority of adenocarcinomas of the ethmoid sinus are stage T2 (32%) and T4 (40%). Lymph node invasion is detected in 10% of squamous cell carcinomas of the maxillary sinus and 2.4% of adenocarcinomas of the ethmoid sinus [6,7]. Distant metastases are present in only about 2% of paranasal sinus cancers at the time of the initial diagnosis [7].

Treatment

Treatment modalities

Surgery

Techniques without skull base resection comprise all transfacial approaches [8], including lateral rhinotomy, Rouge-Denker rhinotomy, and the buccal vestibular or ''degloving'' approach.

Skull base resection can be performed via several approaches. The mixed approach combines a subfrontal approach with a transfacial approach, either lateral rhinotomy, or, less commonly, a bilateral sublabial approach (degloving) [9] or a transmaxillary approach [10]. Pure transcranial approaches (bicoronal incision) have the advantage of avoiding a facial incision [11]. Finally, skull base resection can be performed via a purely transfacial approach, which has the advantage of allowing management of unexpected intraoperative findings [12,13].

For a long time, endonasal surgery was reserved for small tumours, but improvement of instrumentation and neuronavigation now allows resection of much larger tumours (Fig. 5) [14—18]. The European Rhinologic Society held a meeting in 2010 to more clearly define and classify the indications and the surgical technique itself [1]. It recommended that endonasal surgery be reserved to teams already experienced in conventional skull base surgery and endonasal surgery in general, and that a learning curve be observed by starting with small tumours without invasion beyond the sinus.

Radiotherapy [19—26]

The recommended dose for exclusive radiotherapy or postoperative macroscopic residual tumours is 70 Gy for the tumour and metastatic lymph nodes. A dose of 50 to 66 Gy is delivered to zones at high risk of microscopic extension.

For adjuvant radiotherapy, the dose prescribed to the tumour site is 50 to 66 Gy, with a dose of at least 60 Gy to residual tumour and lymph nodes with capsular effraction. Fractionation consists of five fractions of 1.8-2 Gy per week.

The tumour target volume together with its microscopic extensions only comprises all of the affected sinus when tumour extension is strictly confined to the sinus. The target volume is extended to adjacent structures in the presence of documented effraction, such as the orbit in the case of periosteal effraction of the orbital wall, the nasal fossa, an adjacent sinus or the pterygomaxillary fossa.

Radiotherapy is made complex by the proximity of target volumes and vital structures (eye, brain and hypothalamo-pituitary axis). Three dimensional conformal radiotherapy, based on the initial CT treatment planning, has reduced the treated volumes and consequently the dose delivered to vital organs. Conformal intensity-modulated radiotherapy (IMRT) allows modulation of the intensity of irradiation beams during the treatment session. IMRT can be used to irradiate concave tumours, while sparing adjacent healthy tissues. IMRT allows the use of simultaneous integrated boost (SIB), simultaneous modulated accelerated radiation therapy (SMART) and dose escalation (new dose painting concept) techniques.

Chemotherapy

The protocols most widely used at the present time comprise concomitant administration of cisplatin at a dose of 100 mg/m^2 on D1, D22 and D43. The combination of platinum + 5FU + cetuximab (extreme protocol) can be used as first-line treatment for inoperable recurrent and/or metastatic tumours.

Complications are haematological (anaemia, thrombocytopenia), cardiac, neurological (neuropathies), nephrological, cutaneous (particularly with cetuximab), otological and gastrointestinal (mucositis, diarrhoea).

Rational bases [6,7,25,27,28]

Treatment of the tumour

The combination of surgery and radiotherapy is more effective than radiotherapy alone. The sequence of surgery

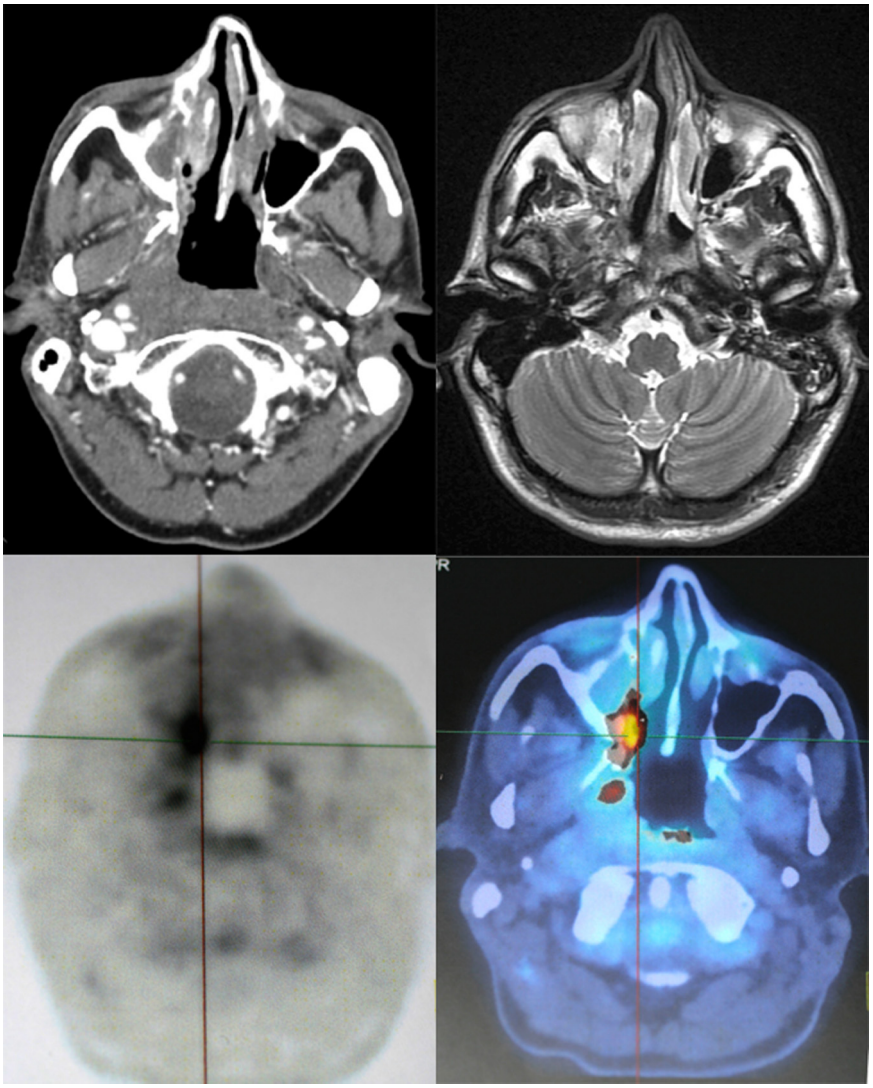

Figure 4 PET-CT, axial scan. PET demonstrates significant uptake (SUVmax 12) in the right pterygopalatine fossa (lower images), while recurrence is not clearly visualized on contrast-enhanced CT (left upper image) and MRI axial sections (right upper image).

followed by radiotherapy allows better local control than the reverse sequence. The prognosis of very large tumours is highly dependent on tumour resectability. Surgery alone may be sufficient for stage T1 tumours except in the case of invaded margins, perineural invasion or an undifferentiated contingent.

Endonasal surgery allows at least identical survival for adenocarcinomas or even better survival for esthesioneuroblastomas with decreased morbidity, but it requires particular skills [1,29,30].

Treatment of lymph nodes [5—7,31]

The risk of lymph node invasion is higher for squamous cell carcinomas (10%), esthesioneuroblastomas and lymphomas, in the presence of invasion of the facial skin or the maxillary infrastructure. Radiotherapy to N0 zones significantly decreases the lymph node recurrence rate in these territories. The treatment of choice of N+ tumours is a combination of exenteration followed by adjuvant radiotherapy. There is a correlation between lymph node recurrence and the risk of distant metastases.

IMRT has been demonstrated to reduce acute and late toxicities [1,32] and improve quality of life [33]. Its benefit on reduction of hyposialia has been demonstrated in three randomized trials, but not specifically concerning paranasal sinus tumours. The few available retrospective, non-randomized series comprised a small number of patients with paranasal sinus tumours treated by IMRT [23—26] and demonstrated improved survival and less toxicity compared to historical series without IMRT. 3D conformal radiotherapy can be used when IMRT is not available (REFCOR 2009).

Only limited data are available specifically concerning chemotherapy for paranasal sinus cancer. The studies by Solero et al. [34], Roux et al. [35,36] and Georges et al. [37] suggested the possible value of induction chemotherapy in selected cases. Roux et al. [35,36] reported a complete response confirmed by histology on the operative specimen in 14% of patients (11 out of 76 patients), none of whom relapsed. The actuarial 10-year survival remains 100%

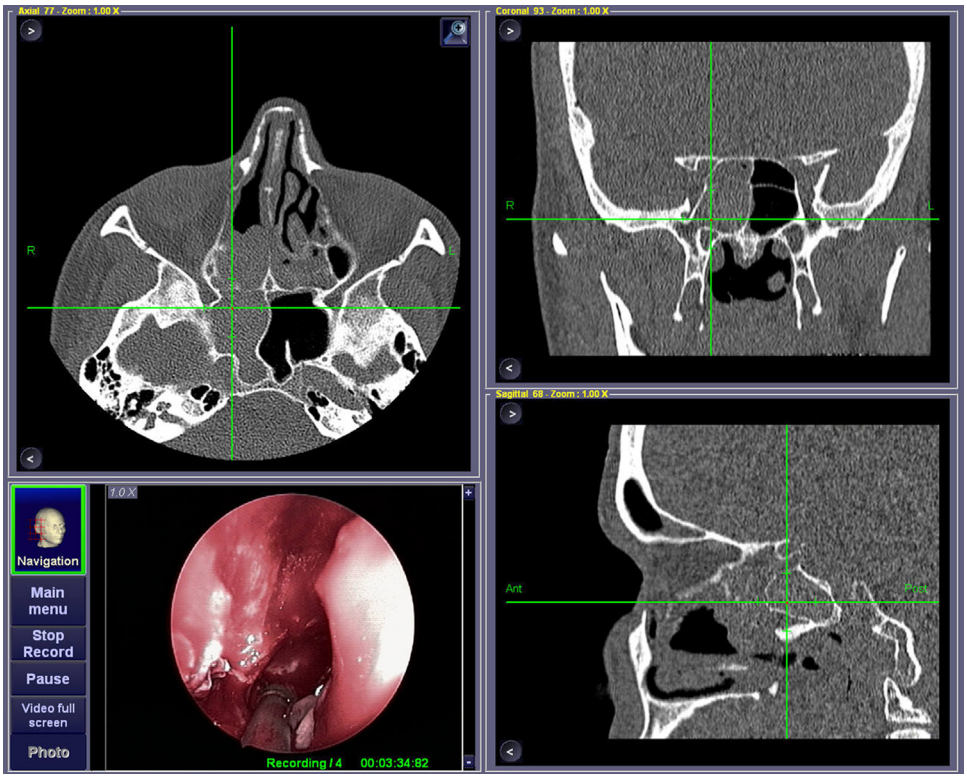

Figure 5 Neuronavigation. The neuronavigation control screen provides the surgeon with real-time navigation on the preoperative CT scan and provides information on anatomical relations with vital structures.

for these patients. However, the tumour stage of these 11 complete responder patient was not specified and partially responding patients had a less favourable survival than non-responders. Georges et al. [37] reported a complete response rate of only 6% in a series of 31 patients. The impact of chemotherapy on overall survival has not been clearly demonstrated, but a complete response may constitute a factor of good prognosis. The place of chemotherapy has yet to be defined, as the sample sizes of published series are too small to demonstrate a real benefit in terms of survival.

Indications [6,7,25,29]

In clinical practice, management therefore depends on patient-related factors (operability, comorbidities, personal preferences), tumour-related factors (TNM, histology, site, resectability), and surgical team-related factors (expertise).

Treatment according to tumour site are the following:

- when the tumour is resectable, the treatment of choice is a combination of surgery and adjuvant radiotherapy. Adjuvant radiotherapy may be unnecessary in cases with a good prognosis: stage T1-T2 adenocarcinoma, stage T1 squamous cell carcinoma, grade A and B olfactory esthesioneuroblastoma (Kadish classification) with negative resection margins. A combination of concomitant chemotherapy and adjuvant radiotherapy (optional) can be performed in cases of squamous cell carcinoma with positive resection margins;
- the treatment for unresectable tumours is radiotherapy alone or a combination of concomitant radiotherapy and chemotherapy for squamous cell carcinoma.

Below are the cases of the treatment of lymph nodes:

- in the case of clinical or radiological lymph node invasion, a modified radical dissection must be followed by adjuvant radiotherapy;
- in the absence of clinical or radiological lymph node invasion, situations at high risk of lymph node invasion must be treated by cervical node irradiation: squamous cell carcinoma, melanoma, high-grade esthesioneuroblastoma. A wait-and-see approach to lymph nodes can be proposed in other cases;
- the decision taken in multidisciplinary meetings must then be proposed and explained to the patient. Information concerning the advantages and disadvantages of the various treatments must be explained, ideally in the context of another diagnosis disclosure consultation. The treatment plan is recorded in a personalized treatment plan given to the patient with a copy in the patient's medical file.

Curative treatment must be associated with symptomatic treatment and appropriate supportive care, which requires a preliminary assessment of the patient, also recorded in the patient's medical file:

- pain (VAS: visual analogue scale);
- nutrition (body mass index, possibly serum albumin);

- psycho-oncology;
- geriatric oncology;
- social aspects;
- aesthetic aspects.

Palliative situations must take all of these data into account and the intervention of a specialized structure in palliative cares is highly desirable.

Results

Survival

The prognosis is essentially determined by local control. In the Gettec multicentre study based on 418 patients, Choussy et al. reported a local recurrence rate of 38% and a 5-year overall survival of 63%. In 2001, in a meta-analysis combined with a large series of new cases, Dulguerov reported a highly variable 5-year survival rate as a function of histological type (78% for adenocarcinomas, 60% for squamous cell carcinomas), site (62% for maxillary sinus, 48% for ethmoid sinus), and stage (91% for T1, 49% for T4) [7].

Functional results

The majority of patients suffer from chronic crusting rhinitis, lacrimation, and sometimes sensory loss of the maxillary division of the trigeminal nerve following lateral rhinotomy.

Few studies have reported the functional results, particularly in terms of the quality of life of these patients. In our experience based on 31 patients operated by transfacial anterior skull base resection between 2005 and 2010, a significant impact on quality of life was observed for the fatigue, pain, and dyspnoea items of the EORTC QLQ30 questionnaire; 88% of facial heaviness/nasal respiratory discomfort with the Rhino-QOL questionnaire, and 10% of dysexecutive behavioural disorders with the DEXT questionnaire (Bordigoni et al., in press).

Follow-up

In line with the SFORL 2008 guidelines, follow-up must concern the disease and the patient: clinical examination every two months for the first year, every three months for the second year, then every six months for life; MRI every 3 months after treatment, then in the light of clinical examination; chest x-ray at 6 months then once a year. Annual dental, ophthalmological and pituitary function follow-up is also essential.

Compensation

In 2008, 70 primary cancers of the ethmoid and facial sinuses and 10 nasal fossa cancers were recognized as occupational diseases. This figure includes cases recognized in the context of Occupational Disease tables (paragraph 2 of Article l 461-1 of the French Social Security Code) (data derived from the Eurogip 2010 report. Source: CNAMTS, Occupational risks department; http://www.eurogip.fr/docs/RA_EUROGIP2010_F.pdf).

This low occupational cancer compensation rate can be essentially explained by the absence of declaration, directly related to the doctor's lack of awareness of work-related health problems. Furthermore, because of the long latency between exposure and diagnosis of cancer (generally at least 10 years and sometimes more than 40 years), work-related cancers are often diagnosed a long time after the subject has left the job concerned. Declaration as a chronic disease is often wrongly considered to be more important than declaration as an occupational disease.

The individual advantage of declaration as an occupational disease is better compensation and job protection (French law dated 7 January 1981). The advantage for the community is to ensure funding by the employer-funded ''Work accidents - Occupational diseases'' branch of Social Security, and to improve protection measures.

Table 47 of the General Social Security Scheme and Table 36 of the Agricultural Social Security Scheme define the conditions of recognition of wood dust- and nickel-related occupational diseases: histology (carcinoma), site (sinuses and nasal fossae), causal factor (wood dust or nickel), minimal exposure time (5 years), time to management (40 years). In the other cases, an application must be submitted to the Commission Régionale de Reconnaissance des Maladies Professionnelles (Regional occupational disease recognition commission) (CRRMP, Law 93-121 dated 27/01/1993).

Progress

A significant survival gain has been observed over recent decades. This survival gain has been observed for the surgery + radiotherapy combination, but not with other treatment modalities, for cancers of the maxillary sinus and ethmoid sinus, but not for cancers of the nasal fossae and squamous cell carcinomas. A less significant survival gain has been observed for adenocarcinomas [7,38].

In the field of diagnostic imaging, MRI, but also metabolic imaging (PET/CT), have allowed more accurate delineation of these tumours in which the prognosis is related to local control. Among other things, this has allowed the development of neuronavigation and images fusion techniques for radiotherapy.

Progress in surgery has concerned skull base reconstruction techniques, decreased morbidity of surgical approaches, and especially endoscopic or endonasal surgery guided by neuronavigation, by single or double teams (4-hand endoscopic surgery).

In the field of radiotherapy, arc therapy techniques (similar to tomotherapy, but using a standard linear accelerator) will probably rapidly allow the widespread use of IMRT techniques. The Cyberknife® (robotic radiosurgery system), allowing irradiation with millimetric precision, is also being developed in many centres.

Conclusion

Paranasal sinus cancers are rare, but aggressive tumours. Delayed management is partly related to neglect of symptoms by patients but also underdiagnosis by general

practitioners, otorhinolaryngologists, dentists, and occupational health physicians.

Technological progress has been made in surgery and radiotherapy, allowing more precise treatment of the tumour while sparing healthy tissues. Survival has been considerably improved over the last 40 years, but this disease still has a poor prognosis due to poor control local.

Improvement of primary prevention measures and early screening will probably play a fundamental role in the future to reduce the mortality of these cancers.

Disclosure of interest

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

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