



DIFFUSE SMALL-CELL CELLS (ABOUT 20 CASES)

M. Toreis*, A. Z. Bazine, Y. Touimri and M. Fetohi



*Corresponding Author: M. Toreis

Article Received on 27/09/2024

Article Revised on 17/10/2024

Article Accepted on 07/11/2024

ABSTRACT

Lung cancer is the leading cause of cancer death worldwide in men, and, after breast cancer, for women. The two categories of lung cancer are small cell carcinoma and non-small cell carcinoma. SCLC are strongly linked to tobacco consumption and their diagnosis on histological evidence. With a non-specific clinic. But in the majority of cases the patients present themselves under a noisy picture. Small cell lung cancer accounts for 10-15% of all lung cancers. Its incidence has decreased to 13% of all lung cancers. The objective of our study is to study the clinical, para-clinical, therapeutic, progressive and prognostic epidemiological profile of metastatic small cell lung cancer in the medical oncology department of the Moulay Ismail military hospital in Meknes. This is a retrospective descriptive analytical study spread over a period of six years (from January 2004 to December 2019) concerning 20 cases in the medical oncology department of the Moulay Ismail military hospital in Meknes. Despite the proven chemosensitivity of SCLC, their poor prognosis is due to the precocity of local and distant relapses. Metastatic locations are frequent at the time of diagnosis. Systemic chemotherapy represents the main therapeutic weapon for disseminated forms; the combination of a platinum salt and Etoposide is a first-line therapeutic standard in metastatic forms, the complete response rate reached 25% in our series. The median overall survival was 7.22 months with a One year survival of 10%. Palliative care is systematically integrated into the therapeutic plan of each patient with bronchial carcinoma and all of our patients have benefited from supportive palliative care during their care as well as adequate psychological support.

INTRODUCTION

Bronchial cancer is the 2nd leading cause of cancer mortality in women worldwide. Women after breast cancer^[1], while it ranks first in men.^[1]

There are four main types of primary bronchial tumour according to the WHO histological classification: squamous cell carcinoma, adenocarcinoma, undifferentiated large cell carcinoma and small cell lung cancer (SCLC).^[2]

In terms of incidence, small-cell lung cancer accounts for 10-15% of all lung cancers. It is important to note that its incidence has fallen to 13%^[3] of all bronchial cancers. However, despite this low incidence, this type is considered to be the most aggressive of all types of lung cancer, with a 5-year survival rate of less than 5% in metastatic forms.

In addition, it is extremely important to point out that the main aetiological factor in small-cell lung cancer is tobacco, since it is incriminated in over 90% of cases. This risk increases in parallel with the dose, but also with the duration of exposure to tobacco (number of pack-years). Other environmental factors have also been

mentioned, but these often act in synergy with tobacco.^[4]

It should be remembered that the positive diagnosis of CBPC is essentially based on histological evidence with an immunohistochemical study.

Compared with other bronchial cancers, PBC has a very rapid doubling rate of around 30 days and is of neuroendocrine origin.^[5] As far as treatment is concerned, chemotherapy is the main therapeutic weapon in the fight against lung cancer. Currently, scientific research is focusing on the following therapies given the effects reported in the literature.

In order to evaluate the management of small cell lung cancer in the medical oncology department of the Moulay Ismail military hospital in Meknes, we conducted a retrospective study including twenty cases over a six-year period, from January 2014 to December 2019. We evaluated the epidemiological, anatomopathological, diagnostic and therapeutic aspects of this bronchial cancer and compared them with those in the literature.

MATERIALS AND METHODS

This is a descriptive retrospective observational study of 20 cases of small cell lung carcinoma collected in the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes over a 6-year period from January 2014 to December 2019.

I. Aims of the study

The objectives of our study can be stratified according to the following points

- To determine the frequency of small cell lung carcinomas.
- Describe their clinical, paraclinical and anatomopathological aspects.
- Assessing therapeutic options.
- Evaluate the results of treatment.

II. Target population

The target population is all patients with small cell lung cancer treated in the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes, over a 6-year period from January 2014 to December 2019.

III. Data collection

Our data source was

- The hospital register of the medical oncology department at the Moulay Ismail military hospital in Meknes.
- Medical records from the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes.

the following criteria inclusion criteria in our study, including registration errors, patients with non-small cell lung cancer, secondary lung tumours and histologically unconfirmed lung cancers.

Finally, we included in our analysis 20 patients from the medical oncology department of the Moulay Ismail military hospital in Meknes.

IV. Data entry and analysis

The various data collected were coded and reported on an Excel document (Windows). Qualitative variables were represented as numbers or percentages, while quantitative variables were represented as mean $\pm$ standard deviation for variables with normal distributions, and as median for variables with asymmetric distributions.

RESULTS

I. Epidemiological profile

Between January 2014 and December 2019, 20 patients were diagnosed with small cell lung cancer in the medical oncology department at Moulay Ismail Military Hospital in Meknes. This rate represents 5% of all bronchial cancers diagnosed during this period, and it is important to note that the incidence of small cell lung carcinoma is gradually decreasing over the years.

A. AGE

In our series, the median age was 61 years, with patients of a younger age over 65 years of age in 20% of cases, i.e. four patients.

As a first step, we eliminated all files that did not meet

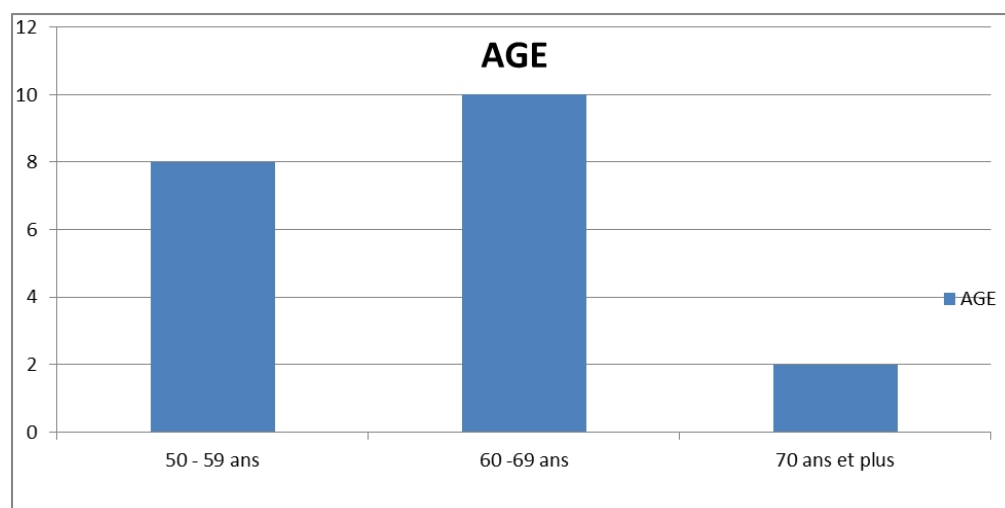


Figure 1: Age distribution of patients.

B. Sex

The predominant sex was male; in our study we found 19 male patients, i.e. 95% of cases, compared with a single female patient, i.e. 5% of the population studied (sex ratio = 0.05).

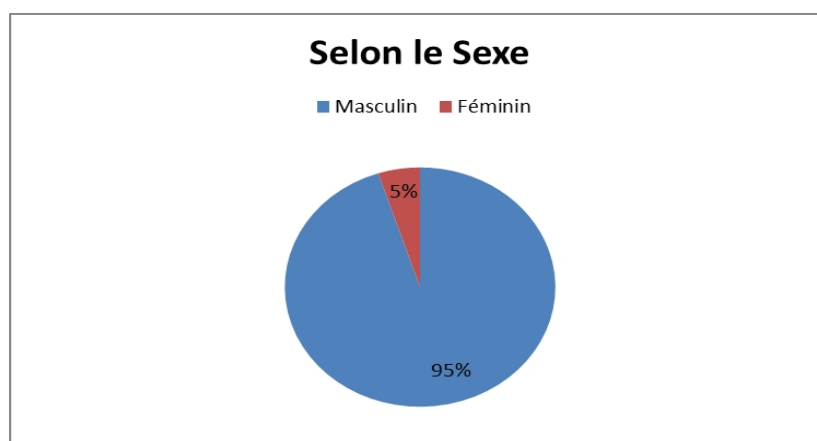


Figure 2: Breakdown of cases by gender.

II. Risk factors

A. Tobacco

In our series, the notion of chronic active smoking was found in 19 patients, i.e. 95% of cases, all males with an

average tobacco consumption of thirty packs/year, most of whom had stopped smoking at the time of their first consultation. However, the notion of passive smoking was reported by the only female patient.

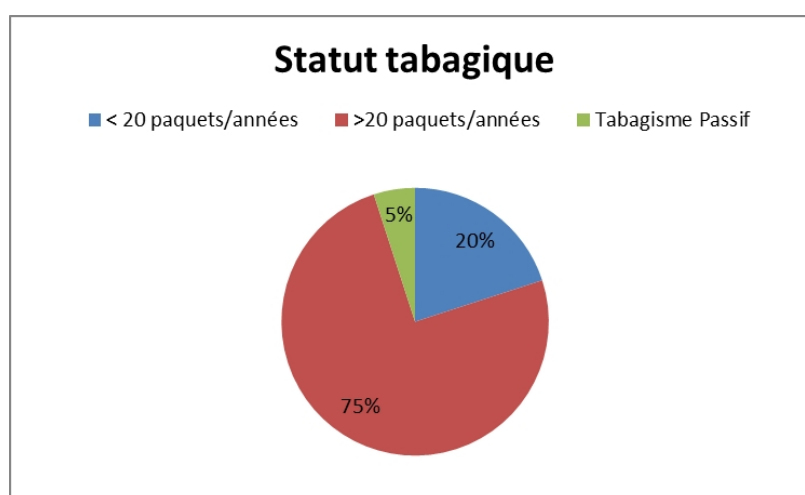


Figure 3: Breakdown of patients by smoking status.

B. Alcohol

Alcoholism was reported by four patients (20% of cases).

one of whom was detoxed at the time of diagnosis.

C. Cannabis

Cannabism was found in two patients, i.e. 10% of cases,

D. Occupational origin

It should be noted that none of the patients in our study had occupational exposure.

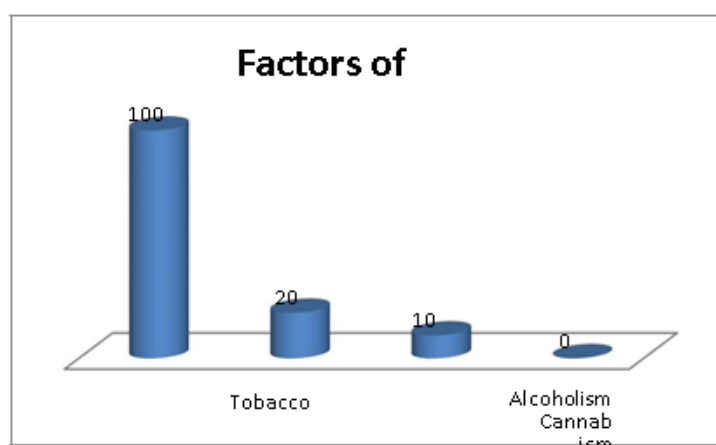


Figure 4: Distribution of cases according to risk factors.

III. Clinical data

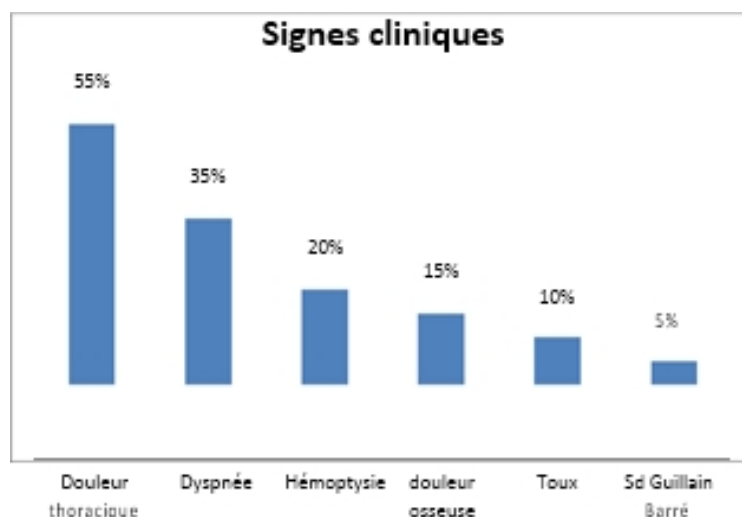


Figure 5: Initial clinical signs of PBC in our patients.

A. Circumstances of discovery

19 of our patients had presented respiratory signs at the time of diagnosis. These signs were distributed as follows: The most frequent initial clinical presentation was chest pain in 11 of the patients (55%), followed by dyspnoea in seven patients (35%), haemoptysis in four (20%), bone pain in three (20%) and respiratory symptoms in four (20%). (15%) and cough in two

patients (10%). Only one patient presented with Guillain-Barré syndrome (5%) without any respiratory symptoms.

B. Clinical examination

1. WHO Statute: ANNEX II

With regard to WHO status, 18 cases had a WHO status of less than or equal to 2, i.e. 90%, while 2 patients had a WHO status of greater than 2, i.e. 10% of cases.

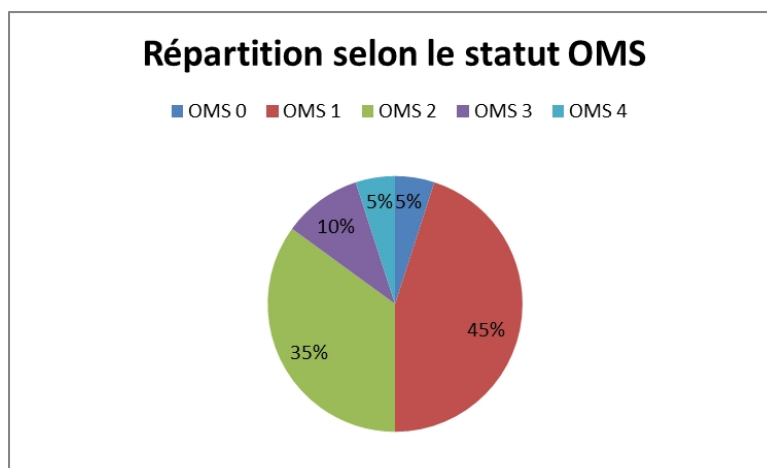


Figure 6: Distribution of patients according to WHO status.

IV. Anatomopathological study

All patients in our study had a histological diagnosis of small cell lung carcinoma. An immunohistochemical complement was performed in all patients in our study, confirming the diagnosis of CBPC.

V. Paraclinical data

A. Chest X-ray, front and profile

Chest X-rays (front and side) are the first additional examination requested from patients, but they are still used as a "stop-gap" examination. A CT-PET scan is also prescribed for all patients.

It is used to assess pleural damage, especially pleurisy,

parenchymal lesions, mediastinal localisations, costal lysis or other local metastases, and to detect ventilatory disorders.

All our patients had a standard X-ray.

B. Thoracic-abdominal-pelvic computed tomography (TAP CT) + PC

Injected thoracic CT was the first-line radiological assessment to be requested, and was carried out in all twenty patients in our series. The aim is to diagnose the disease and also to assess locoregional thoracic extension. Complementary abdomino-pelvic tomography was also performed in all patients in our series.

C. Bone scan

Bone scintigraphy was part of the extension work-up in all our patients, and showed secondary bone locations in 15% of cases in our series, with diffuse bone dissemination and axial rather than peripheral involvement.

D. Brain imaging

A cerebral CT scan was performed in all patients in our series, showing secondary cerebral locations in 20% of

cases. Five of our patients also underwent cerebral MRI.

E. Classification

Primary tumour (T) and regional adenopathies (N)

The majority of tumours were found to be locally advanced, with T4 tumours accounting for over 60% of cases, N2 lymph node involvement in 35% of tumours, and N3 in eight patients (40% of cases).

Table 1: Distribution of tumours according to T and N classification.

T	Percentage	N	Percentage
T1	0%	N0	20%
T2	15%	N1	5%
T3	35%	N2	35%
T4	60%	N3	40%

• Distant metastases

All our patients were seen at an advanced metastatic stage, and the majority had more than one metastatic site identified during the extension work-up. The most

common metastatic sites were the lung, pleura, bone, brain, liver and adrenal glands. The number of metastatic sites in our patients was ≥ 2 in 55% of cases.

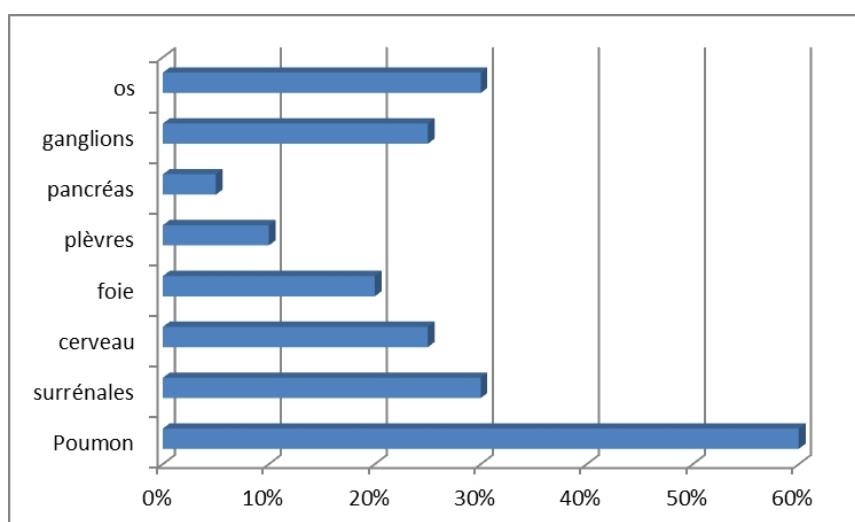


Figure 7: Rates of different metastatic sites.

VI. Pre-therapy assessment

A. Biological check-up

In all our patients who were candidates for treatment, a pre-treatment biological work-up was carried out, including a complete blood count (CBC), liver and kidney function tests and a complete blood ionogram.

This assessment showed anaemia in 10% of our patients and lymphopenia in 5%. Hypoalbuminemia was diagnosed in 20% of cases. An elevated lactate dehydrogenase level was found in 25% of cases, and an elevated alkaline phosphatase level in 40% of patients.

Hypercalcaemia was observed in 5% of cases and an alteration in creatinine clearance was found in 2 other patients, i.e. 10% of all our patients.

B. Cardiological check-up

A complete cardiac work-up was carried out in all our patients. This pre-therapeutic cardiac work-up is mainly based on a complete cardiovascular clinical examination and electrocardiogram (ECG) and trans-thoracic echocardiography (TTE).

The cardiological work-up was satisfactory in the majority of patients studied, but showed signs of hypertensive cardiopathy in one patient (5%) with no effect on systolic ejection fraction, and heart failure in another patient (5%).

C. Respiratory function

All our cases were seen in the respiratory department, but none of the patients in our study had their lung function investigated, given the advanced stage of all the cases studied at the time of their first consultation.

All patients in our series benefited from oral care prior to initiation of calcium biphosphonate treatment to prevent mandibular necrosis.

VII. Treatment

A. PALLIATIVE CHEMOTHERAPY

1. The first line of treatment

❖ Treatment received

First-line chemotherapy was prescribed for 15 of our patients, i.e. 75%, but palliative care was recommended from the outset for 5 other patients (i.e. 25%) who were ineligible for chemotherapy either because of significant and/or rapid deterioration in their performance status (WHO status) or because of a contraindication to chemotherapy, particularly of a cardiological or

haematological nature.

The first-line chemotherapy chosen was based on the combination of a platinum salt with etoposide. Just 5 patients (33%) were eligible for treatment with Cisplatin, while ten other patients received Carboplatin as first-line treatment combined with Etoposide.

The number of cycles of palliative chemotherapy received by our patients was between 1 and 6 cycles with an average of three cycles. Of the patients who received first-line chemotherapy, only 12 were evaluable at the end of their first-line chemotherapy cycles. The other patients were either lost to follow-up during the course of their treatment, or discontinued first-line chemotherapy.

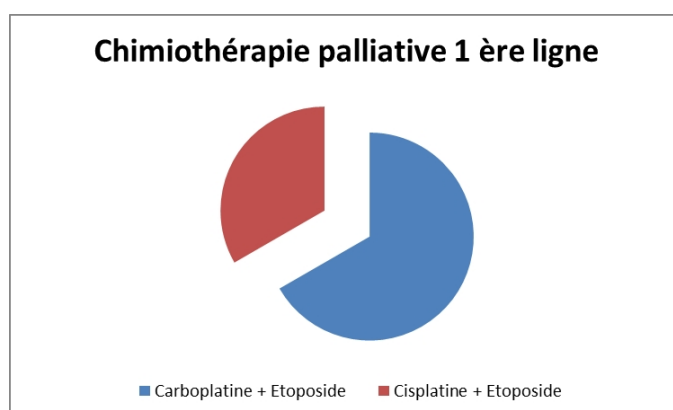


Figure 8: 1st-line palliative chemotherapy.

□ Evolution

A clear clinical improvement was noted in all patients treated in our oncology department at the Moulay Ismail military hospital in Meknes, with a clear benefit on respiratory symptoms and general condition. Patient response to first-line chemotherapy was as follows

□ A complete answer

A complete response was observed in 3 patients, i.e. 25% of the 12 patients evaluated after first-line chemotherapy.

□ A partial answer

5 patients, or 33% of the 12 patients assessed after first-

line chemotherapy, showed a partial response to treatment.

□ Stability

Radico-clinical stability was maintained in 03 patients, i.e. 25% of the 12 patients evaluated after first-line chemotherapy.

□ Progress

Two rapid progressions were observed during the systematic follow-up of patients on chemotherapy (17%) of the 12 patients evaluated after first-line chemotherapy.

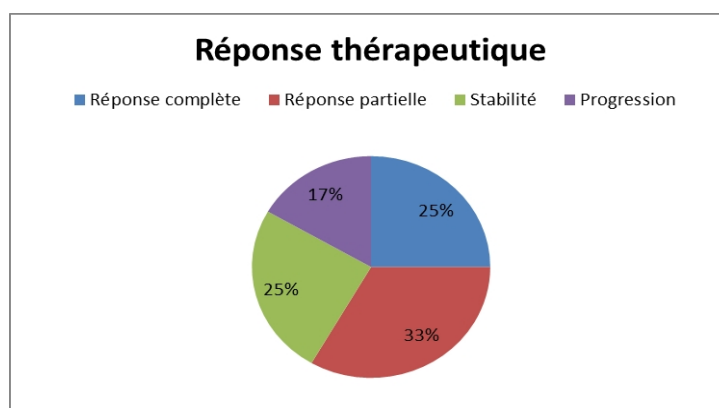


Figure 9: Response to first-line chemotherapy.

2. The second line of treatment

❖ Treatment received

Second-line treatment was prescribed for five of our patients. Second-line chemotherapy was based on carboplatin + etoposide in two platinum-sensitive patients (progression > 3 months) and based on Irinotecan in two patients and Paclitaxel in one patient, for three platinum-resistant patients (relapse < 3 months).

❖ Evolution

The five patients who received second-line chemotherapy progressed rapidly on treatment within the first three months of second-line treatment.

3. Chemotherapy toxicity: A. Haematological toxicity

a) Anemia

Anemia was observed in 13 of our patients, i.e. 65% of those who received systemic chemotherapy, and was poorly tolerated in three of them, who subsequently

required a blood transfusion of packed red blood cells globular.

b) Neutropenia

Neutropenia was observed in 10 cases (50%), 2 of whom (20%) had febrile neutropenia.

c) Thrombocytopenia

Thrombocytopenia occurred in 3 cases (15%), while no haemorrhage or haemorrhagic syndrome was recorded.

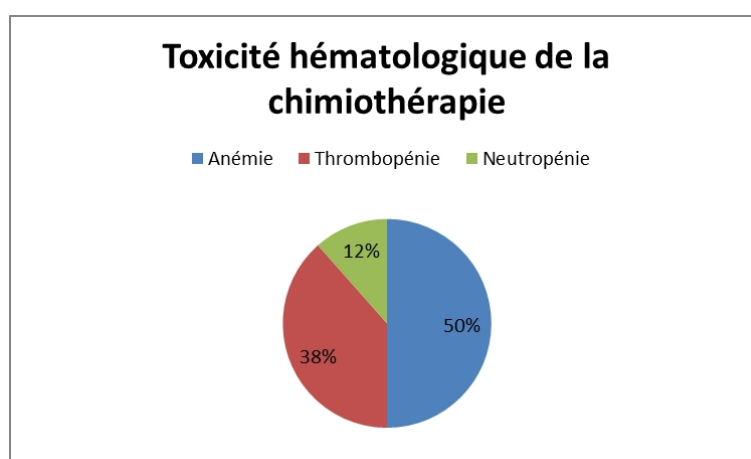


Figure 10: Haematological toxicities of chemotherapy.

B. Renal toxicity

Two of our patients developed tubulopathy under platinum salt treatment, with a significant fall in creatinine clearance. One of these patients was able to recover satisfactory renal function.

C. Digestive toxicity

In our series, 5 cases, i.e. 25% of those studied, presented with vomiting during chemotherapy treatments despite adequate premedication, necessitating their hospitalisation to prevent hydro-electrolytic disorders and dehydration.

Three of our patients had developed inflammation of the oral mucosa (mucositis) and received appropriate treatment, and six other patients had diarrhoea requiring treatment in our department.

D. Neurological toxicity

Of the patients studied in our series, 8 (40%) had shown signs of peripheral neuropathy.

E. Others

Generalized asthenia was observed in 14 patients (70% of cases), and no ototoxicity was observed in our study.

B. RADIOTHERAPY

Radiotherapy was used for palliative purposes in patients with neurological signs or high metastatic risk. Radiotherapy was given to the brain in patients with brain metastases, i.e. 5 patients, or 25% of the cases studied.

Prophylactic cerebral radiotherapy was indicated in four patients, three of whom showed a complete response after chemotherapy and one a partial response with a perfectly preserved general condition.

Two patients were offered radiotherapy to the thoracic region, one with a complete response and one with a partial response after chemotherapy.

C. BONE MODULATING TREATMENTS

Bone modulating treatment was administered to all

patients with bone pain or secondary bone locations. It is based on treatment with calcium biphosphonates.

Clinical improvement in bone pain was observed in all six patients with symptomatic bone metastases, and only one case of pathological bone fracture was recorded in our series.

D. Supportive care

All our patients received supportive care throughout their treatment in our department, but 85% of our patients required analgesic treatment (bone pain, severe headaches), 70% of whom received morphine-based treatments from the outset.

All patients in our series were given antiemetic treatment with chemotherapy, based on serotonin receptor antagonists (Ondansetron).

Four patients with pleural metastases required at least one pleural evacuation with study of the pleural fluid (bacteriological, chemical and cytological), and one patient underwent talcation.

Smoking cessation advice was systematically sought from all patients who had not been weaned at the time of diagnosis.

None of our patients required the injection of growth factors concomitantly with chemotherapy.

Patients who were hospitalised in the medical oncology department at HMMI during their treatment also benefited from psychotherapeutic follow-up.

VIII. SURVIVAL

In our study, the median overall survival was 7.22 months, with a 1-year survival rate of 10%.

DISCUSSION

I. EPIDEMIOLOGICAL STUDY

A. Incidence and geographical distribution

1. Worldwide

In 2020, 19.3 million new cases of cancer were revealed that were diagnosed, including 11.4% of bronchopulmonary cancers and unfortunately 10 million deaths are caused by this disease, according to figures published this year (December 2020) by the International Agency for Research on Cancer (IARC).^[66]

In 2012, according to the Globocan International Agency for Research on Cancer, lung cancer was the most common cancer in the world, accounting for around 1.8 million new cases (13% of the total) and the leading cause of death from cancer, accounting for around 1.6 million deaths (19.4% of the total).

Around 60% of cases worldwide occur in less developed regions.^[7] In Europe, the incidence of bronchopulmonary

cancer ranks 3rd after colorectal cancer and breast cancer, and just ahead of prostate cancer, with 391,000 cases, or 12.2% of all cancers. But lung cancer remains by far the most fatal, with a total of 342,000 deaths, or 20% of all cancers.^[8]

In France, the incidence of bronchopulmonary cancer was estimated at 39,495 cases in 2012, all sexes combined. This form of cancer ranks 4th after colorectal cancer, accounting for 7.3% of incident cancers in France in 2012.^[9]

In Africa: the incidence of bronchopulmonary cancer ranked 8th with 30314 new cases, representing 3.58% of all cancers in 2012.^[7]

But this incidence may be due to a lack of screening and diagnostic facilities for cancers in general, and bronchopulmonary cancers in particular.

In Tunisia, the incidence of lung cancer is 21.9%, with a standardised incidence of 30.2 cases per 100,000 population.^[10]

2. At national level

In France, small cell lung cancer accounts for 13% of all primary bronchial cancers, with an overall incidence of around 10%.7 new cases/100,000 population.

There has been a marked decline in the incidence of the disease in recent years, mainly due to advances in anatomopathology.^[3]

According to the Greater Casablanca Regional Cancer Registry Years: 2008 -2012: The proportion of lung cancer cases recorded was around 11.4% for both sexes. In men, lung cancer accounted for 22.8% of cases.

A total of 2,762 cases of lung cancer were recorded during this study period. The crude incidence in males was 25 per 100,000 males compared with 2.8 in females. The standardised rate for the world population was 32.8 in men and 3.4 in women.^[11]

Table 2: Standardised incidence of lung cancer in Casablanca between 2008 and 2012.

	Femmes	Hommes	Deux sexes
Nouveaux cas	288,0	2474,0	2762,0
Incidence brute	2,8	25,0	13,7
Incidence standardisée sur la population Maroc	2,7	25,9	13,9
Incidence standardisée sur la population Monde	3,4	32,8	17,4
Incidence cumulée 0-64 ans	0,3	2,4	1,3
Incidence cumulée 0-74 ans	0,4	4,2	2,2

According to the cancer register for the Rabat region, 2006-2008

It is the most common cancer in men in Rabat (19.8% of cases). More than 60% of cases are diagnosed at the stage of metastasis, and only 10% of lung cancers are treated curatively.^[12]

The incidence of lung cancer in Rabat is very similar to that found in other Maghreb countries, but remains much lower than in some European and Asian countries or in North America.

Over six years, between January 2014 and December 2019, there were 20 cases of small cell lung cancer in the Medical Oncology Department - Hôpital Militaire Moulay This rate represents 5% of all bronchial cancers diagnosed during this period, and a decrease in incidence has been noted over the years of our study.

B. Breakdown by age and gender

The median age at diagnosis of small cell lung carcinoma varies between countries, levels of care and smoking habits. In the United States, the median age is currently 70, and two-thirds of patients are at least 65 at the time of diagnosis.^[8]

Age-specific incidence in France shows that peak incidence was reached in men in the 70- 74 age group. In women, there is a plateau between the ages of 50 and 80, with no real peak in incidence.^[13]

In our series, the average age was 61 years, with extremes ranging from 50 to 80 years. The age group most affected was between 60 and 69, with a male predominance in 95% of cases (sex ratio = 0.05).

Table 3: Distribution of CBPC according to incidence and age.

Study series	Region	CBPC	AGE
Moussoki 2014 ^[19]	France	19,12%	66 years old
A Ben Amar et al 2005-2010 ^[20]	Tunisia	17 ,5%	60 years old
Ndiaye et al 2010-2013 ^[20]	Senegal	7,5%	years old
Cadelis et al 2009-2010 ^[23]	Caribbean	N/A	65 years old
RCRC ^[17] 2005-2007	Morocco	15%	59.5 years old
EL-ACHHAB D ^[19]	Fez	0,43%	59 years old
Our study	Meknes	13%	61 years old

Risk factors

1. Tobacco

Tobacco is by far the most incriminating risk factor for lung cancer, and according to the International Agency for Research on Cancer (IARC) is responsible for more than 90% of cases in men. Smoking gives smokers a 15% greater risk of developing lung cancer than non-smokers.

The effects of passive smoking on the health of non-smokers have been scientifically proven, and the risk of lung cancer in non-smokers is 26%.^[14]

In all the studies, the risk of lung cancer increases with daily tobacco consumption, the length of time smokers

smoke, the intensity of smoke inhalation and how early they start smoking.

a. Daily tobacco consumption

Daily tobacco consumption, in whatever form, is the most incriminating factor in various lung cancers^[4], being responsible for 99% of squamous cell cancers, 95% of small cell bronchial cancers, 90% of large cell carcinomas and 70% of bronchopulmonary ADK.

b. Duration of smoking

It has been shown that the increase in risk is 20 times greater after 30 years of smoking than after 15 years, and 100 times greater after 45 years of smoking than after 15 years.^[15]

c. Age of onset

The young age at which smoking begins clearly appears to be a risk-increasing factor, with the relative risk rising from 14 to 20 depending on whether the first cigarette was smoked after the age of 25 or before the age of 16.

d. Smoke inhalation

Whether or not you inhale the smoke changes the risk by a significant factor - from a factor of 12 to a factor of 20 - depending on whether you inhale the smoke or just crap without inhaling it.

In our series, 19 of our patients were chronic smokers, 60% of whom had stopped smoking at the time of diagnosis. Although this risk directly concerns smokers, the effects of The impact of passive smoking on the health of non-smokers has also been scientifically proven, and the risk of lung cancer in non-smokers is 26%. In our series, the notion of passive smoking was reported in the female patient.

2. Occupational origin

In men, an estimated 15% of lung cancers are not linked to regular smoking, and are mainly associated with certain occupational activities.

The number of cases is higher than average among professionals in contact with asbestos, radon (uranium mines), arsenic, nickel, chromium, tar, etc. The synergy or combination of risk factors (tobacco + occupational exposure, etc.) is a major factor in the development of the disease. exposure to asbestos) considerably increases the probability of developing the disease.^[16]

In our series, none of the patients were occupationally exposed.

3. Other risk factors

Regular use of cannabis is also a risk factor. Cannabis smoke contains 4 times more tar than tobacco smoke, and contains more carcinogens. Finally, the active ingredient in cannabis, THC, dilates the bronchial tubes, making it easier for the smoke and its toxic substances to penetrate the lungs.^[16]

In our series, alcoholism was found in four patients, i.e.

20% of cases, and cannabism in two of our patients, i.e. 10% of cases.

III. POSITIVE DIAGNOSIS

A. Clinical aspects

The most important part of the fight against small cell lung cancer is to diagnose it as early as possible, which requires knowledge of the different ways in which the disease presents clinically, and a standardised and effective diagnostic procedure in order to begin treatment as soon as possible. Any functional or clinical sign persisting for more than 15 days in a smoker or ex-smoker, with no obvious aetiology, should raise the suspicion of bronchial cancer.^[17]

1. Respiratory signs^[18]

They are not specific but are often the reason for the initial consultation.

- A cough that worsens or changes recently, has a coughing fit, or persists despite the usual treatment, should suggest lung cancer.
- Dyspnoea: inspiratory dyspnoea with or without wheezing should attract attention and raise suspicion of bronchial obstruction.
- Chest pain: variable in location but fixed and persistent, often resistant to standard analgesic treatments.
- Haemoptysis: this is an alarming symptom which, in the absence of any known respiratory pathology in the patient, is an indication for bronchial endoscopy.

Acute respiratory episodes It should be pointed out that any unusual respiratory infectious episode in a smoker or ex-smoker warrants a radiological check-up, or even bronchoscopy and a chest CT scan in the event of incomplete resolution after appropriate treatment or frequent recurrences.

In our study, chest pain was by far the main reason for consultation, with a rate of 55%, which confirms that by the time of the first consultation in the majority of cases, the disease has already spread and is not in its early stages.

Table 4: Distribution of respiratory signs at the time of diagnosis in the various studies.

Series	Region	Respiratory signs			
		Chest pain	Cough	Haemoptysis	Dyspnoea
EL-Achhab D. ^[19] 2017	Fez	47%	21%	9%	23%
Ndiaye et al. ^[20] 2010-2013	Senegal	48%	40%	-	30%
Our series	Meknes	55%	10%	20%	35%

2. Locoregional signs

When the involvement is locoregional, it may result in superior vena syndrome, dysphonia or dysphagia

- Venous involvement: superior vena cava syndrome.^[19,20]

Superior vena cava syndrome is of neoplastic origin in

90% of cases, resulting from obstruction of blood flow in the superior vena cava, linked to extrinsic lymph node compression, sometimes to tumour invasion or thrombosis.

Clinical signs can be divided into 3 groups

- Haemodynamic signs with oedema of the face, oedema of the upper limbs, turgidity of the jugular veins and thoracic collateral venous circulation.
- Respiratory signs such as dysphagia, dyspnoea, cough, dysphonia and stridor. Neurological signs may include syncope, headache, dizziness, confusion or even obtundation.

In our series, a superior vena cava syndrome was revealed in 3 patients, it was progressed favourably on chemotherapy in two patients, but led to death in the other.



Figure 11: Clinical image of a woman with facial oedema presenting with superior vena cava syndrome.^[17]

• Nerve damage^[18]

Nerve damage to the left recurrent nerve results from compression of the nerve under the aortic arch by a PDA or the tumour itself; clinically it manifests as hoarseness, a bitonal tract or dysphonia.

In our series, dysphonia was reported in one patient (5%). In the Loudadsi series^[21], dysphonia was reported in 4% of cases. In Bamba Salia's study, the rate of dysphonia was 2%.

In the case of the phrenic nerve, clinical symptoms include hiccups. In the case of the cervical sympathetic nerve, the clinical manifestation is Claude Bernard-Horner syndrome.

Involvement of the brachial plexus manifests as shoulder pain radiating to the inner aspect of the corresponding arm and forearm. Pancoast Tobias syndrome is often associated with bronchial tumours of the lung apex which invade the pleural dome, the brachial plexus (C8_D1), the sympathetic stellate ganglion and the posterior arch of the first 2 ribs. It is associated with scapular pain radiating to C8_D1 and Claude Bernard Horner syndrome.^[20]

• Oesophageal involvement

The main symptoms are dysphagia and vomiting.^[18] This symptomatology was reported in 3 of our patients.

• Cardiac involvement

It can lead to signs of heart failure, pericardial effusion

or rhythm disorders.^[18]

• Pleural involvement

It is manifested by the presence of pleurisy of great abundance associated with parietal pain.^[18]

Pleurisy was observed in four of our patients, and metastasis was confirmed in three of them (15% of the cases studied).

• Supra-clavicular adenopathy

In our series, peripheral adenopathy was noted in one patient (10%). Loudadsi^[21] found peripheral adenopathy in 29% of cases in his series.

3. Signs related to metastatic extension^[23,24]

The most frequent secondary locations are

- Liver (with hepatomegaly)
- Bones (pathological fracture, bone pain, hypercalcaemia): Bone metastases are multiple from the outset in 80% of cases, with pain being the main revealing symptom.

In our series: Extension work-up revealed bone metastases in 6 patients (30%).

- Adrenal: metastases are frequent but usually asymptomatic.

In our study, adrenal metastases were found in 25% of cases.

Central nervous system: Cerebral metastases are manifested acutely by intense headaches, partial or generalised convulsions, hypertension, etc.

Other more progressive symptoms may be the telltale signs, such as headaches, nausea or vomiting, focal neurological signs, cognitive problems or impairment of higher functions. In 10% of cases, they are asymptomatic.

Secondary cerebral localisations were observed in 5 of our patients, i.e. 25%.

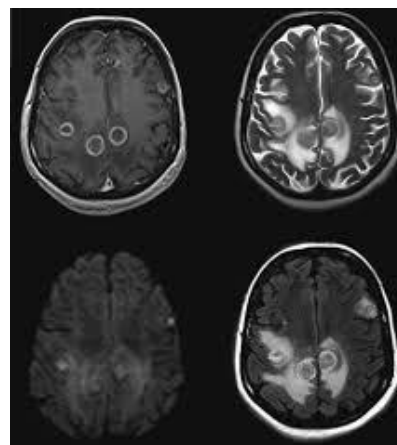


Figure 12: Brain MRI showing brain metastases.

4. General signs

Signs of deterioration in general condition: weight loss, anorexia, asthenia and fever are frequent general signs which often come to the fore and which may lead to other pathologies. They are not specific, but when they are present, they have a poor prognosis. General condition can be quantified using the WHO performance status index.

In our series, weight loss was reported in 8 patients (40%). 18 cases had a WHO status of less than or equal to 2, i.e. 90%, compared with 2 patients with a WHO status greater than 2, i.e. 10%.

5. Paraneoplastic syndromes^[2]

This refers to the occurrence of clinical, biological or radiological signs during the course of a cancer, which may be independent of the metastatic process or related to it.

5.1. SCWARTZ-BARTTER syndrome: SIADH

This syndrome is a high secretion of antidiuretic hormone. This leads to fluid retention resulting in severe hyponatremia associated with intracellular hyperhydration.

It can present in a variety of ways, with general asthenia. Digestive symptoms may include anorexia, nausea and vomiting. Neuropsychological symptoms can range from simple irritability to headaches, drowsiness, mental confusion, temporo-spatial disorientation and even coma. Treatment is based mainly on water restriction, salt intake and loop diuretics, with monitoring of inputs and outputs.

5.2. CUSHING syndrome

It is characterised by ectopic secretion of ACTH by an extra-pituitary tumour. It accounts for approximately 10 to 15% of ACTH-dependent Cushing's syndromes. It may precede, accompany or follow the discovery of cancer.

The clinical picture is varied, with arterial hypertension, amyotrophy, asthenia, mental disorders, oedema of the lower limbs and hyperpigmentation of the skin.

This syndrome includes hypokalaemia, metabolic alkalosis and hyperglycaemia.

5.3. LAMBERT-EATON syndrome

Lambert-Eaton myasthenic syndrome is a paraneoplastic neuromuscular disorder in which there is an autoimmune response directed against a small cell lung tumour that cross-reacts with antigens in the neuromuscular junction. It accounts for 2% of all cases of lung cancer and is the most common cause. In the majority of cases, this syndrome precedes the diagnosis of CBPC.

5.4. Anti-HU autoantibody syndrome

They are grouped together under the term subacute

polyencephalomyelitis (PEMS). They include: limbic encephalitis, rhombencephalitis, cerebellar degeneration, subacute myelopathy and Denny-Brown sensory neuropathy.

Less than 0.5% of PBCCs are responsible for 80% of these syndromes. The presence of anti-epitropic antibodies common to both the tumour and the neurons.

It often precedes the clinical manifestations and discovery of the disease. The prognosis is poor. The course is independent, with the syndrome sometimes remitting thanks to treatment of the CBPC.

No paraneoplastic syndrome is specific to a particular cancer, but their frequency is significantly higher in small cell lung cancers.

B. Physical examination

An exhaustive clinical examination is imperative in cases of suspected lung cancer, and its main purpose is prognostic. It is used to assess the patient's general condition, weight and nutritional status; to look for associated pulmonary, cardiac or hepatic defects; and to look for direct or indirect signs of locoregional or metastatic spread.

C. Paraclinical

1. Diagnostic tests

• Chest X-ray^[19]

Chest X-rays (front + side) are the initial imaging test for any presenting sign, and are used to rule out the possibility of a pulmonary tumour process; a normal chest X-ray does not rule out the diagnosis, but justifies further investigations in the event of suspicion of malignancy. Peripheral tumours are usually nodular, rounded or oval. The likelihood of malignancy increases with size, irregular and speculated or lobulated boundaries, absence of calcifications and progression. Central tumours often appear as a polycyclic peri hilar opacity with an internal boundary confused with the mediastinum and a rounded but irregular external boundary with or without atelectasis. All these features are inconstant, and other aspects are possible, such as abscesses upstream of bronchial stenosis, pleurisy, or a central excavation with irregular contours.

- Thoracic CT scan with injection of contrast medium.^[25]

Bronchopulmonary cancer is a major public health problem, contributing significantly to mortality and morbidity, especially in smokers. Small cell carcinoma (SCC) accounts for 20% of all primary malignant bronchopulmonary tumours.^[26] It stands out from other primary bronchial cancers because of its very rapid doubling time and early metastatic spread, with secondary sites in more than 70% of cases at the time of diagnosis, compared with 28% in non-small cell carcinomas.^[27,28] Treatment options are limited to

chemotherapy, radiotherapy or a combination of the two. Despite the advantages of these therapeutic methods, five-year survival remains minimal, with a median survival of eight to ten months for disseminated forms and 12 to 16 months for forms localised to the thorax.^[29] Despite the interest it has aroused in the medical community, little work has been done on the imaging of CPC. Computed tomography (CT) is a very effective tool for detecting the tumour, carrying out a precise extension assessment and establishing a staging plan on which the treatment modalities depend. CT is the most widely used method for tumour staging. It is the basic examination used to study the locoregional extension of the tumour and to detect intrathoracic adenomegaly.^[29,30]



Figure 13: Axial section after injection of PDC in the mediastinal window: large proximal right tumour process with a dual parenchymal and mediastinal component, associated with adenomegaly of the right and left anterior mediastinal chains (arrows).

- Characteristics of the tumour

The majority of authors note that approximately 90-95% of CPCs present as proximal tumours, developed upstream of a segmental bronchus, with mediastinal extension.^[26,31] Much more rarely, they are peripheral tumours arising downstream of a segmental bronchus. In a series of 38 cases of CPC published in 1999, 39% of tumours were peripheral, but in this series the old anatomopathological classification was taken into account: atypical carcinoid tumours were included.^[10] When the tumour is peripheral, it is often subpleural, simulating an adenocarcinoma, but when it is associated with peribroncho-vascular thickening or hilar or mediastinal adenopathies, the diagnosis of CPC should be suggested.^[32] Tumours are irregularly contoured in central locations and lobulated in peripheral locations.^[33] Signs of retraction in the form of converging pulmonary vessels or pleural indentation are common rare. This is probably due to the scarcity of fibrous tissue in this histological type compared with non-small cell carcinomas.^[33] Areas of necrosis and calcifications are rare in CPC.^[33] A series of 33 cases of CPC published in 1984, probably including carcinoid tumours, reported intratumoral calcifications in 23% of cases, which is not

confirmed by more recent series.^[34] Areas of tumour necrosis are rarely observed, unlike other histological types of primary bronchopulmonary cancer, in particular carcinoma, squamous cell carcinoma.^[33,34]



Figure 14: Axial section through the parenchymal window: peripheral lingular tumour process with pleural.

- Involvement of lymph nodes attachments (arrow).

In primary bronchopulmonary carcinomas, lymph node involvement is a more important prognostic factor than tumour size. A hyper-trophied lymph node is considered suspicious of malignancy if its smallest axis is greater than or equal to 1 cm, bearing in mind that there are many false positives and false negatives. The only absolute CT criterion is peri-node infiltration, indicating capsular penetration.^[35] In CPC, lymph node involvement occurs in 0-30% of tumours less than 1 cm in size, 17-36% of tumours 11-20 mm in size and 19-45% of tumours 21-30 mm in size.^[36,37] Involvement of hilar or mediastinal lymph nodes is rarely absent. On chest X-ray, 80% of patients with CPC have hilar and/or mediastinal adenomegaly. On CT, hilar lymph node involvement is seen in 84% of cases and mediastinal lymph node involvement in 92% of cases. This proportion rises to 100% in autopsy series.^[32] Pearlberg et al. found, in a series of 37 patients with CPC, that 92% of tumours were accompanied by mediastinal adenomegaly, whether or not associated with hilar adenomegaly. Involvement is predominant in the right subcarinal and laterotracheal chains.^[18] Mediastino-hilar lymph node metastases in peripheral tumours are less frequent than in central forms. With the exception of adenomegaly adjacent to the initial tumour process, positron emission tomography (PET) is clearly superior to CT in the detection of metastatic adenopathies, by detecting their metabolic activity. It has a sensitivity of 100% and a specificity of 98%, compared with 70% and 94% respectively for CT.^[38,39] PET scans are used in the evaluation of tumour response to chemotherapy, particularly in the assessment and treatment of metastatic adenopathy characterisation of persistent adenopathy.^[40]

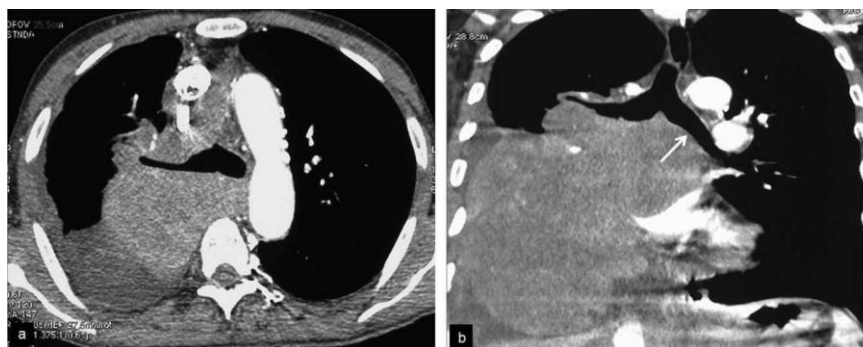


Figure 15: A: Axial section after injection of PDC in the mediastinal window: large proximal right mediastinopulmonary tumour process invading and narrowing the homolateral main and upper lobar bronchi; b: same patient, coronal reconstruction in the mediastinal window: the tumour invades the carina and contralateral stem bronchus (arrow).

- Mediastinal invasion

CT is the key examination for diagnosing invasion of mediastinal structures

It has a sensitivity of 50% and a specificity of 97% (airways and vascular structures). This performance is highly dependent on the CT criteria used.^[20] Invasion of the stem bronchus is considered if the bronchus is sheathed around its entire circumference by the tumour mass, if it is narrowed or if it is the site of endoluminal budding. In the majority of cases, CPC develops at the expense of the proximal bronchi, with peribronchial tumour extension. This extension is best analysed on coronal reconstructions with a multi-detector CT scanner. It appears as peribronchial thickening and corresponds to submucosal tumour infiltration on anatomopathological examination. This type of tumour extension with preservation of the lumen and internal bronchial wall, contrasting with a large tumour volume, is characteristic of CPC.^[32] This explains the large number of positive bronchial biopsies and cytologies, whereas bronchial endoluminal abnormalities are sometimes minimal or even absent.

The angioinvasive nature of CPC is one of its hallmarks. Vascular invasion is secondary either to direct invasion by the tumour process or by mediastino-hilar adenopathies.^[33] Invasion of an arterial structure is retained if it was encompassed over more than 180° of its circumference, stenotic, deformed or in the presence of an endoluminal bud. The superior vena cava was considered invaded when it was obstructed or the site of an endoluminal bud. Pearlberg et al. found in their study that 68% of patients have large vessel infiltration at the time of initial diagnosis.^[41] The most frequently invaded vascular structure is the pulmonary artery homolateral to the tumour process, followed by the thoracic aorta and superior vena cava. Invasion of the oesophagus, defined as complete envelopment, especially if there is overlying dilatation, is unusual in non-small cell lung carcinoma and relatively more frequent in CPC due to its large size.

Invasive and infiltrative. Cardiac invasion in CPC is not exceptional and is a poor prognostic factor correlated with early relapse and shorter life expectancy.^[33] Signs

of cardiac extension on CT are deforming compression of a cardiac cavity or an endocavitary tumour bud. In addition, CPC may extend intrapericardially or intra-left atrial via the pulmonary vein.^[33]

- Pleuroparenchymal signs

The frequency of ventilatory disorders downstream of the tumour process, as a consequence of bronchial obstruction, varies according to the authors, ranging from 7.3% in the series by Kazawa to 30% in the series by Chong et al.^[26,33] The rarity of ventilatory disorders in CPC, compared with other bronchopulmonary tumours, is due to the minimal impact of this tumour on the bronchial lumen.

Peritumoral lymphangitic diffusion is frequent in CPC, in the form of peritumoral micronodules, septal thickening or peribroncho-vascular thickening. In addition, in peripheral forms, diffusion under the bronchial mucosa is responsible for a thickened, rigid and deformed appearance of the bronchovascular walls. It is therefore necessary to include CPC in the differential diagnosis of peripheral pulmonary nodules, particularly when associated with peribronchovascular thickening. This thickening may appear in the form of nodules along the bronchial axis.^[32]

Pleural invasion in CPC occurs mainly by contiguity. It occurs in 33% to 39% of cases, depending on the series.^[34,41]

- Secondary extrathoracic locations

CPC is a rapidly progressive tumour, characterised by distant lymphatic and haematogenous metastases at the time of initial diagnosis, necessitating an exhaustive extension work-up. Metastatic disease, whether symptomatic or not, occurs in a large number of patients. The search for metastases should include brain imaging, abdominal imaging and bone scintigraphy. Bone scans should be carried out systematically, even in the absence of clinical symptoms. A CT scan can be used to assess the extent of the disease outside the thorax. When coupled with a PET scan, it provides better detection of secondary extra-thoracic locations. Analysis of various

studies shows a variable frequency of extensive forms at the time of initial diagnosis, ranging from 31% to 54% of cases.^[32,40] The most frequently reported site is the liver, followed by bone.^[33,41] PET is clearly superior to CT in the detection of adrenal and liver metastases. It is superior to bone scintigraphy in the detection of secondary bone locations and superior to bone marrow biopsy in the detection of bone marrow invasion. However, CT, and especially MRI, remain clearly superior to PET in detecting secondary cerebral locations.^[40] Several studies have shown that PET changes tumour staging from limited to extensive in 8-27% of patients.^[38,40] A study by Brink et al. involving 120 patients with CPC showed the superiority of PET in tumour staging compared with a battery of complementary investigations including thoraco-abdominal CT, bone scintigraphy and bone marrow biopsy.^[19] PET therefore reduces the number of investigations and saves time. Finally, this study proposes a strategy for staging CPCs that includes a combination of thoracic CT, brain MRI and whole-body FDG-PET.

2. Examinations for anatomopathological confirmation

Diagnosis of the disease is based on histological evidence.

This histological proof could be obtained by several means, the selection of which is best made by multidisciplinary RCP.^[35]

Bronchial fibroscopy with bronchial biopsy.

Puncture under CT for distal lesions of subpleural topography, Transparietal biopsy under CT has very good sensitivity (90%) and specificity (97%) and has been used to diagnose small cell lung carcinoma in 25% of cases.^[42]

- Mini-probe lung biopsy

Bronchial echo-endoscopy with trans-bronchial biopsy or surgical mediastino-scopy: These 2 methods make it possible to take lymph node samples when bronchial fibroscopy does not allow the diagnosis to be made.

- Thoracic surgery of a single suspicious lesion may be the mode of revelation of the disease.
- Surgery or biopsy of a distant metastasis if diagnosis is the only option.
- Biopsy puncture under CT has a high risk of pneumothorax (20%) but drainage is rarely necessary.^[43]

D. Anatomopathology

Anatomopathological study is a fundamental step in the management of bronchopulmonary cancers. In the case of any suspicious lesion, biopsy or cytological samples are used to make a positive diagnosis of primary lung cancer and, consequently, to rule out differential

diagnoses (metastasis, inflammatory lesion).

Anatomopathology also has a prognostic role, enabling differentiation between CBPC and CBNPC. Molecular biology studies of tumours can identify specific targets for treatment by targeted therapy.

Most primary bronchopulmonary cancers are carcinomas, with other histological types (lymphomas, sarcomas) accounting for less than 1% of cases.^[30]

The latest anatomopathological classification^[31] is essentially based on the study of tumour characteristics using light microscopy. It also uses immunohistochemistry.

• Contribution of anatomopathology

In the case of mediastino-pulmonary CBPC, the anatomopathological diagnosis is most often made by fibroscopy, more rarely by mediastinoscopy or peripheral lymph node biopsy. In the absence of a tumour bud, bronchial endoscopy must include multiple staged biopsies and be combined with cytological sampling.

An exploratory thoracotomy or video-surgery for diagnostic purposes is sometimes necessary if the above examinations fail. An extemporaneous examination is desirable to ensure that samples have been taken from the tumour zone.

Anatomopathological and cytological analysis is also of prognostic interest and will also help to clarify the effects on the tumour of any initial chemotherapy or radiotherapy.

2. Macroscopic forms

CBPC is a proximal, hilar tumour with mediastinopulmonary extension. Much more rarely it takes the form of a peripheral pulmonary nodule.

Hilar CBPC: develops from the mucosa of the bronchial trunks and spreads to the rest of the body along the bronchial axes in a hiliform fashion, infiltrating the walls with narrowing irregular lumina. It extends to the lymph nodes, which explains the enlargement of the bronchial spurs and the extrinsic compression seen on bronchial endoscopy.

Peripheral CBPC: this is the nodular variant of CBPC. It tends to fill the spaces without causing septal lesions. On section, the tumours are whitish and very friable.

4. Microscopic and immunohistochemical aspects

CBPCs are defined as tumours that develop from neuroendocrine cells that are normally dispersed in the bronchial mucosa.

Macroscopically, the tumours are often proximal, perihilar and frequently involve lymph nodes.

Histological, histochemical, immunohistochemical and ultrastructural criteria for CBPC as defined by the WHO (2004).

- Endocrinoïd architecture: nests, spans, palisading clumps, rosette formation or in the form of sheets
- Narrow cytoplasm
- Finely granular chromatin
- Nucleoli not visible
- High mitotic index
- Positive Grimelius stain
- Immunohistochemistry: chromogranin +, synaptophysin +, CD56 + and TTF1+.
- Electron microscopy: intracytoplasmic neuroendocrine granules.

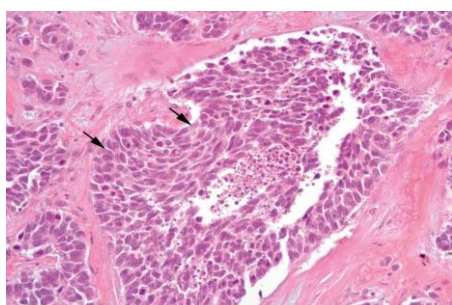


Figure 16: Poorly differentiated neuroendocrine carcinoma (malignant epithelial tumour).

5. Place of small cell lung cancer in the WHO classification (1999)

CBPCs must not be confused with other neuroendocrine tumours: large cell neuroendocrine carcinomas (NCECCs) or typical and atypical carcinoids.

Simplified WHO Classification

1. Squamous cell carcinoma

2. Small cell carcinoma

- Variant: CPC composite: CPC + NSCLC.

3. Adenocarcinoma

4. Large cell carcinoma

- Variant: Large cell neuroendocrine carcinoma (LCNEC): Endocrinoïd architecture, clear chromatin, positive neuroendocrine markers.
- Variant: CNEGC composite: CNEGC + adenocarcinoma or squamous cell carcinoma. A NSCLC with a CPC component is considered to be a CPC.

5. Carcinoid tumours

- Typical carcinoid: with mitoses of less than 2/10 fields ($G=\times 400$), no necrosis, no pleomorphism of nuclei (5 to 15% of metastases lymph nodes).
- Atypical carcinoid: with mitoses greater than 2/10 and less than 10/10 fields ($G=400$), focal necrosis, pleomorphism of nuclei (40-50% lymph node

metastases, 20% distant metastases).

E. Anatomoclinical stages

Unlike non-small cell lung cancer (NSCLC), the TNM classification is generally used, as surgery is not used in the treatment of NSCLC.

A distinction is made between two forms: those limited to the thorax (which can benefit from local treatment, radiotherapy) and other forms known as disseminated (where local treatment is of no use). This classification is based on whether or not radiotherapy is technically feasible.

- Stage limited to the thorax (1/3 of cases): Tumour confined to the thorax with adenopathy hilar homolateral, adenopathies mediastinal homo- or contralateral mediastinal adenopathies homo- or contralateral lesions. All lesions can be treated in a single course of radiotherapy. Treatment is based on a combination of radiotherapy and chemotherapy.

- Disseminated forms (2/3 of cases): Bilateral hilar or pulmonary lesions, invasion of the pleura and/or metastases. The treatment is based on palliative chemotherapy.

IV. Assessment of extension

The balance sheet must include

- A clinical examination,
- Biological work-up (ionogram, liver work-up, LDH, NFP, coagulation work-up),
- Bronchial fibroscopy,
- A chest and abdominal CT scan, an MRI or brain scan and a bone scan,
- A PET scan should be carried out when local treatment is envisaged.
- OPTION: spinal cord exploration if all these sites are negative.
- The work-up can be stopped as soon as the first metastatic site is identified.

The order of investigations will be determined by the clinical situation, the difficulty of the procedure, the ease of access to additional tests and the frequency of metastatic sites (marrow, brain, liver, bone, etc.). On the other hand, the work-up may be exhaustive if there is a possibility of inclusion in a clinical trial.

- When thoracic radiotherapy is being considered, a respiratory assessment combining EFR and DLCO is recommended.

It is not necessary to measure a tumour marker for the diagnosis, prognosis or follow-up of the patient. Geriatric assessment: determination of the G8 score is recommended, although there is currently no validated geriatric score for thoracic oncology. A geriatric assessment may be suggested as an aid to patient management.

V. Prognostic factors

Favourable pre-therapeutic prognostic factors are known and are still stage I to III, Performans Status (PS = 0 or PS = 1) and female gender.

The TNM classification plays an important role in the choice of appropriate treatment and post-treatment prognosis, as does a performance index (WHO PS). Depending on the population studied (CBPC operated or not), other factors have been summarised in order to complete the prediction of prognosis.^[44]

For the 7th edition of the TNM classification, prognostic factors were studied on the basis of IASLC data. Certain factors were proposed as having a very important prognostic role, and are summarised as follows: the patient's clinical stage (localised or diffuse), the performance status index (WHO PS), age at onset, male sex, and in certain cases, histological type, SUVmax on PET and certain biological parameters: in particular, natraemia and albuminemia.^[45]

Table 5: Prognostic factors for lung cancer identified by IASLC by level of evidence.^[45]

Variable	CPC
Clinical stage	++++
Performance index Age	+++
Male Calcaemia	++
Albuminemia	++
Natrema	-
Leukocytosis	+
Haemoglobinaemia	+
	-
	-

VI. Therapeutic management

A. TREATMENT OF STAGE IV CBPC

Treatment of diffuse CBPC is essentially based on chemotherapy and immunotherapy. It is palliative, and only in exceptional cases does it allow survival of more than 2 years. Without treatment, survival is short (3 to 6 months); with treatment, the median life expectancy is around 10-12 months, with a marked improvement in quality of life.

1. First-line chemotherapy

The IMPower-133 (Carboplatin-Etoposide +/- Atezolizumab) and CASPIAN (platinum- Etoposide +/- durvalumab) trials demonstrated a benefit in terms of overall survival and progression-free survival of adding immunotherapy to standard chemotherapy in extensive small cell cancer.^[42,43]

After a partial or complete response, the value of continuing chemotherapy beyond 6 cycles has not been demonstrated.

Recommendations - 1st-line chemotherapy / Stage IV: - carboplatin (AUC 5, Calvert1 formula) D1, etoposide (100mg/m²) D1, D2, D3, and atezolizumab (1200mg) D1

(IV) every 3 weeks, 4 cycles then maintenance with atezolizumab (1200mg) every 3 weeks, if PS 0 or 1 and in a post-ATU setting at the time of writing.

- Platinum salt (carboplatin AUC 5 -6 or cisplatin 75 - 80 mg/m²) D1, etoposide (80- 100mg/m²) D1, D2, D3 and durvalumab (1500 mg) D1 (IV) every 3 weeks, 4 cycles then maintenance with durvalumab (1500 mg) every 4 weeks, if PS 0 or 1 (as part of a cohort ATU).
- Cisplatin 80 to 100 mg/m² D1 OR carboplatin AUC 5 (Calvert formula) and etoposide 80 to 120 mg/m² D1, D2, D3 (IV); every 3 weeks, 4 to 6 cycles. NB: Do not exceed 400mg/m² of carboplatin.

2. Second-line and subsequent chemotherapy

Patients who relapse after an initial response are classified as

- "Highly sensitive" if re-evolution occurs more than 6 months after stopping first- line chemotherapy,
- "between 3 and 6 months,
- "resistant" in the event of relapse before 3 months,
- or "refractory" in the event of progression under treatment.

These patients receive second-line chemotherapy, which depends on the patient's condition, response to the first line and co-morbidities.^[46,47]

Recently, Lurbinectedine, at a dose of 3.2 mg/m² IV every 3 weeks, has enabled second-line patients to achieve a median recurrence-free survival of 3.9 months and a median overall survival of 9.3 months.

2.1. In "highly sensitive" and "sensitive" patients
Resumption of the cisplatin or carboplatin and etoposide regimen. Topotecan has been shown to be effective in patients for whom resumption of etoposide and platinum-based chemotherapy is not appropriate. CAV and carboplatin-paclitaxel combinations can also be used.

2.2. In "resistant" patients

There is no standard treatment. Possible options are topotecan or CAV. Recommendations

- 2nd-line chemotherapy / Stage IV

Sensitive and highly sensitive patients

- Cisplatin 80 to 100 mg/m² D1 (must depend on the dose already received in first line) or carboplatin (AUC 5) (Calvert formula) and etoposide 80 to 100 mg/m² D1, D2, D3 (IV).
- If cisplatin-etoposide not appropriate
- Topotecan 1.5 mg/m² D1 to D5 every 21 days or 3 to 4 mg/m² D1, 8, 15 and repeat at D28
- Topotecan 2.3 mg/m² D1 to D5 per os every 21 days
- Resistant patients
- Topotecan 1.5 mg/m² D1 to 5 every 21 days or 3 to 4 mg/m² D1, 8, 15 repeat at D28
- Topotecan orally 2.3 mg/m² D1 to 5 every 21 days

- CAV (cyclophosphamide 1000 mg/m², adriamycin 50 mg/m², vincristine 1.4 mg/m² not to exceed 2 mg)

OPTION: carboplatin and paclitaxel after discussion at a multidisciplinary consultation meeting.

OPTION: Lurbinectedine (3.2mg/m² IV every 3 weeks) as monotherapy and as second-line treatment or beyond under a nominative ATU.

2.3. In "refractory" patients

If there is no standard treatment, treatment should be discussed at a multidisciplinary consultation meeting.

3. Supportive care

The use of G-CSF from the first course of chemotherapy is optional for primary prophylaxis (prevention of leuko-neutropenia from the first course) and recommended for secondary prophylaxis (prevention of leuko-neutropenia for courses following neutropenia). In the case of risk factors for neutropenia (poor PS (> 2), hypo-albuminemia, high age, bone marrow invasion, history of treated cancer, lymphocytes < 0.7 giga/l), the use of G-CSF as primary prophylaxis is recommended. The use of an erythropoiesis-stimulating agent (ESA) is useful for improving patients' quality of life as soon as haemoglobin levels fall to 10g or less, with a target level of 12g. Treatment should be suspended or modified above 12g. The use of an ESA should be reserved for patients receiving chemotherapy.

B. TREATMENT OF STAGE I TO III CBPC

1. Radiotherapy and chemotherapy treatment

Treatment of stage I to III small cell cancer is based on a combination of systemic chemotherapy and thoracic radiotherapy.

Only patients with stage I to III cancer can expect a survival of 15 to 30 years.

25% at 5 years. Treatment should therefore be curative, particularly in the case of small tumour masses.^[48]

The recommended treatment consists of a combination of 4 courses of chemotherapy and thoracic radiotherapy delivering a minimum of 60 Grays with conventional fractionation (or dose equivalent).

The recommended treatment is a concomitant combination of radiotherapy and chemotherapy [49]. in elderly patients and/or patients with a PS > 2, a sequential combination is permissible.

1.1. Chemotherapy

Chemotherapy is a combination of Cisplatin and Etoposide.

It is possible to reduce doses by 20% for cycles of chemotherapy delivered from concomitantly with radiotherapy.

Recommendation: Chemotherapy for stages I to III cisplatin 80 to 100 mg/m² D1 and etoposide 80 to 120 mg/m², IV, D1 to 3 every 21 days (carboplatin AUC 5, Calvert formula, if contraindication to cisplatin) - 4 cycles.

1.2. Thoracic radiotherapy

Radiotherapy is started no later than the 6th week of the treatment programme: single- or dual-fraction radiotherapy delivering a biological dose equivalent to at least 60 Gy.^[50] A recent phase III trial showed no difference in terms of response, progression-free survival and overall survival between radiotherapy started during the 1st cycle of chemotherapy and that started during the 3rd cycle.^[51] Conformal radiotherapy must be used. The quality criteria for radiotherapy were updated in 2016.^[52]

2. Prophylactic cerebral irradiation

Following the assessment, patients under 75 years of age, PS 0 to 2, and undergoing treatment should benefit from early prophylactic treatment (ICP).^[53] Dose: 25 Gy in 10 fractions (Option: 30 Gy in 15 fractions of 2 Gy).

If there is a complete response after cerebral radiotherapy, this should be discussed on a case-by-case basis depending on the patient's clinical condition. It is recommended that chemotherapy should not be given at the same time as cerebral radiotherapy.

Partial response patients may benefit from PCI.

Relapses will be treated as described in the previous paragraph.

3. Surgical treatment

Exceptional very localised forms of small cell cancer without mediastinal extension proven by mediastinoscopy or other techniques may benefit from first-line surgical resection.

Surgery to remove the entire tumour (minimum lobectomy), including complete lymph node dissection. Complete lymphadenectomy including all lymph node tissue is recommended. It is recommended that the operation be carried out by an experienced specialist surgeon in a hospital that can cope with complicated post-operative after-effects. The decision must be taken in a multidisciplinary consultation meeting.

Surgery should be followed by chemotherapy^[50] and thoracic radiotherapy should be discussed in the PCR, followed by PCI as for forms limited to the thorax.

VII. Monitoring

A. Monitoring objectives^[34]

- Early detection of local or distant relapses and recurrences.
- Combating smoking and detecting second cancers early.
- Detecting late side effects linked to chemotherapy

treatment in particular.

- Organising comfort care. Ensuring patients' quality of life.
- To provide social support and help with professional reintegration when this is possible.

B. PROCEDURES^[18]

Follow-up of patients who have received curative treatment

Chest CT scan postoperatively or after adjuvant treatment, to be used as a reference examination.

- Comprehensive clinical examination, full biological work-up and standard X-rays every three months.
- Upper thoracic and abdominal CT (liver and adrenals) every six months for two years, then at intervals for patients with localised non-metastatic CBPC treated as part of a curative strategy.
- Bone scans and brain CT scans are not prescribed for asymptomatic patients.
- Bronchial fibroscopy every six months, with biopsies if lesions are suspicious, for patients diagnosed with a relapse or recurrence who may benefit from a new treatment plan (stage I or II operated on by lobectomy and likely to benefit from pneumonectomy in the event of homolateral recurrence).
- FDG-PET: no place in monitoring patients undergoing surgery.
- No interest in measuring tumour markers.
- Monitoring becomes semi-annual from age 2 and then annual from age 5 Follow-up of patients who have received palliative treatment:
- Clinical examination every three months.
- Chest CT scan with upper abdominal sections +/- bone scan and other targeted examinations depending on initial targets every three or six months. Examinations adapted to co-morbidities.

VIII. Prevention

Prevention of PBCC undoubtedly involves the fight against smoking. It should be pointed out here that the benefits of smoking cessation exist whatever the age of the smoker, and are all the greater the earlier the cessation. The risk of developing CBPC is reduced by 40- 90% in the 10 years following cessation of smoking, and the efforts made by addiction centres should be encouraged for their contribution to the fight against tobacco in particular, but also against alcoholism and cannabism, which are among the risk factors for CBPC.

Primary prevention: is based on a significant increase in sales tax and the selling price of cigarettes, a ban on sales to minors under the age of 16, strict enforcement of the ban on smoking in public places, and a ban on advertising all types of cigarettes. Not to mention protective measures in high-risk professions (handling asbestos).^[45]

Secondary prevention: The aim is to detect pre-

neoplastic lesions and patients who are still asymptomatic at an early stage. Assistance be provided before or at the time of a CT scan of the thorax, carried out as part of screening for CBPC or as part of the initial cancer assessment.

Tertiary prevention: aimed directly at patients to help them stop smoking; current recommendations for the management of small-cell lung cancer place smoking cessation at the top of the agenda, whatever the stage (advanced or not).

CONCLUSION

Small cell lung cancer is a public health burden. Its incidence will continue to rise in our country, given current smoking habits among younger and younger people, but it remains a cancer that can be largely prevented by a combination of anti-smoking measures and exposure in the workplace.

The diagnosis of small cell lung cancer is based on a combination of suggestive clinical symptoms, suspicious chest imaging and histological evidence. Diagnosis generally takes a long time, as patients often consult a specialist at a late stage, which is why it is important not to overlook any persistent respiratory symptoms or those that do not respond to the usual treatments, especially in smokers or ex-smokers, and to carry out an exhaustive pleuropulmonary examination and a frontal and lateral chest X-ray if there is any doubt. The vast majority of patients present with a diffuse stage from the outset and require multidisciplinary management.

Systemic chemotherapy is the main treatment for disseminated forms; the combination of a platinum salt and etoposide is the standard first-line treatment for metastatic forms, with a response rate of 35% in our series.

Despite the generally poor prognosis, undeniable progress has been made in standardising its management, with better coding of treatment, and further research using targeted therapy offers hope against this burden.

On the basis of the results of our study and in the light of the literature review, we feel it is essential to

- Implement a genuine policy to combat cancer in general, and primary bronchopulmonary cancer in particular, either by combating risk factors, especially smoking, or by screening for cancer at an early stage.
- Providing ongoing training for medical and paramedical staff, particularly in oncology departments in Morocco.
- The management of patients with primary bronchopulmonary cancer can only be improved by
 - Screening and early diagnosis.
 - A therapeutic decision made by multidisciplinary consultation meetings.
- Reduce prices to facilitate access to antimitotics and

make them available to all patients.

- Improving the quality of supportive care by training staff specialising in this area.
- Primary prevention through the fight against smoking.
- Set up a genuine regional and national cancer registry to provide a simple way of assessing the epidemiological profile of the disease. bronchopulmonary cancer.

REFERENCE

1. Ferlay J et al. <<Cancer incidence and mortality patterns in Europe: estimates for 40 countries over 2012>>. European journal of cancer, 2013; 49(6): 1374-1403.
2. HYBIAK Coraline these N° 2015-105, FACULTE OF MEDICINE OF AMIENS <<<Evaluation of chemotherapy in 2nd line small cell lung cancer between 2004 and 2014 in Picardie>>>.
3. Govindan R. et al. <<Changes in the epidemiology of small cell lung cancer in the United States over the past 30 years: an analysis of the surveillance, epidemiology, and final outcomes database>> Journal of clinical oncology, 2006; 24(28): 4539-4544.
4. Nathan R Foster et al. <<<Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage SCLC: findings on the basis of North Central Cancer Treatment>>> Group trials. Cancer., 2011; 117: 1262-1271.
5. William D Travis & al: <<<The 2015 World Health Organization classification of lung tumours: impact of genetic, clinical and radiological advances since the 2004 classification>>>Journal of Thoracic Oncology, 2015; 10(9): 1243-1260.
6. Pesch B. et al. <<Cigarette smoking and lung cancer & relative risk estimates for the major histological types from a pooled analysis of case-control studies>>.
7. International Agency for Research on Cancer: <<<World cancer incidence and mortality 2012>>>. Website: www.globocan.iarc.fr
8. E. Quoix et al: Epidemiology of primary bronchial cancer: classic aspects and new developments. Revue des Maladies Respiratoires, Oct 2011; 28(8): 1048-1058.
9. M. Locatelli-Sanchez, S. Couraud, P.-J. Souquet: Epidemiology of bronchial cancer: current evidence. Journal of Respiratory Diseases News, Nov, 2015; 7(4): 285-289.
10. F Chermiti Ben Abdallah, et al. Revue des maladies respiratoire, 2014; 31(3): 214-220.
11. Haut- commissariat au plan <<<Statistical directory of the Greater Casablanca region>>>.website: www.hcp.ma .
12. Mohammed A. Tazi et al <<Prevalence of the main cardiovascular risk factors in Morocco: Result of a National Survey>>, 2000. Journal of Hypertension, 2003; 21: 897-903.
13. J. Mazières: <<Epidemiology of bronchial cancer: from general considerations to the molecular aspect>>. Revue des Maladies Respiratoires Actualités, 2014; 6: 305- 310.
14. E. Quoix, E. Lemarié, <<<Epidemiology of primary bronchial cancer: classical aspects and novelties>>>, Revue des Maladies Respiratoires, 2011; 28: 1048- 1058.
15. MILLERON B. <<<Cancer bronchique:épidémiologie et facteurs étiologiques du cancer bronchique.>>Paris, Laboratoire Sandoz, 1995; 258p
16. LIGUE NATIONALE CONTRE LE CANCER :BRK005 - September– Réalisation graphics site :www.ligue-cancer.net, 2009.
17. F. Barlesi, P. Tomasini, C. Fournier L. Greillier and al. <<<Clinical presentation and diagnosis of bronchial cancer>>. Revue des Maladies Respiratoires Actualités, 2014; 6: 341-345.
18. J. mazières et al.<<< Primary and secondary lung tumours>>> . faculté de medecine de toulouse item 157 site: www.medecine.upstlse.fr.
19. Mellas N EL-ACHHAN D. : <<< Small cell lung cancer CHU Fes>>>>.thesis, 210/17.
20. S. Bellefqih, et al: Mise au point <<<syndrome cave supérieur d'origine malignes>>. Department of radiotherapy, national institute of oncology, Mohammed-V Souissi university, journal of clinical pulmonology, 2014.
21. F. Loudadsi, M. Elbiaze, A. Bakhatar, N. Yassine et al/ :<<< Primary bronchial carcinomas>>>. Revue des Maladies Respiratoires, part 2, 2006; 23(4): 115.
22. BAMBA Salia DIAKITE Mahamane Talphi: <<<Etude épidémiologique du cancer broncho-pulmonaire dans l'Est algérien>>. Université des Frères Mentouri Constantine Faculté des Sciences de la Nature et de la Vie, 2015.
23. F. Goldwasser: <<<Bone metastases during bronchopulmonary cancers>>>. Revue des Maladies Respiratoires Actualités, 2013; 5: 538-546.
24. A. Roche <<< Brain metastases of bronchial cancers>>. Revue des Maladies Respiratoires Actualités, 2014; 6: 169-172.
25. KAPTUE Y. :<<< Problématique du cancer broncho-pulmonaire primitif dans le service de pneumologie de l'hôpital du point G>>> .thèse de médecine, 2005.faculté de médecine de Bamako. Mali.
26. Chong S, Lee KS, Chung MJ, et al. Neuroendocrine tumors of the lung: clinical, pathologic, and imaging finding. Radiographics, 2006; 26: 41-58.
27. Lassen U, Osterlind K, Hansen M, et al. Long term survival in small-cell lung cancer.
28. Post-treatment characteristics in patients surviving 5 to 18+ years: an ana-lysis of 1714 consecutive patients. J Clin Oncol, 1995; 13: 1215-20.
29. Earnest F, Ryu JH, Miller GM, et al. Suspected non-small cell lung cancer: incidence of occult brain and skeletal metastases and effectiveness of imaging for detection-pilot study. Radio-logy, 1999; 211:

- 137-45.
30. Martini N, Heelan R, Westcott J, et al. Comparative merits of conventional, computed tomographic, and magnetic resonance imaging in assessing mediastinal involvement in surgically confirmed lung carcinoma. *J Thorac Cardiovasc Surg*, 1985; 90: 639-48.
 31. Hauber HP, Bohuslavizki KH, Lund CH, et al. Positron emission tomography in the staging of small-cell lung cancer: a preliminary study. *Chest*, 2001; 119: 950-4.
 32. Forster BB, Müller NL, Miller RR, et al. Neuroendocrine carcinoma of the lung: clinical, radiologic, and pathologic correlation. *Radiology*, 1989; 170: 441-5.
 33. Hashimoto M, Heianna J, Okane K, et al. Small cell carcinoma of the lung: CT findings of parenchymal lesions. *Radiat Med.*, 1999; 17: 417-21.
 34. Kazawa N, Kitaichi M, Hiraoka M, et al. Small cell lung carcinoma: eight types of extension and spread on computed tomography. *J Comput Assist Tomogr.*, 2006; 30: 653-61.
 35. Whitley NO, Fuks JZ, McCrea ES, et al. Computed tomography of the chest in small cell lung cancer: potential new prognostic signs. *AJR Am J Roentgenol*, 1984; 142: 885-92.
 36. Frija J, Bourrier P, Zagdanski AM, et al. Diagnosis of a tumour node. *J Radiol*, 2005; 86: 113-25.
 37. Lemarié E, et al. Radiological screening for bronchial cancer. *Rev Mal Respir.*, 2005; 22: 8S9-18S.
 38. Chen MY, Chiles C, Choplin RH, et al. Bronchogenic carcinoma: a survey of CT protocols for staging disease. *Acad Radiol.*, 1997; 4: 687-92.
 39. Brink I, Schumacher M, Mix M, et al. Impact of [18 F] FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging.*, 2004; 31: 1614-20.
 40. Ohtsuka T, Nomori H, Ebihara A, et al. FDG-PET imaging for lymph node staging and pathologic tumor response after neo-adjuvant treatment of non-small cell lung cancer. *Ann Thorac Cardiovasc Surg.*, 2006; 12: 89-94.
 41. Kut V, Spies W, Spies S, et al. Staging and monitoring of small cell lung cancer using [18 F] fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). *Am J Clin Oncol.*, 2007; 30: 45-50.
 42. Pearlberg JL, Sandler MA, Lewis JW, et al. Small-cell bronchogenic carcinoma: CT evaluation. *AJR Am J Roentgenol*, 1988; 150: 265-8.
 43. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med.*, 2018 Sep 25.
 44. Slotman BJ, van Tinteren H, Praag JO, Kneijens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet.*, 2015 Jan 3; 385(9962): 36-42.
 45. Ouarssani A. Ait ali ben alla S <<<PRIMITIVE BRONCHIAL CANCER: about 228 cases Experience of the pneumology department of the Moulay Ismail military hospital in Meknes>>>Thesis reference 953 year, 2016.
 46. M. Underner, G. Peiffer, J. Perriot:<<< Management of smoking>>>. *Revue des Maladies Respiratoires Actualités*, 2014; 6: 320-334.
 47. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol.*, 1999 Feb; 17(2): 658-67.
 48. Song Z, Shao L, Lin B, Zhang Y. Single-agent chemotherapy compared with combination chemotherapy as second-line treatment in extensive-stage small cell lung cancer: a retrospective analysis. *Clin Transl Oncol.*, 2013 Oct; 15(10): 843-8.
 49. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.*, 2013 May; 143(5 Suppl): e400S-19S.
 50. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med.*, 1992 Dec 3; 327(23): 1618-24.
 51. Turrisi AT, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med.*, 1999 Jan 28; 340(4): 265-71.
 52. Sun J-M, Ahn YC, Choi EK, Ahn M-J, Ahn JS, Lee S-H, et al. Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer. *Ann Oncol.*, 2013 Aug; 24(8): 2088-92.
 53. Giraud P, Lacornerie T, Mornex F. [Radiotherapy for primary lung carcinoma]. *Cancer Radiother.*, 2016 Sep; 20 Suppl: S147-156.