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CAVUM METASTATIC CANCER EXPERIENCE OF THE MEDICAL ONCOLOGY DEPARTMENT OF THE MOULAY ISMAIL MILITARY HOSPITAL IN MEKNES (BASED ON 15 CASES)

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ABSTRACT
Cavum cancers represent a specific entity different from the rest of head and neck cancers. In Morocco, cavum cancer is the second most common cancer of the head and neck after laryngeal cancer. We conducted a retrospective study of 15 cases of metastatic cavum cancer collected in the medical oncology department of the Moulay Ismail military hospital in Meknes over a five-year period from January 1, 2014 to December 31, 2019. The patients were 10 men (70%) and 5 women (30%) with an average age of 50 years with extremes of 27 and 66 years. Diagnosis is often late with a revealing symptomatology dominated by cervical adenopathy (87%). The most dominant histological type was UCNT in all cases. 80% of our patients had secondary bone localizations, associated in 26.66% of cases with extra-bone metastases (lung, liver, lymph nodes...). The treatment was based on palliative chemotherapy, with platinum salt as first-line treatment, administered in 86.7% of our patients. Second-line chemotherapy was introduced in 46.7% of patients. Cavum radiotherapy was performed in 66.7% of patients, of which 7 patients were metastatic at the outset. The average overall survival of our patients was: 20 months and 1 week with extremes between 6 months and 36 months.

INTRODUCTION
Cavum cancers represent a specific entity different from the rest of head and neck cancers. In Morocco, cancer of the cavum is the second most common head and neck cancer after cancer of the larynx.

The diagnosis of cancer of the cavum has benefited enormously in recent years from advances in endoscopy, CT and magnetic resonance imaging and isotopic explorations, which also help to determine its extent. However, diagnosis remains late, with advanced forms even metastatic at the time of diagnosis in less than 5% of cases. Over the course of its development, this cancer has a high rate of lymph node and visceral metastases, which explains some of the therapeutic failures, despite its marked chemosensitivity and radiosensitivity, which means that the primary tumour can be controlled relatively frequently.[1,2]

Radiotherapy is the mainstay of treatment for this type of cancer in the non-metastatic phase, but little research has been carried out into the metastatic phase. The role of chemotherapy in this situation is currently well established, attested by a high rate of objective responses with durable remissions and some long survivals. The aim of our work is to analyse the epidemiological, histological, clinical, therapeutic and evolutionary aspects of metastatic cancers of the cavum through a retrospective study of 15 cases collected in the medical oncology department of the Moulay Ismail Military Hospital in Meknes over the period from 2014 to 2019.

MATERIALS AND METHODS
Type of study
Our work is a retrospective study of 15 cases spread over a period of five years, from 1 January 2014 to 31 December 2019, including patients with metastatic cancer of the cavum and treated in the medical oncology department of the Moulay Ismail Military Hospital in Meknes, with the aim of analysing the various epidemiological, clinical, paraclinical, therapeutic and evolutionary data on cancer of the cavum in these patients.

Inclusion criteria
All patients treated for metastatic cancer of the cavum who have received medical treatment, whether chemotherapy and/or radiotherapy combined with surgery or not.

Exclusion criteria
However, patients presenting the following criteria were

excluded from the study

- An unusable file or one containing incomplete data.
- Any patient with non-metastatic cancer of the cavum.

Data collection

Data were collected through an exhaustive search of medical records and radiological, operative and pathological reports.

An information sheet was drawn up to collect all the information needed to meet the objectives of our study.

This enabled us to carry out a descriptive analysis of each variable.

V. Data entry and analysis

Data entry and analysis were carried out using Microsoft Excel 2010.

The data was analysed using a descriptive approach, which involved calculating percentages for qualitative variables and measures of central tendency (mean, median) and dispersion (standard deviation, minimum, maximum) for quantitative variables.

VI. Ethical considerations

The study complied with the ethical recommendations of the Declaration of Helsinki, and data were collected anonymously.

RESULTS

I. Epidemiological data

A. Total number of patients

We enrolled 15 patients with metastatic cancer of the cavum during the 5-year study period in the oncology department of the Moulay Ismail military hospital in Meknes.

B. Incidence of cases by year

This study included 15 patients with metastatic cancer of the cavum.

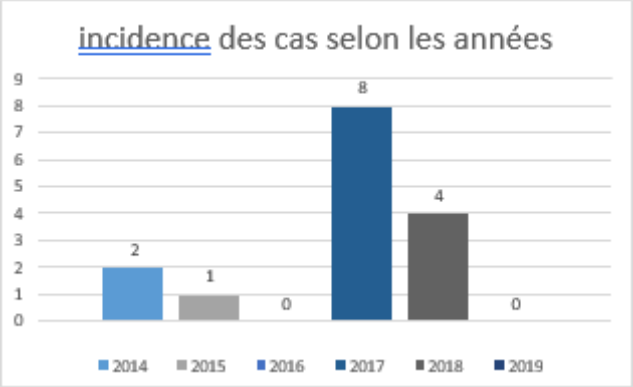


Figure 1: Breakdown of patients by year.

C. Breakdown by age

The average age of the patients was 50, with extremes of 27 and 66.

The 50-59 age group was the most common with 7 cases (46%), followed by the 60-69 age group with 4 cases (26%). Approximately 14% of patients, i.e. 2 patients, were aged between 20 and 29, and 14% were aged between 30 and 39 and 40 and 49.

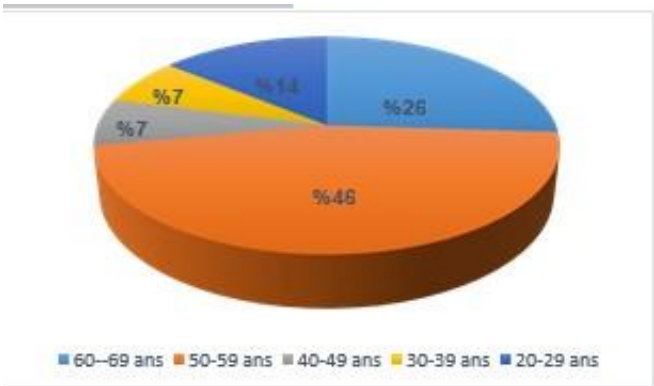


Figure 2: Breakdown of cases by age group.

D. Breakdown by sex

In our study, 10 men (70%) and 5 women (30%) with metastatic Cavum cancer were enrolled.

Table 1: Breakdown of cases by sex.

Gender	Number of cases	Percentage
Male	10	67%
Female	5	33%

E. Patients' place of residence

The majority of our patients were of urban origin with a percentage of 60%, divided into 8 cases from Meknes, 3 cases from Taza-Tahla, and the rest from Taoujtate Missour Taounat.

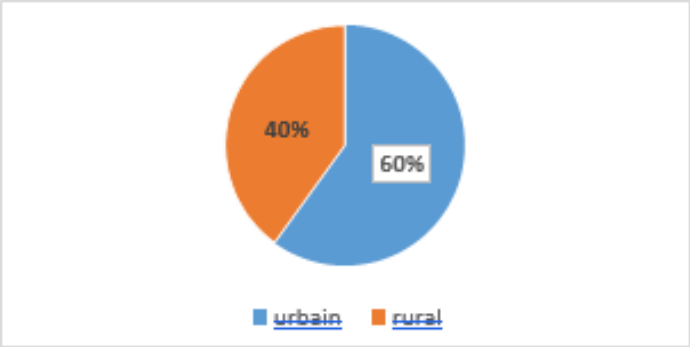


Figure 3: Breakdown of patients by location.

F. Breakdown by terrain

In our series, 06 cases, i.e. 40%, had a history of toxic smoking and alcoholism, while 08 cases, i.e. 53%, had an ENT infection, the nature of which was divided between angina and otitis, and 05 cases, i.e. 34%, had a diet rich in meat and salty fats.

Table 2: Breakdown of patients by personal history.

Antecedents	Nombres des cas	Pourcentage
Toxiques	6	40%
Infections ORL	8	53%
Régimes alimentaires	5	34%

G. Family history

Two patients presented with a family history of ENT infection (recurrent angina), and 06 patients presented with familial neoplasia, either pulmonary or gynaecological.

II. Clinical data

A. Duration of symptoms

In our study, the delay between the appearance of clinical signs and the first consultation varied between 1 and 13 months, with an average delay of 6 months.

Table 3: Breakdown of time between first symptom and consultation.

DUREE	NOMBRE DE CAS	POURCENTAGE
≤3 mois	5	33%
3-6 mois	4	27%
≥ 6 mois	6	40%

B. Circumstances of discovery

The symptoms of cancer of the cavum are divided between ENT and extra- ENTL signs, and are characterised by a direct link between the location of the cavum and its modes of extension and the clinical manifestations, which are often delayed and misleading.

In our series, all of our patients were symptomatic. A lymph node syndrome was present in 13 of the cases, i.e. 87%, a logical rhino syndrome was present in 12 of the cases, i.e. 80%, an otological syndrome was present in 9 of the cases, i.e. 60%, a neurological syndrome was present in 5 of the cases, i.e. 34%. AEG was present in 05 cases (34%).

Table 4: Breakdown of clinical signs according to how they were discovered.

Circumstances of discovery	Number of cases	Percentage
Lymph node disorder	13	87%
Sd Rhino logic	12	80%
Ear disease	9	60%
Neurological symptoms	5	34%
AEG	5	34%

C. Clinical manifestations

➢ **Lymph node syndrome**

The clinical picture is polymorphic, and lymph node syndrome is the most frequent functional sign in our series, occurring in 13 cases (87%), of which 6 cases (50%) are bilateral, 3 cases (16%) are right-sided, and 4 cases (34%) are left-sided.

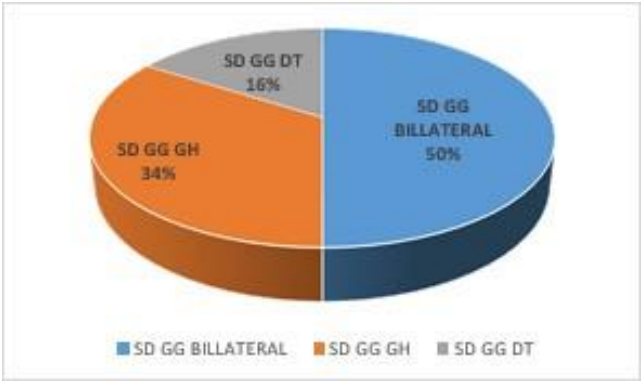


Figure 4: Distribution of patients according to adenopathy location.

➢ **Rhino logical syndrome**

Rhino-logical signs were also a frequent reason for consultation in our study, occurring in 12 cases (80%), of which 6 cases (50%) had epistaxis, and 11 cases (73.34%) had a nasal obstruction.

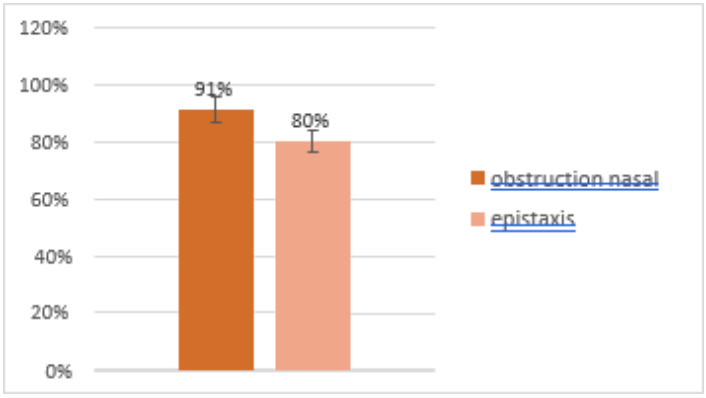


Figure 5: Distribution of cases according to Rhino logical syndrome.

➢ **Ear syndrome**

Otological signs were also a frequent reason for consultation in our study, being found in 9 cases (60%), of which 06 cases (67%) had hearing loss, 04 cases (44%) had otalgia, 02 cases (22%) had tinnitus, and only one case (11%) had unilateral otorrhoea.

➢ **Neurological syndrome**

In our series, a neurological syndrome was present in 5 cases (33%), including 4 cases (80%) with headache, 02 cases (40%) with trismus, 01 cases (20%) with diplopia and one case with dysphagia.

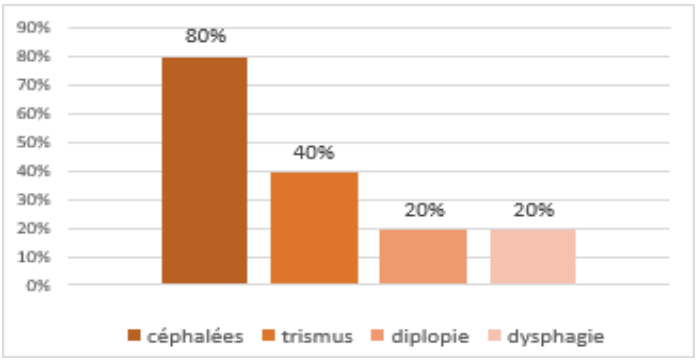


Figure 6: Breakdown of cases by neurological syndrome.

➢ **Changes in general condition and WHO score**

We were able to note an alteration of the general state in the majority of our patients divided into WHO scores, WHO 1 in 8 patients, i.e. 53%, WHO 2 in 4 patients, i.e. 27%, WHO 3 in 1 patient and WHO 4 in 2 patients.

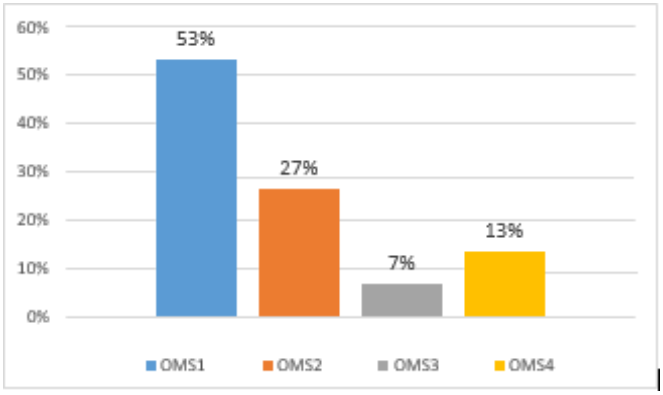


Figure 7: Breakdown of cases by WHO status.

III. Paraclinical data

A. Anatomopathological study

1. Site of biopsy

All patients in our series underwent biopsy of the tumour or cervical adenopathy in order to obtain an anatomopathological diagnosis.

The examination is carried out under local anaesthetic, and the fibroscopy is performed either nasally or buccally.

In our patients, the diagnosis was confirmed by Cavum biopsy in 13 patients (87%), and by lymph node biopsy in 2 patients (13%).

2. Histological type

In all patients in our series, the biopsy was consistent with metastasis of an undifferentiated carcinoma (UCNT), i.e. 100% of all biopsies.

B. Study radiology

1. Local extension assessment

Cavum and cervical scanner

Once the diagnosis of cancer was confirmed, a CT scan of the cavum and cervix was performed in all patients. Axial, coronal and sagittal C- and C+ slices were used to determine the location of the tumour and its extension to neighbouring structures.

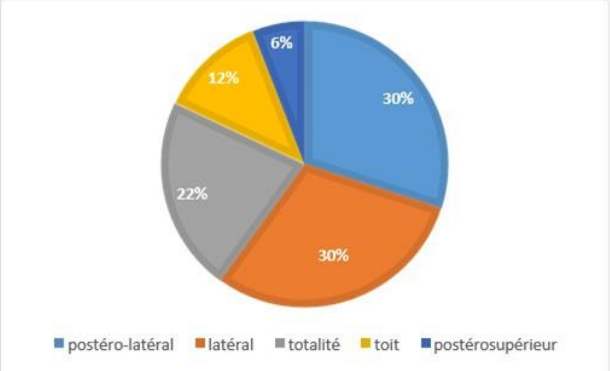


Figure 8: Distribution of cases according to extension to cavity walls.

2. Assessment of distant extension

a. Chest X-ray

Chest X-rays were carried out in all patients in our series, and were pathological in 4 patients (26.66%) with pulmonary and mediastinal lymph node metastases.

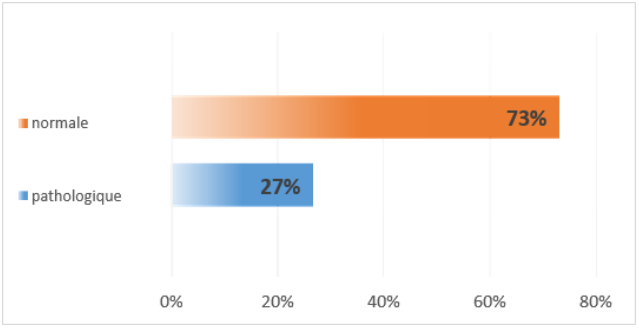


Figure 9: Distribution of cases according to chest X-ray findings.

b. Abdominal ultrasound

Abdominal ultrasound was performed in all patients, and in 3 cases (20%) revealed images consistent with liver metastases.

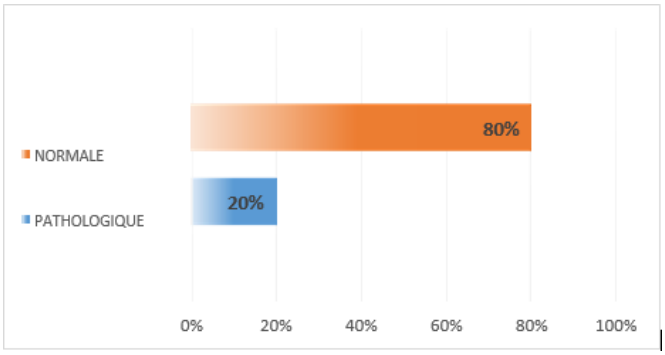


Figure 10: Distribution of cases by abdominal ultrasound result.

c. Bone scan

Bone scintigraphy was performed in patients presenting with warning signs such as bone pain, which was the case in all our patients, and revealed foci of hyperfixation of the radioactive product in 12 of them, i.e. 80%.

d. Thoracic-abdominal-pelvic CT (TAP)

Thoraco-abdominal CT scans were requested in all patients, and the presence of foci of metastases, especially hepatic, pulmonary and bone metastases, as well as the size, dimensions and number of metastases, were identified in all our patients.

C. TNM classification

In our series, CT showed that in only one patient was the primary tumour found with para-pharyngeal extension (T2), in 7 patients, i.e. 46.6%, there was invasion of the bony structures of the base of the skull and/or the para-nasal sinuses (T3), in 3 cases (20%) the tumour was found to have endocranial extension and/or involvement of the cranial nerves, hypopharynx, orbit, or with extension to the infra-temporal fossa/masticatory space (T4).

In only 4 patients (26.66%) was the primary tumour visualised as confined to the nasopharynx, or extending into the oropharynx and/or nasal cavity without parapharyngeal extension (T1).

CT scans of the cavity and neck also enabled us to determine the extent of regional lymph node involvement. In 12 patients (80%) there was bilateral cervical lymph node involvement of less than or equal to 6cm in its greatest dimension above the supra-clavicular fossa (N2). While 3 patients (20%) had metastases in a lymph node > 6cm and/or in the supra-clavicular fossa (N3), none of the cases were N0 or N1.

Table 5: Distribution of patients according to TNM classification.

TNM	Number of patients	Percentage
T1-T2	5	33,34%
T3-T4	10	66,66%
N0-N1	0	0%
N2-N3	15	100%
M1	15	100%

Metastatic site

In our series, secondary localisations were mainly bone metastases in 12 patients, distant adenopathies in 6 patients, pulmonary in 4 patients, hepatic in 3 patients, and the rest divided into cerebral, adrenal and cutaneous metastases.

Table 6: Breakdown of cases by metastatic site.

METASTATIC SITE	NUMBER OFCASES	PERCENTAGE
Bone	12	80%
Remote ADP	6	40%
Pulmonary	4	26,66
Hepatic	3	20%
Cerebral	1	6,66
Adrenal	1	6,66
Cutaneous	1	6,66

IV. Treatment

A. Tolerance test

1. Echocardiography

Echocardiography was systematically requested in all patients who had received Doxorubicin chemotherapy.

2. Dental care

All patients undergoing radiotherapy treatment had their teeth cleaned, treated and any loose or decaying teeth extracted. Fluoride trays were also fitted.

3. Biological check-up

All our patients were asked to undergo a biological work-up including a blood count, a complete ionogram, and a renal and liver work-up.

B. Therapeutic means

1. Radiotherapy

Radiotherapy was recommended in 10 patients (67% of cases), 7 of whom had metastatic disease

- 04 Patients received chemotherapy followed by CCR.
- 06 Patients received chemotherapy followed by radiotherapy alone.

2. Chemotherapy

Chemotherapy was initiated in all our patients in 02 situations, either as first-line treatment in 13 patients or as second-line treatment in 7 patients.

CMT 1st line

5 patients received chemotherapy based on Doxorubicin combined with Cisplatin, and 3 patients received the TPF Protocol (Docetaxel + Cisplatin + 5FU), while in 4 patients 2 received the Cisplatin Protocol combined with Gemcitabine and 2 others received chemotherapy based on Doxorubicin + Carboplatin, and only one patient received the Cisplatin Protocol combined with Capecitabine.

CMT 2nd line

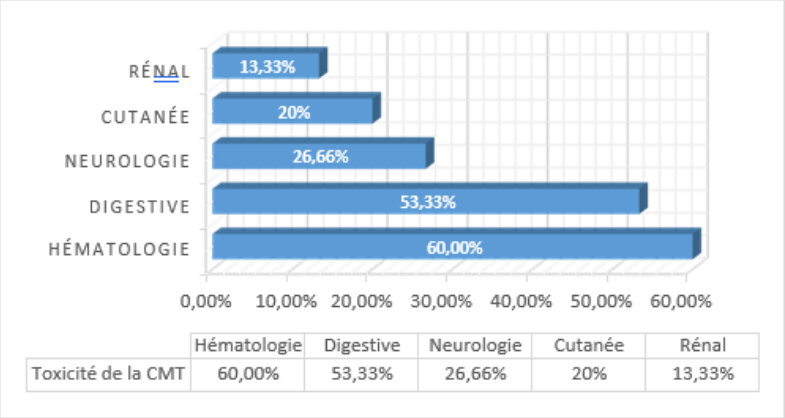
3 patients received docetaxel-based chemotherapy, 2 patients received capecitabine and 2 others received a gemcitabine-based Protocol.

Table 7: Breakdown of patients by chemotherapy protocol.

Chemotherapy	Protocol	Patient number	Percentage
CMT on the front line	Doxorubicin+Cisplatin	5	33,33%
	TPF	3	20%
	Cisplatin+Gemcitabine	2	13,33%
	Doxorubicin+Carboplatin	2	13,33%
	Cisplatin + Capecitabine	1	6,66%
CMT in 2nd line	Docetaxel	3	20%
	Capecitabine	2	13,33%
	Gemcitabine	2	13,33%

C. Evolution and Overall Survival

Medical treatment, especially chemotherapy, was complicated by various toxicities, the main ones being haematological in 09 patients, digestive in 08 patients, followed by neurological toxicity in 04 patients, cutaneous toxicity in 03 patients, and renal toxicity in 02 patients.



	Hématologie	Digestive	Neurologie	Cutanée	Rénal
Toxicité de la CMT	60,00%	53,33%	26,66%	20%	13,33%

Figure 11: Distribution of the different toxicities found in our patients.

Among the 15 patients included in our series, no patient was lost to follow-up, and the mean overall survival for patients treated for metastatic cavitary cancer in the oncology department of the Moulay Ismail military hospital in Meknes was 20 months and 1 week, with extremes ranging from 6 months to 36 months.

DISCUSSION

I. Fundamental reminders

A. Anatomy

1. Anatomical situation

The cavum or nasopharynx or rhinopharynx is the upper segment of the pharyngeal cavity. It is located behind the posterior choanae, in contact with the base of the skull.

It is an organ consisting of a musculoaponeurotic wall delimiting an odd, median cavity. Schematically, it is shaped like a cube open at the front, measuring in adult men: 40 mm wide, 30 to 40 mm high and 20 mm long anteroposterior axis.[3]

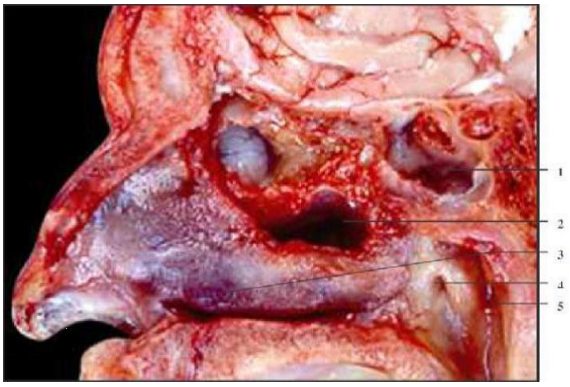


Figure 12: Sagittal section of the face showing the cavum.[4]

1. Sphenoid 2-Maxillary sinus 3-Inferior concha 4-Tubal orifice 5- Cavum.

2. Cavum walls

The anatomical relationships of this deeply situated cavity help to explain much of the symptomatology of cancerous lesions of the cavum. It has 6 walls.[5]

- **Front wall**

It communicates with the nasal cavity via the choanae, separated on the midline by the dorsal edge of the nasal septum.

- **Back wall**

Extending backwards from the upper wall, it corresponds to the retro pharyngeal space, a virtual space located between the pharyngeal mucosal space and the prevertebral fascia. Through this space, the nasopharynx connects to the lower part of the posterior cerebral fossa.

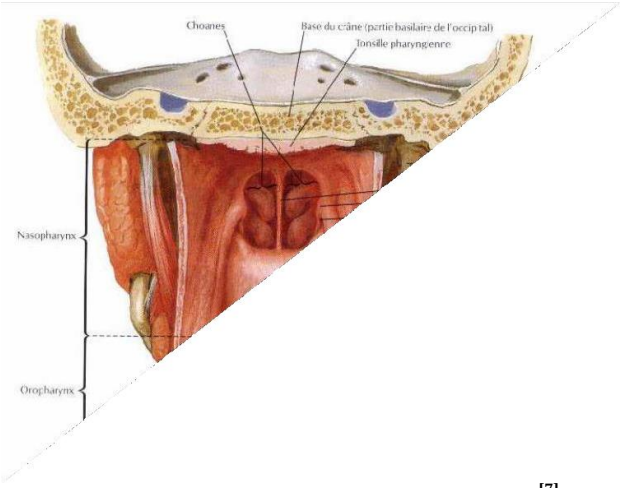


Figure 13: posterior view of nasopharynx.[7]

- **Top wall**

The upper wall consists of a plane of bone sloping downwards and backwards, formed by the body of the sphenoid on which the sphenoid sinus rests. Further back, the wall continues at a gentle slope with the clivus (which corresponds to the fusion of the quadrilateral blade of the sphenoid bone and the basilar blade of the occipital bone). Further down, the wall is formed by the atloido-occipital ligament, behind which lies the upper cervical spine.

- **Lower wall**

It is formed by the dorsal surface of the soft palate, which slopes downwards and extends the floor of the nasal cavities.

Behind the soft palate, the intrapharyngeal ostium connects the nasopharynx and oropharynx.

- **Side walls**

They are musculoaponeurotic, except at the very front where the mucosa rests on the medial surface of the medial blade of the pterygoid process. This aponeurotic part is crossed by the tubal apparatus, and is essentially formed by the pharyngo-basilar fascia, which constitutes a resistant barrier t o tumour extension. In the shape of a horseshoe open at the front, this thick, fibrous structure separates the mucous space from the peri-pharyngeal spaces and keeps the airway open.

Between the tubal eminence or salpingo-pharyngeal fold and the posterior wall of the nasopharynx is a deep depression known as Rosenmüller's fossa. This excavation has two sides: one posterior, formed by the posterior wall of the nasopharynx; the other anterior, formed by the protruding posterointernal wall of the fibro-cartilaginous tube.

3. Anatomical relationships

The nasopharynx responds

- Above: the body of the sphenoid and the sphenoidal sinus.
- Posteriorly: to the posterior cerebral fossa via the clivus.
- Sideways
  - Above, to the auditory tube and the internal carotid artery in the cavernous cavity;
  - Down to the oropharynx and especially the tonsil cavity;
  - Forward to the nasal cavities, maxillary sinuses, orbit and ethmoid.

4. Deep spaces of the face

The deep spaces of the face or peri-pharyngeal spaces are organised around the naso-oropharynx and are located between the middle layer of the base of the skull and the hyoid bone. They communicate with each other and are routes of extension for pharyngeal inflammatory and tumour processes.

Classically, we recognise

a. Retro pharyngeal space

- Virtual, located between the pharyngo-basilar fascia at the front and the prevertebral aponeurosis at the back.
- Extends downwards into the retrovisceral space of the neck, which descends into the posterior mediastinum.
- Contains cellulo-fatty elements and ganglion chains.
- Content not distinguishable on imaging in a normal subject.

b. Pre-vertebral space

- Located behind the prevertebral fascia.
- Contains the prevertebral muscles.

c. Lateral pharyngeal space

- Communicates externally with the parotid cavity.
- Divided by the stylian diaphragm into :
- Retrostylial space: vascular and nervous (IX X XI XII) rich in lymphatic chains. It communicates medially with the retropharyngeal space via the dehiscence of the sagittal septum.

- Prestylial or parapharyngeal space: fatty, connected to the parotid space by the deep extension of the parotid gland.

d. Infra-temporal fossa / Masticatory space

- The infra-temporal fossa is bounded laterally by the mandibular ramus and the zygomatic arch.
- Its internal border forms the external border of the lateropharyngeal space.
- The masticatory space encompasses the infra-temporal fossa and the structures outside the mandibular ramus and above the zygomatic arch.

e. Parotid lodge

- Located between the retrostylial region and the parapharyngeal region medially, and the infra-temporal fossa anteriorly.
- Contents: parotid facial nerve, external carotid artery and external jugular vein.

5. Vascularisation

The nasopharynx is vascularised by the external carotid system. The ascending pharyngeal artery constitutes the main supply of a rich submucosal network, which also includes branches of the maxillary artery and the facial artery.[6]

6. Booking

The nasopharynx is innervated by a pharyngeal plexus formed by nerves IX (glossopharyngeal nerve), X (vagus nerve) and branches of the upper cervical sympathetic ganglion. The maxillary nerve (V3) is involved in the sensitive innervation of the roof of the nasopharynx.[6]

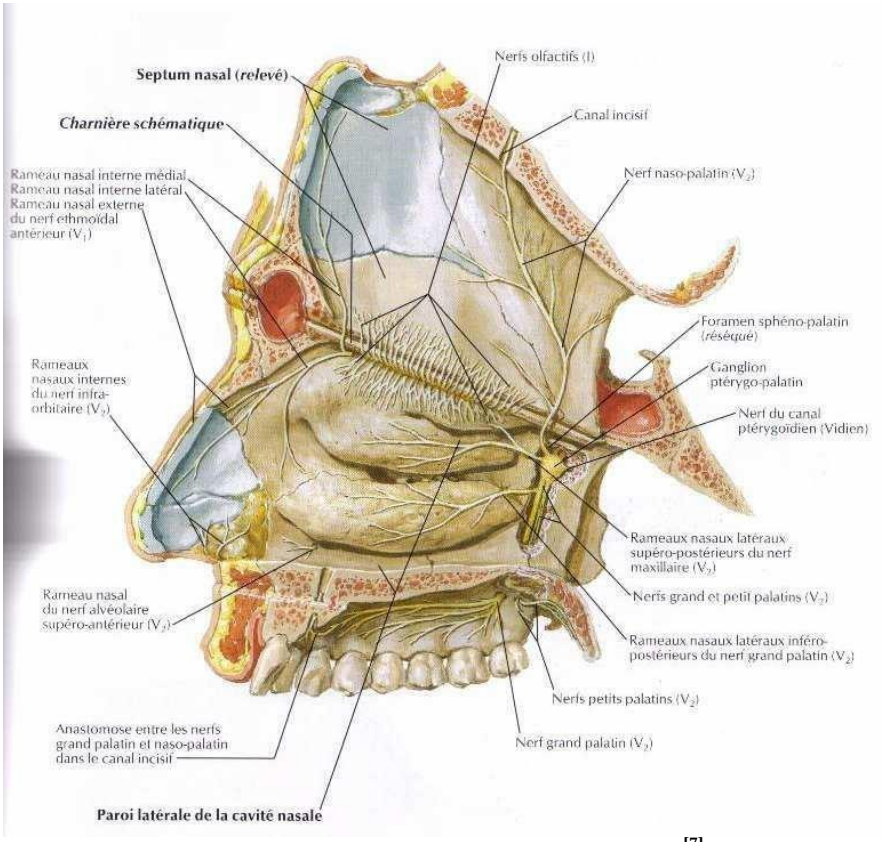


Figure 15: Innervations of the nasopharynx.[7]

7. Lymphatic drainage

The nasopharynx has a rich sub-mucosal lymphatic network, leading to particularly frequent lymph node invasion (75-90%), which can be a fairly frequent reason for discovering cancer. Given the median position of the cavum, these lymph nodes are often bilateral.

Lymphatic drainage occurs at all levels of the neck following the jugular vein and the accessory spinal nerve, the first relay of which is located in the retro pharyngeal space of Rouvière, close to the cranial nerves IX, X, XI (jugular foramen) and XII (anterior condylar canal). The second drainage route is at the confluence of the accessory spinal vein and the jugular vein, with a lymph node located at the tip of the mastoid, characteristic of nasopharyngeal tumours. The third drainage route is to the subdigastric lymph nodes.[8,9]

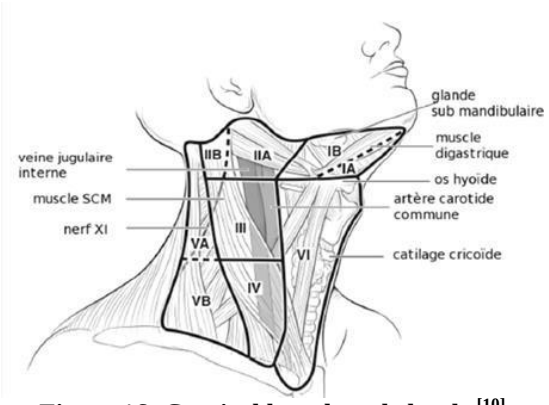


Figure 16: Cervical lymph node levels.[10]

- IA: submental lymph nodes
- IB: sub-maxillary lymph nodes
- II: superior jugulocarotid nodes
- III: middle jugulo-carotid nodes
- IV: inferior jugulocarotid nodes
- V: spinal ganglia
- VI: anterior lymph node territory

➢ **Histology**

The mucosa This is a respiratory-type epithelium with two reliefs

- The lateral pharyngeal recess or Rosenmüller fossa. Lymphoid tissue, particularly developed on the posterior surface of the nasopharynx, forms the pharyngeal tonsils.
- The tubal torus, located behind the pharyngeal ostium of the Eustachian tube.

B. Anatomopathology

The mucosa of the cavum is lined with variable epithelium: respiratory, non-keratinising squamous or intermediate. It contains seromucosal glands and abundant lymphoid follicles. Cancers of the cavum most often arise in the Rosenmüller fossa and invade the mucosa and submucosa to reach adjacent areas: nasal cavities, oropharynx, parapharyngeal spaces and the base of the skull (with possible involvement of the cranial nerves). Macroscopically, it is mainly the budding form that is most frequently described, less frequently the infiltrating and ulcerated form. There are several histological types: carcinomas, lymphomas and other tumours.[11]

➢ **Carcinoma**

Non-glandular carcinomas account for over 90% of cancers arising in the cavum. The old classification used is that of the WHO (1991), which recognises 3 histological types

- Well-differentiated keratinising squamous cell carcinoma (type I), comparable to that found in other areas of the VADS.

This histological type accounts for 30 to 40% of NPCs occurring in areas of low incidence of the disease, while its incidence is extremely low in endemic areas.

- Non-keratinising squamous cell carcinoma (type II) (15 to 20% of cases).

- Undifferentiated carcinoma of the nasopharyngeal type (UCNT) (type III), linked to genetic factors and EBV (Epstein-Barr virus) infection. The histological appearance is distinctive, characterised by the presence of large tumour cells with indistinct borders, with large, clear nuclei containing large nucleoli associated with abundant lymphocytes. This histological form is the most common, found in the majority of studies, which report a frequency varying between 64% and 99%, depending on whether the area is low or high risk.

These histological features of UCNT can help in the diagnosis of nasopharyngeal carcinoma metastasis. Sometimes, similarities may exist with other malignant tumours or lymphomas, justifying the interest of immunohistochemical techniques and EBV serology, which use specific monoclonal and especially polyclonal antibodies directed against one or more antigenic determinants.[12,13]

➢ **Lymphoma**

These are the most common non-epithelial tumours in Western Europe (10% to 15%). They are often nasosinusal and nasopharyngeal lymphomas, usually of diffuse architecture and most often consisting of large cells, often immunoblastic, of high malignancy. Angiocentric T lymphoma, mainly responsible for necrotising nasosinusal lesions, may involve the nasopharynx in the form of thick, ulcerated mucosa. Biopsies must be deep to be informative. Some T lymphomas are accompanied by significant squamous pseudotumour hyperplasia.[11]

➢ **Other tumours**

Rhabdomyosacroma of the cavum is a tumour with striated muscle differentiation, and is common in children.

Adenocarcinomas and their variants, as well as all tumours developed from bone or supporting tissue, can

be seen in the cavum, but are very rare, even exceptional in adults.[11]

C. Terms and conditions

NPCs most often originate in Rosenmüller's fossa, and extend mainly submucosally or intramucosally, along muscle fibres, fibrocartilaginous planes, nerve sheaths, into the periosteum and medullary cavity.[14] They grow through areas of lesser resistance and invade more resistant structures: tubal cartilage and pharyngobasilar fascia.

The extension is multidirectional

- In front, it is directed towards the nasal cavities, the anterior stage (pterygoid process, posterior part of the maxillary sinus and ethmoidal cells, posterior part of the orbit);
- Laterally, towards the Eustachian tube (otitis, hypoacusis), the parapharyngeal space, the pterygoid muscle (causing trismus), the retrostylial space (affecting the IX, X, XI, XII), the prestylial and subparotid space, upwards towards the base of the skull, in particular the sphenoidal sinus, the cavernous sinus and the middle temporal fossa,
- Node metastases are very frequent in undifferentiated carcinoma (80-90% of cases) and are often bilateral. The sub-mastoid and retro pharyngeal lymph nodes are frequently invaded. Keratinising squamous cell carcinoma is less often metastatic, but tends to recur locally.

The incidence of metastases is higher for NPC than for other VADS carcinomas. The occurrence of visceral metastases is strongly correlated withlymph node involvement. The most frequent metastatic sites are bone (70%), lung, liver and extracervical lymph nodes (axillae, mediastinum, retroperitoneum, etc.).[14]

II. Epidemiological study

A. Incidence

According to Global cancer statistics of 2018 (GLOBOCAN), approximately 129,079 cases of cavum cancer were diagnosed worldwide or 0.7% and the number of deaths is estimated at 72,987 cases or 0.8%, making it the 25th most common cancer in the world.[26]

Nasopharyngeal cancer is a good example of the variation in the geographical distribution of cancers around the world, with an incidence of between 0.5 and 2/100,000 people.[27]

There are three levels of frequency

- The epicentre of high incidence is in South-East Asia, particularly southern China, where the incidence reaches 30 to 80 cases/100,000 inhabitants/year.
- Areas of intermediate incidence include Taiwan, Vietnam, Thailand, Malaysia, the Philippines, the Caribbean, the Mediterranean basin (Maghreb and Middle East), Alaska and Greenland, where the incidence varies from 8 to 12 cases/100,000 inhabitants/year.
- The low incidence zone concerns Europe and the United States, with an incidence of 0.5 to 2 cases/100,000 inhabitants/year.[19,20,21]

Our country, Morocco, belongs to an intermediate risk zone with an estimated incidence of around 3.8/100,000 inhabitants/year and a rate of 4.1% of all cancers reported by the Casablanca Regional Cancer Registry (CRCR 2012 edition).[22]

B. Breakdown by age

Nasopharyngeal cancer can occur at any age, with a peak between the ages of 40 and 50. In South-East Asia, nasopharyngeal cancer is observed from the age of 20, with a peak around the age of 50. Inintermediate-risk areas, such as North Africa, the distribution is bimodal, with a first peak between the ages of 10 and 24 and a second peak at 50. In low-risk populations, nasopharyngeal cancers are observed with two peaks in frequency, the first in the 15 to 24 age group and the second in the 65 to 74 age group.[23,24,25]

Our patients ranged in age from 27 to 66, with an average age of 50. The age groups most affected were 60-69 and 50-59.

Table 8: Comparison of average age between different series.

Auteur/Reference	Notre série	Sarra Ouni [36]
Paye	Maroc	Tunisie
Année	2019	2016
Tranche d'âge	27–66 ans	10–78 ans
Age moyen	50ans	49ans

C. Breakdown by gender

Males are significantly more affected by cavum cancer than females.[26,27,28,29]

In our series, the sex ratio for our patients was 2 (10 M / 5 F), which is in line with the literature.

Table 9: Comparison of gender between different series.

Auteur/Référence	Notre série	Sarra Ouni
Sex-Ratio	2	6,1

D. Etiopathogenesis

1. Environmental factors

The contribution of environmental factors in the etiopathogenesis of nasopharyngeal carcinomas has been the subject of numerous studies which tend to show the decisive role of certain traditional culinary habits.[30,31,32]

Food factor

A series of case-control studies has shown that the consumption of salted and smoked products from an early age is a major cause of nasopharyngeal cancer in the Chinese population.[31,32,33]

Volatile nitrosamines, carcinogens present in these foods, have been implicated in the development of nasopharyngeal cancer. Exposure to these dietary carcinogens very early in childhood appears to be an aggravating factor.

Other substances found in traditional Chinese cuisine (salted soya, preserved salted vegetables and salted green vegetables with mustard) and in certain medicinal preparations (infusions, herbal teas) are thought to activate EBV. Other factors such as vitamin E and the consumption of green vegetables could have a protective effect against the development of NPC.[31,32]

In North Africa, certain preparations of dried salted meats (khlie...), Harr brines or all forms of piquant: pepper, hrissa (a mixture of olive oil, red pepper salts and varvi) are incriminated, although it is not possible to say what their statistical significance is.

In our context, certain factors may be linked to the onset of PNC, including the consumption of smen (fermented butter), khlii (dried meat, salted, cooked and preserved in rendered bovine fat), brines, hot condiments in all their forms: pepper, harissa (a mixture of olive oil, salt, red pepper, garlic and caraway) and hot pepper, although it is not possible to state their statistical significance.[17]

In North African populations, early exposure to spicy foods or foods containing harissa is associated with a high incidence of UCNT.[18]

In our series, the dietary history of our patients revealed excessive consumption of spicy condiments in puréed form (harissa), dried and salted meat and fermented butter in 05 patients (33.34%) of all cases.

Toxic factors

Tobacco and alcohol consumption are risk factors for the onset of WHO type 3 NPC, which has been demonstrated in populations with a very low incidence of the disease.[19]

B-J FENG showed in his large study carried out in North Africa that the risk of nasopharyngeal cancer is increased by tobacco consumption whatever the histological type, and the results of BENDJEMANA also showed a strong association between alcohol and tobacco consumption and the risk of developing nasopharyngeal cancer.[34,35]

In our study, alcohol and tobacco consumption was observed in 6 patients, i.e. 40% of the population studied.

Genetic factors

The malignant nature of NPC epithelial cells results from the combined effect ofseveral alterations in the cellular genome and the presence of viral elements.[20] Numerous genetic and epi-genetic alterations have been detected, mainly in tumour suppressor genes. The most frequent have been identified in chromosomes 3, 9, 11, 13, 14 and 16.[21]

Several cases of familial aggregation have been reported in areas of high incidence, suggesting a genetic predisposition.[12] Loss of heterozygosity on chromosome 1, which is very common in normal nasopharyngeal epithelium (74%) and dysplastic lesions (75%), could represent an early stage in the tumorigenesis of NPC.[22]

AMMOR in his series reported the presence of a family history of cancer in 23% of patients without specifying the neoplastic type, whereas OUNI.S reported the presence of this history in 13.73%, in 7.84% it was cancer of the cavum, and in the remaining cases it was cancer of the breast, colon and larynx.[36,37]

In our series, familial cancer was present in 06 patients, i.e. 40% of patients. The above-mentioned results and our own do not allow us to consider a family history of neoplasia as a risk factor for nasopharyngeal cancer.

Profession

Our study only concerned the military population and their relatives, and we were unable to identify any specific occupational exposure.

2. Viral factors

ENT infection

Repeated ENT infections have been cited as a risk factor by the HAS (Haute autorité de la santé). In our series, 8 patients (53.33%) presented with ENT infections

(angina, sinusitis and otitis). The pathogenic role of these infections in nasopharyngeal cancer could be explained by frequent invasion of the nasopharynx and Rosenmüller's fossa, making this anatomical zone fragile and more exposed to nitrosamines.[38]

- **EBV infection**

EBV exists in two phases, latent and lytic[25]
During the latent cycle, the genome remains constant and EBV expresses a number of nuclear proteins (Epstein Barr Virus nuclear antigen (EBNA)) and latent membrane proteins (LMP).

During the lytic or productive cycle, there is sequential expression of numerous immediate, early and late viral antigens.

Genes in the latent cycle include (2)
- EBNA-1: Nuclear protein that maintains the viral genome in the episomal state in infected individuals.
- EBNA-2: Nuclear protein involved in B lymphocyte immortalisation.
- EBNA-LP: Nuclear protein which enables the growth of lymphoblastoid cell lines by increasing their sensitivity to cell growth factors.
- LMP-1: Membrane protein essential for the transformation of B cells into lymphoblastoid cell lines.

Genes involved in the lytic cycle include (2)
- Immediate early antigens
- ZEBRA (or EB1): Nuclear protein enabling the transition from the latent cycle to the lytic cycle and also enabling the induction of EA (early antigen) expression.
- Early antigens of the lytic cycle
- EA (R) = restricted: Cytoplasmic protein with function enabling induction of viral genome replication.
- EA (D) = diffuse: Nuclear and cytoplasmic function protein.
- Late antigens of the lytic cycle
- VCA = viral capsid antigen Protein with cytoplasmic structure.
- LMA = late membrane antigen Structural membrane protein.

EBV infection is a cofactor associated with nasopharyngeal cancer and contributes to its oncogenesis. Increased serum levels of antibodies to EBV viral proteins are of great interest for the diagnosis and screening of nasopharyngeal cancers in endemic areas.[39,40]

III. Clinical diagnosis

A. Clinical signs

The deep location of NPC explains the multi-varied symptomatology, due toinvasion of neighbouring structures, but above all the non-specific nature, which means that diagnosis is often delayed for 7 to 11 months[41,42], compared with our series where the average delay was 6 months, and this can be explained by the ease of access to care in the military population with appropriate consultation appointment times.

There are four syndromes
- A lymph node syndrome
- An otological syndrome
- A logical rhino syndrome
- A neurological syndrome
- Signs due to metastatic invasion.

➢ **Lymph node syndrome**

Cervical adenopathy is the most frequent reason for consultation in 60 to 90% of cases. These are hard, painless, mobile adenopathies that increase rapidly in volume. They usually develop in the sub-mastoid region and may then involve the internal jugular chain and the spinal chain, as well as the lymph nodes in the supra-clavicular fossa. Involvement may be unilateral or bilateral.[43,44,45]

In our series, cervical adenopathy was found in 13 cases (87%), of which 6 cases (50%) were bilateral, 3 cases (16%) were right-sided and 4 cases (34%) were left-sided.

➢ **Ear syndrome**

The appearance of a tumour in the vicinity of the Eustachian tube causes a sensation of fullness in the ear which is intermittent at first, then becomes constant and is accompanied by ringing in the ears, but it is only the often unilateral hypoacusis and the appearance of otalgia which are likely to bring the patient to consult a doctor. In our patients, we distinguished 9 cases, i.e. 60%, made up of hypoacusis, otalgia, tinnitus and otorrhoea.

➢ **A logical Rhino syndrome**

Representing 20% of the reasons for first consultation, it is related to anterior invasion of the choanae and nasal cavities.

These include progressive unilateral or bilateral nasal obstruction, unilateral or bilateral epistaxis, purulent rhinorrhea or nasal voice.[43]

Nasal obstruction predominates in the Rhino logical syndrome in our series (73.33%), which was very marked in 11 patients.

➢ **A Neurological Syndrome**

It results from compression of the cranial nerves by extension of the tumour process to the base of the skull. Its clinical expression is essentially neuralgia and paralysis; theoretically, the tumour process can reach all the cranial pairs.[43,45]

In our series, a neurological syndrome was present in 5 cases (33%), consisting of headache, trismus and

dysphagia.

➢ Signs due to metastatic invasion

Cavum cancer may be discovered by the presence of clinical signs associated with the presence of metastases at the time of the first consultation, either

- Bone metastases (bone pain)
- Liver metastases (check for jaundice and liver pain),
- Pulmonary metastases (discovered by dyspnoea or systematic chest X-ray),
- Brain metastases (discovered by an epileptic seizure, for example) Nearly 40% of the patients in our series had clinical signs linked to the presence of metastases at the time of the first consultation, consisting of bone and liver pain.

Table 10: Comparison of circumstances of discovery between series.

Syndrome	Notre série	M.Sonne [46]	S.Ouni [36]
GANGLIONAIRE	87%	90%	92,15%
RHINOLOGIQUE	73%	62%	56,8%
OTOLOGIQUE	60%	53%	41,2%
NEUROLOGIQUE	33%	40%	43,1%
METASTATIQUE	40%	-	24%

Our results are in line with the Caméron series by M. Sonne[46] and the Tunisian series by S. Ouni[36] following the same order of frequency of syndromes, whereas for metastatic signs there was a clear increase compared with the series by S.Ouni which focuses solely on metastatic cases.

B. Clinical examination

The presence of any of the above signs should prompt a thorough and careful ENT examination

- Examination of the nasal cavities: involves anterior rhinoscopy using a nasal cavity speculum and posterior rhinoscopy (cavoscopy) using a laryngeal mirror directed towards the nasopharynx or an optic (nasofibroscopy or rigid optic): the tumour is most often unilateral (unless it is a large tumour), rarely visualised during anterior rhinoscopy (unless it is a large tumour) but during posterior rhinoscopy: tumour most often budding and of variable volume.

- Biopsies are taken during rhinoscopy (at the end of the clinical examination) under local anaesthetic for anatomopathological examination, which alone will confirm the diagnosis.

A full clinical examination should pay particular attention to

- Otoscopy: which shows serous otitis homolateral to the lesion, due to direct obstruction of the eustachian tube by the tumour, resulting in conductive hearing loss;
- Cervical palpation of lymph nodes: to look for metastatic adenopathy ;
- Neurological examination: mainly focused on the cranial pairs (II, III, IV, V, VI, IX, X, XI, XII) in search of a deficit indicating invasion of the parapharyngeal spaces or the base of the skull.
- Ophthalmological examination to look for an oculomotricity disorder with diplopia or exophthalmos.[47]

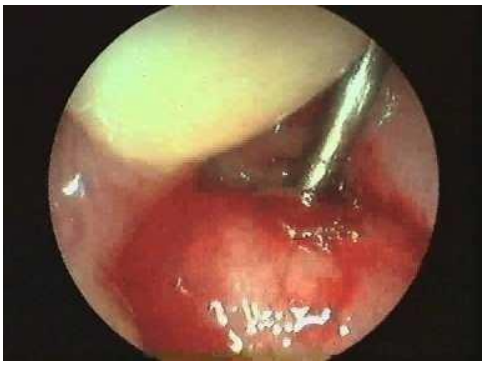


Figure 19: Deep biopsies for histological examination.

C. Examinations Para-clinical

1. Anatomopathology

In order to obtain a diagnosis, the patient must undergo a biopsy of the tumour, cervical adenopathy or biopsy of the site of metastasis, especially in the event of distant relapse.

However, endoscopic biopsy of the cavum remains the most commonly used examination for making a positive diagnosis. It enables the tumour to be visualised, its size, local spread and histological type to be determined, and it can be schematised.

The examination is carried out under local anaesthetic, and the fibroscopy is performed either nasally or orally.

Malignant epithelial tumours account for more than 90% of cancers arising in the nasopharynx.[48] The classification used is that of the WHO, based on the degree of differentiation

- WHO 1: keratinising squamous cell carcinoma
- WHO 2:non-keratinising squamous cell carcinoma
- WHO 3: undifferentiated nasopharyngeal carcinoma (UCNT) Other types are rarer, including glandular tumours, lymphomas and connective tissue tumours.

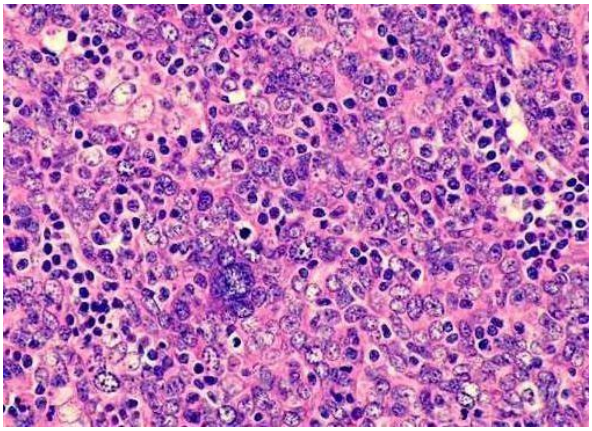


Figure 20: Undifferentiated nasopharyngeal carcinoma.

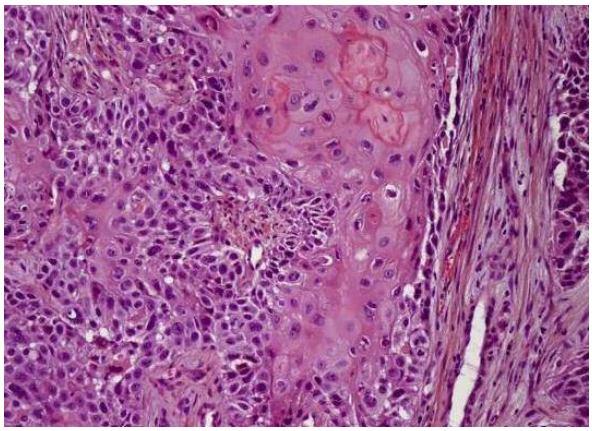


Figure 21: Nasopharyngeal squamous cell carcinoma.

Table 11: Breakdown of patients by histological type.

	Notre Etude	Y.Elkholti	L.Saleh.Ibrahimi
OMS 1	-	-	6%
OMS 2	-	9%	12%
OMS 3=UCNT	100%	91%	82%
AUTRES	-	1%	-

Our study showed that all the metastatic cases were of UCNT origin, which is somewhat in line with the literature, where UCNT is at the top of the pyramid, with a percentage of between 80 and 90%.

2. Radiological examinations

Imaging is used to determine locoregional tumour extension to deep spaces and neighbouring structures not detected by clinical examination or endoscopy, as well as

lymph node involvement and metastases. It thus helps in the TNM classification of nasopharyngeal cancer and in determining the limits of the radiation field. Finally, it contributes to post-treatment monitoring.

a. CT-MRI

Computed tomography (CT) with iodine injection

This is a practical imaging tool for nasopharyngeal tumour pathology. It is used to carry out a pre-treatment assessment of cavitary cancer, enabling tumour volume and locoregional extension to be evaluated. Helical acquisition is performed from the skull to the upper orifice of the mediastinum in order to explore the base of the skull, the cavum and all the cervical lymph nodes, and to determine the location of the tumour and its extension to neighbouring endocranial, orbital, parapharyngeal structures and the base of the skull.

MPR reconstructions (multi-planar reconstruction) are necessary in the different planes of space, as well as reconstructions in the bone window in search of lysis.

The most frequent location is the lateral wall of the cavum, at the level of Rosenmüller's fossa, more rarely the tumour sits on the roof of the cavum. The most common CT appearance is that of a budding lesion occupying part or all of the cavum. However, it may be a simple thickening of a wall or an obliteration of one of the reliefs (Rosenmüller fossa, orifice of the Eustachian tube) making the diagnosis more difficult.[49]

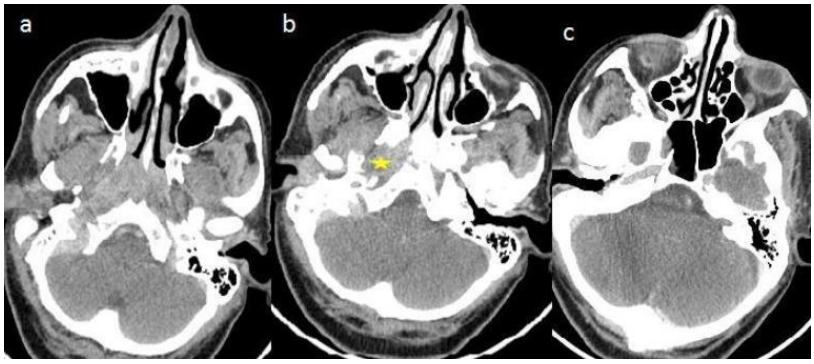


Figure 22: Axial CT scan of the nasopharynx showing thickening of the right posterolateral wall of the nasopharynx extending to the choanae (a), lysing and enlarging the foramen lacerum (yellow star), with extension into the right sphenoidal sinus (c).

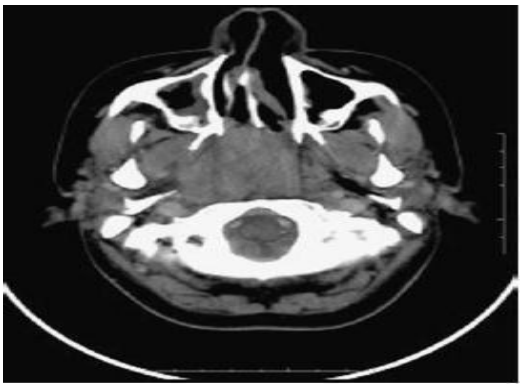


Figure 23: CT axial section after injection of iodinated contrast.

Tissue process taking up the entire lumen of the cavum, obstructing the choanae with parapharyngeal extension on the right.[50]

- **MRI of the cavum and cervix**

Increasingly used in the diagnostic and complementary work-up. It is less effective than CT in assessing extension into the cortical bone, but is more effective in a s s e s s i n g spinal cord, muscle, peri-nervous and intracranial invasion. In particular, MRI detects prerineural extension through the foramen at the base of the skull, such as the fifth cranial nerve in the foramen ovale[51], not forgetting its major role in invasion of the retropharyngeal lymph node, which constitutes the first lymph node relay.[52]

The scan must be performed using a head-neck antenna and the examination must include the following sequences

- A high-resolution T2 turbo spin echo (TSE) sequence to define the boundaries of the tumour;
- A T1 sequence without injection and without saturation of the fat signal centred on the base of the skull to detect any tumour extension to bony structures;
- A T1 sequence with gadolinium injection and fat signal saturation (fat sat) in the axial and coronal planes for analysis of deep tumour extension and in

particular peri-nerve and endocranial extension;
- A T2 TSE axial sequence to study the lymph nodes. Local imaging is best performed using a combination of CT and cranio-cervico- facial MRI.[53]

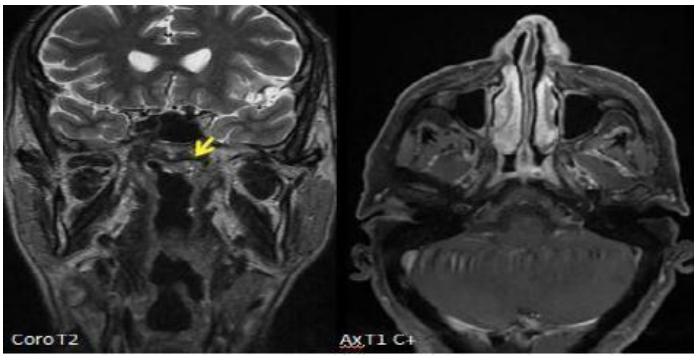


Figure 24: MRI of the cavum showing a well-limited thickening of the upper left lateral wall of the cavum with no locoregional extension classified as T1.[50]

Therefore, local and regional imaging is best performed using a combination of CT and cranio-cervico-facial MRI, as was done in our series; CT was performed in 10 patients and MRI in 13.

b. Assessment of distant extension

Tumours of the nasopharynx are the most common head and neck tumours to give rise to distant metastases. The potential for metastasis is higher in cases of advanced tumour extension to the parapharyngeal spaces or adenopathy in the supraclavicular recesses.

The high incidence of metastases may be partly explained by the anatomy of the parapharyngeal venous plexus adjacent to the nasopharynx. Tumours that have spread to the parapharyngeal spaces may directly enter the venous system, leading to secondary distant localisations.[57] The most frequent sites of metastases in decreasing order are bone (20%), lung (13%), liver (9%), and more rarely brain and spleen.[56]

To do this, an extension work-up is carried out to look for sites of distant metastasis in patients with warning signs such as bone pain, jaundice or liver mass, dyspnoea or haemoptysis, etc.

A front and side chest X-ray and liver ultrasound should be systematically ordered, whereas bone scans and brain CT scans should only be ordered in the presence of warning signs.[54,55]

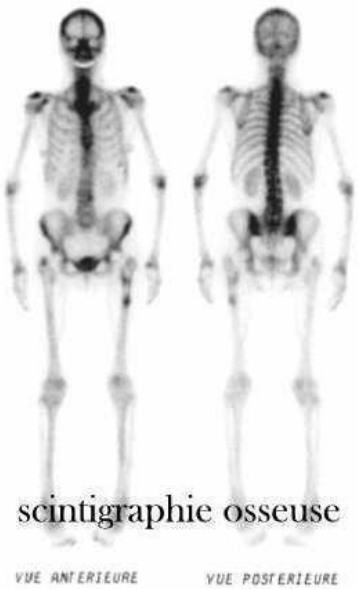


Figure 28: Bone scan showing foci of hyperfixation.

In our series, the assessment of haematogenous extension was based on a combination of abdominal ultrasound and chest X-ray in all our patients, with 7 patients showing images in favour of pulmonary and hepatic metastases. CT-PET and scintigraphy were also performed in all patients (100%).

Table 12: Distribution of metastatic location compared with other studies.

Tumeur primitive	Tx	La tumeur primitive ne peut être évaluée
	T0	Pas de tumeur décelable
	Tis	Carcinome in situ
	T1	Tumeur limitée au nasopharynx ou étendue aux tissus de l'oropharynx et/ou à la fosse nasale
	T2	Tumeur avec extension parapharyngée
	T3	Invasion tumorale des structures osseuses de la base du crâne et/ou des sinus maxillaires
	T4	Tumeur avec extension intracrânienne et/ou atteinte des nerfs crâniens, de l'hypopharynx, de l'orbite ou avec extension à la fosse sous temporale/espace masticateur
Adénopathies cervicales	Nx	Les adénopathies régionales ne peuvent être évaluées
	N0	Pas d'adénopathie régionale métastatique
	N1	Atteinte unilatérale d'un ou plusieurs ganglions lymphatiques cervicaux, et/ou atteinte unilatérale ou bilatérale de ganglions lymphatiques rétropharyngiens, ≤ 6 cm dans leur plus grande dimension, au-dessus du creux sus-claviculaire
	N2	Atteinte bilatérale d'un ou plusieurs ganglions lymphatiques cervicaux, et/ou atteinte unilatérale ou bilatérale de ganglions lymphatiques ≤ 6 cm dans leur plus grande dimension, au-dessus du creux sus-claviculaire
	N3	Adénopathie(s) métastatique(s) :
	N3a	>6 cm
	N3b	au niveau du creux sus-claviculaire
Métastase(s) à distance	Mx	Renseignements insuffisants pour classer des métastases à distance
	M0	Pas de métastase à distance
	M1	Présence de métastase(s) à distance

The order of frequency of the metastatic site in our series is in perfect agreement with the literature, with bone being the most frequent site of metastases, and also for the single or multiple nature compared with the series by S. Ouni.

c. TNM classification and staging

Changes in the TNM classification have given rise to an 8th edition[58], however in our series we have adopted the 2009 Union for International Cancer Control (UICC) TNM classification (7th edition) since the majority of our patients were initially classified according to the latter.

Figure 29 TNM-UICC classification 2009.

The overall stage is based on the grouping of different components of the TNM classification.

Stade	Tumeur T	Ganglions N	Métastases M
0	Tis	N0	M0
I	T1		
II	T1 T2	N1 N0/N1	
III	T1/T2 T3	N2 N0/N1/N2	
IVA	T4	N0/N1/N2	M0
IVB	Tout T	N3	M0
IVC	Tout T	Tout N	M1

Figure 30: TNM staging.

Table 13: Comparison of TNM classification between series.

	Notre série	S.Ouni	I.Rhalem [59]
T1-T2	33,34%	45,4%	53,84
T3-T4	66,66%	52,4%	46,09
N0-N1	0%	20%	59,57
N2-N3	100%	80%	40,41
M1	100%	100%	17%

IV. Prognostic factors

Prognostic factors for nasopharyngeal cancer have been studied in several series, particularly in endemic countries. Some affect local control, and these have been evaluated in retrospective series that have not specifically separated local control from lymph node control, while others affect survival.

A. Patient-related factors

- **Age**

The influence of age at diagnosis is controversial, with a better prognosis in children after adjustment for stage, although contrary results have also been reported.[60]

The study by Haldum et al on a series of 357 patients found a significant difference in terms of overall survival between patients aged over or under 45 years in favour of younger patients.[61]

- **Sex**

Women tend to have a more favourable prognosis in the majority of series where this has been assessed.

Haldum found that women had a better prognosis than men in terms of overall survival at 2 years, 5 years and 10 years, and in terms of relapse- free survival at 2 years and 5 years.[61]

Mu-Tai Liu also found a significant difference in terms of overall survival in favour of the female sex.[62]

B. Factors linked to the disease

- **TNM stage**

The TNM stage of the WHO classification is a key prognostic element within which three independent prognostic factors can be distinguished: the initial size of the tumour (T). Node involvement (N), the existence of distant metastases (M).[64,65]

Node metastases are a prognostic factor for local control and survival. There is a strong correlation between the presence of lymph node involvement and the occurrence of distant metastases, particularly in N3a patients. Low or fixed cervical lymph nodes increase the risk of metastasis. Bilateral lymph node involvement does not appear to be a particularly unfavourable factor.[67,64]

Most studies show no difference in clinical outcome according to extension into the nasopharynx (TI), although the local relapse rate is clearly higher for lesions classified as T3 and T4, and there are differences in prognosis for these stages according to the structures invaded.[67,64] Involvement of the cranial nerves has a major impact on the probability of local control and overall survival, whether or not there is an association with bone invasion. Intracranial extension is also associated with a very low probability of survival.[66]

- **Histological type**

Histological type clearly has an impact on clinical outcome, with a poorer prognosis for well-differentiated NPC, with 37% survival at 5 years. In contrast, WHO type lll appears to be associated with a good prognosis with 65% survival at 5 years.[68,64]

C. Treatment-related factors

The type of treatment, the dose of radiotherapy and the spread of radiotherapy play an important role in the prognosis of cavitary cancer, not forgetting the IMRT irradiation technique, which has made it possible to achieve local control rates of over 90% for all stages combined.[63]

D. Biological factors

Circulating EBV DNA in serum: appears to be the strongest biological prognostic factor. A high level before treatment is a poor prognostic factor. On the other hand, a detectable level after treatment indicates a high probability of relapse. A rise in DNA l e v e l s may precede relapse by 6 months.[63]

Serum levels of the enzyme lactic acid dehydrogenase (LDH) have also been studied as a prognostic factor by several authors.[63] These biological factors were not investigated in our patients.

Overall, the TNM classification remains the most important prognostic factor and the one most frequently described in the various series carried out in endemic countries.

V. Treatment

A. Goal

- Slowing down the proliferation of tumour cells.
- Reduce the risk of local and distant recurrence.
- Increase survival.

- Maintaining the best possible quality of life.

B. Resources

1. Radiotherapy

External radiotherapy remains the treatment of choice for carcinomas of the nasopharynx. The many technical advances made in recent years and our understanding of the mechanisms of radiobiology have enabled the management of NPC to evolve, allowing an increase in dose to be applied to the tumour volume and lymph node drainage areas without increasing the complication rate.

➢ **Conventional radiotherapy technique**

Radiotherapy techniques vary from one centre to another. In most institutions, the primary tumour is irradiated with two lateral, opposing beams from a 4 to 6 MV linear accelerator or a telecobalt therapy device. In some institutions, an anterior beam is added to even out the dose in tumours that extend into the nasal cavity, but other techniques use two anteroposterior beams or an arc therapy.[69,70,71]

- For small tumours, these techniques made it possible to reduce the dose to the salivary glands, inner ears, eardrum and temporomaxillary joints.
- The total dose delivered varies from 65 Gy to 70 Gy, delivered in fractions of 1.8 to 2 Gy, five times a week. The upper lymph nodes are irradiated with lateral beams which are reduced at the back to a dose of 45 Gy in order to protect the spinal cord.
- The posterior part of the upper lymph nodes is then irradiated with electron beams of variable energy. The lower and middle cervical lymph nodes are irradiated with an anterior photon beam at the junction with the lateral beams.
- If there is no lateral or posterior parapharyngeal invasion, a median shield can be used to protect the larynx, the medulla and the lower part of the pharynx.
- A prophylactic dose of 45 Gy to 50 Gyover 4.5 to 5 weeks in the absence of lymph node involvement is considered sufficient, but in the event of invasion, a further 15 to 20 Gyover 1.5 to 2 weeks is required in the initially invaded areas.

Customised shields are made to protect healthy anatomical regions at a distance from the disease. Itami et al. defined a suitable level of irradiation to achieve an acceptable level of control of the primary tumour. The dose delivered to the tumour volume had to be at least 60 Gy. The volume irradiated should include the entire sphenoidal sinus and the pituitary gland, as well as the posterior half of the nasal cavity. The posterior limit should be at the anterior edge of the medullary canal and the inferior limit at the base of the tonsil compartment.[72]

The Sham et al. study showed that protection of the pituitary gland did not increase the frequency of tumour recurrence in the absence of extension to the skull base.[73]

Carcinomas of the cavum are highly radiosensitive. For tumours classified T1-2, control rates in the order of 80 to 90% have been obtained, while those for patients with locally more advanced tumours or with large adenopathies were in the order of 40 to 60%.[74,75,76,77,78,79,80]

➢ **Improved beam selection**

High-energy X-ray photons provide better dose homogeneity in the tumour volume than gamma photons from cobalt devices. The Kutcher et al. study showed that X-ray photons of energy greater than or equal to 6 MV reduced the irradiation dose to healthy organs compared with cobalt photons.[81]

One of the most important developments in recent years has been the rise of three-dimensional techniques. In cavum cancer, the quantitative superiority of the 3D technique over the 2D technique was illustrated in a series of 13 patients. The authors showed that the lack of coverage of the tumour by the volume surrounded by the 95% iso-dose was 22% with the 2D technique and 7% with the 3D technique.

The mean dose increase in this volume was 13% with the 3D technique compared with the 2D technique. The probability of tumour control without complication was increased by 15% with the 3D technique.[82] In a series of nine patients irradiated using a conformal technique at the Alexis Vautrin Centre, only one tumour recurred, but only 20% of the tumour volume was covered by the 70 Gy iso dose, and for the other eight, at least 90% of the tumour volume was covered by the 95% iso dose.[83]

Proton therapy is a technique underpinned by the ballistic advantages of protons, a finite path characterised by the Bragg peak and a low lateral beam penumbra.[84] These characteristics make it possible to increase the irradiation dose in these tumours and reduce the dose in neighbouring organs at risk of late complications. In various organs, the proton therapy technique has been compared very favourably with the other most recent radiotherapy techniques, such as 3D Conformal photon radiotherapy, with or without intensity modulation.[85,86]

Compared with a photon-only technique, the Brown et al. study showed that proton irradiation could increase the mean dose by 5 Gy in the tumour volume and substantially reduce the dose in organs at risk.[85]

The Hunt et al. study treated 23 patients using inverse dosimetry with intensity modulation. They compared the dosimetry with that obtained using a conventional two- or three-beam technique and a three- dimensional planning technique. The average doses delivered in the planned target volume were 77.3 Gy, 67.9 Gy and 74.6 Gy respectively. This improvement made it possible to cover almost 95% of the tumour volume with the 70 Gy iso-dose using the intensity modulation irradiation technique, compared with 46% with the two parallel

beam technique, but at the cost of a significant increase in the number of beams.

The maximum mean doses delivered to the spinal cord were 34.5 Gy, 49 Gy and 44 Gy. The volume of mandible or temporal lobes receiving more than 60 Gy was reduced by 10 to 15% by intensity modulation compared with those irradiated after conventional or three-dimensional dosimetry. The results of a series of 30 patients with cancer of the cavum were reported with a follow-up of just two years. The rate of local and regional control was 100%.[87] Although the dose delivered to the salivary glands was lower with intensity modulation, its reduction did not make it possible to achieve a dose that could prevent salivary complications.[88]

Dose distribution is significantly improved by intensity modulation compared with complementary irradiation using the 3D technique, with better coverage of the tumour volume and better protection of healthy tissue. The "hot spots" are smaller and easier to manage, making dose increases safer.[88]

- **RADIOTHERAPY IN STEREOTACTIC CONDITIONS**

The Kondziolka and Lunsford study presented the first case of treatment of nasopharyngeal carcinoma by radiosurgery.[89]

Cmelak et al. reported the results of radiosurgery of seven to 16 Gy in one fraction, in 11 patients, in addition to conventional irradiation which had delivered 64.8 to 70 Gy. Although the median duration of surveillance was short, 18 months, no tumour relapsed.[91]

Tate et al. presented a recent update of the results obtained in 23 patients with stage III or IV nasopharyngeal cancer. The median dose of radiosurgery was 12 Gy and was delivered after conventional irradiation with a median dose of 66 Gy. With a 21-month surveillance period, no tumours recurred locally.[92]

The Ahn et al. study presented the results of 19 patients with cavitary cancer treated with stereotactic irradiation. Stereotactic irradiation was fractionated and delivered a median dose of 16 Gy in 2 Gy fractions in addition to a median dose of 55.8 Gy delivered by conventional radiotherapy. With a median monitoring period of 28 months, the local control rate was close to 95%.[93]

One of the limitations of radiosurgery is the availability of equipment and techniques in highly endemic countries. However, the results of dose increases in terms of local control appear to be highly satisfactory.

2. Chemotherapy

For a long time, the first line of treatment consisted of chemotherapy combining cisplatin and 5-fluorouracil. A therapeutic trial published by Zhang et al. established the combination of cisplatin and gemcitabine as the standard of treatment in this situation. This trial included 362 patients, followed for a median of 19.4 months and randomised to chemotherapy with 5FU- cisplatin or gemcitabine-cisplatin. The use of gemcitabine improved progression-free survival, with a hazard ratio (HR) of 0.55 (95% confidence interval [CI]: 0.44-0.68; p<0.0001) and also overall survival (median survival: 29.1 versus 20.9 months; HR: 0.62; 95% CI: 0.45-0.84).[94] There is no standard treatment for second-line and beyond, but molecules such as Taxanes, Carboplatin, 5FU, Antracyclines, Irinotecan, Vinorelbine, Ifosfamide and Oxaliplatin are still active.

No targeted therapy has been granted marketing authorisation (MA) for the treatment of NPC. The main targeted therapies evaluated are epidermal growth factor receptor (EGFR) inhibitors and anti-angiogenic agents. Anti-EGFRs have mainly been evaluated in combination with radiotherapy and cytotoxic chemotherapy. The results of combinations with chemotherapy have been fairly disappointing, apart from the latest phase II study combining Nimotuzumab with Cisplatin and 5FU. Anti-angiogenic agents have shown some activity, but at the cost of significant toxicity, particularly haemorrhage. The selection of metastatic patients with lesions at a distance from the large vessels helps to limit toxicity. Nasopharyngeal carcinoma appears to be highly sensitive to immunotherapy, and a number of treatments are currently being developed that target immune control pathways in general, or cancer or EBV specifically. To date, non-randomised phase 2 studies have been published, confirming the efficacy of programmed cell death 1 (PD1) inhibitors.[95,96]

Randomised trials are underway in second-line treatment (Keynote 122, NCT02611960) or in first-line treatment in combination with Cisplatin+Gemcitabine chemotherapy (NCT03581786 and NCT03707509).

In the case of oligometastatic disease, local treatment (radiotherapy, interventional radiology, surgery) of oligometastatic lesions should be discussed in conjunction with systemic treatment.

- **Special case of synchronous oligometastatic patients**

In the oligometastatic situation (hepatic, pulmonary or bone metastases in small numbers, generally <3), treatment combines initial chemotherapy of the "metastatic type", for example a combination of gemcitabine and cisplatin (rather than TPF, reserved for the induction situation). If there is a good local and metastatic response, treatment continues with full-dose radiotherapy of the primary tumour and cervical areas, followed by local treatment of oligometastases, if these are still accessible. The attitude of treating the primary in metastatic nasopharyngeal carcinoma is supported by a trial presented at the European Society for Medical

Oncology (ESMO) 2019 congress, in which 126 patients with a partial or complete response after three cycles of Cisplatin and 5FU chemotherapy were randomised between continuing chemotherapy (three cycles) only and continuing chemotherapy (three cycles) followed by locoregional radiotherapy. This trial showed a benefit in overall survival (HR: 0.42 [0.23-0.77]; p = 0.004) and progression-free survival (HR: 0.36 [0.23-0.57]; p < 0.001) in favour of local radiotherapy. Two-year survival rates were 76.4% in the locoregional radiotherapy arm compared with 54.5% in the control arm.[97]

3. Surgery

Surgery has a possible but limited role in remedial treatment. Some Asian teams have considerable experience of nasopharyngectomy, although this requires a double otolaryngological and neurosurgical approach.[109]

It may also be indicated for conservative or radical lymph node dissection in the event of residual cervical lymph nodes after treatment, or in the event of isolated lymph node relapse confirmed by a negative distant extension assessment.

- **Supportive care**

The social image of cancer is still associated with death, pain, powerlessness and uncertainty about the future. Depressive episodes can occur when the diagnosis is announced, when treatment is stopped or when the disease recurs.

The undesirable effects of chemotherapy or radiotherapy treatments can encourage the emergence of depressive episodes, in a context of physical disability and restriction of activities and/or social relationships, in a context of chronic pain and the end of life.

Psychological care for these patients involves understanding the patient's feelings and the impact of cancer on daily life, as well as better information and appropriate explanations. Admittedly, this need is hampered by the shortage of doctors, particularly oncologists: it's difficult to give everyone the time they need. Of course, the announcement of the diagnosis is a real trauma, but once the treatment has been completed, the patient must get on with his or her life. This is when the real work of mourning for their life before cancer begins, a period whenthey need the most support. Regaining the continuity of their life, their self-esteem and the pleasure of living is a long process that requires the help of a professional.

Medical and psychological care is part of a multidisciplinary approach to the disease, based on effective coordination between psychiatrists, psychologists and somatic specialists. The aim of this coordination is to exchange information, to enable carers to express and manage their own difficulties, to enable patients to receive the most relevant information possible about their illness and its prognosis, and to develop a common therapeutic strategy.[110]

C. Complications linked to treatments

1. Chemotherapy-related

There are many different toxicities associated with chemotherapy, depending on the therapeutic class used. In addition, the risk of toxicity increases with multiple chemotherapies, and some side-effects are often unacceptable to patients. Acute toxicities are sometimes life-threatening.

- ✓ Haematological toxicity: Normocytic or macrocytic anaemia macrocytic, Thrombocytopenia, Leucopenia.
- ✓ Digestive toxicity: Anorexia, vomiting, intestinal problems such as diarrhoea or constipation.
- ✓ Renal toxicity: Acute or chronic renal failure, tubulopathy and nephropathy.
- ✓ Neurological toxicity: Peripheral neuropathies, Cerebellar syndrome, encephalopathy and aseptic meningitis.
- ✓ Other: Otological toxicity and alopecia.

2. Linked to radiotherapy

Acute toxicity occurs in the first few weeks of radiotherapy, and can last for several weeks after t h e end of irradiation. Acute side effects during irradiation are constant, but their intensity and duration vary according to the dose and the proportion of organ volume affected by irradiation. However, the most frequent complications were mucositis, salivary gland disorders, radiothermitis, endocrine disorders, dysgeusia, osteoradionecrosis and radiation-induced cancers.[111]

D. Indication

In metastatic stages, the choice depends on previous treatment and toxicity

- − 1st line without previous CMT or RCC by CDDP: platinum-based doublets, 5FU platinum most commonly used, gemcitabine-CDDP, Doxorubicin-CDDP, epirubicin-CDDP and Docetaxel-CDDP or Carboplatin, gemcitabine-Vinorelbine or monotherapy: CDDP, Carboplatin, Docetaxel, 5FU, Methotrexate, gemcitabine, Capecitabine, Vinorelbine.
- − 2nd line or pre-treated with platinum salts: no standard
- − Reintroduction of platinum salts depends on PS, previous toxicity and time to relapse
- ✓ 6-12 months: 2nd doublet based on Platinum + Taxanes; Capecitabine or gemcitabine
- ✓ < 6 months: frail patient, WHO=2, gemcitabine, capecitabine or docetaxel-based monotherapy
- ✓ WHO=3-4: suggest BSC.

CONCLUSION

Nasopharyngeal carcinomas (NPCs) are of squamous cell origin and account for 90% of nasopharyngeal malignancies. They are divided into two distinct clinico-histological entities: squamous cell carcinoma and undifferentiated nasopharyngeal carcinoma (UCNT). The

latter has the highest prevalence worldwide.

UCNT differs from other squamous cell carcinomas of the upper aerodigestive tract (UADT) in its histological features, its epidemiology unrelated to alcohol and tobacco intoxication, and its direct relationship with the Epstein-Barr virus (EBV). Its distribution is endemic in certain regions of the world (high in South-East Asia, moderate in North Africa). Its aetiology is multifactorial, involving genetic, viral and environmental factors.

Unlike other head and neck tumours, nasopharyngeal cancer is characterised by a high rate of local or locoregional recurrence and metastatic spread, with around a third of cases relapsing locally or with metastatic spread. In the metastatic phase, the role of chemotherapy is currently well established and has been demonstrated by a high rate of objective responses with durable remissions and some long survival.

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