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2014 update on non-small cell lung cancer (excluding diagnosis)

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Abstract  Lung cancer (LC) is a major public health issue because of its frequency, but especially because of the severity of this disease. The epidemiology has changed with an increased incidence in non-smokers and women. The ATS/ERS/IASLC classification of adenocarcinomas was modified in 2011, and they are now the most frequent histological subtype. More than half the cases of LC are diagnosed at the metastatic stage. Biopsies must provide tissue samples that are quantitatively large enough and of a good enough quality for diagnosis and to search for biomarkers. When the cancer seems to be localized, precise staging must be obtained. Treatment is based on the TNM classification. In localized stages, lobectomy associated with lymph node dissection is the standard therapy. Intraoperative chemotherapy improves survival in case of lymph node infiltration. Stereotactic radiation therapy and radiofrequency can be considered as specific cases. In cases with local progression, treatment is more controversial. In the presence of metastases, the goal is not a cure, but improving survival and quality of life. Numerous advances have been made with personalized treatment, (in particular in relation to the histological type and oncogenic addiction in tumors, access to new drugs, and improved

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Epidemiology of non-small cell lung carcinoma (NSCLC)

With 39,495 cases diagnosed in 2012 in France and 29,949 deaths [1], lung cancer (LC) remains a major public health problem because of its frequency, but especially the severity of the disease. LC is the cause of the greatest number of cancer deaths per year in France (20%) [1]. While mortality from this disease is decreasing in men, it continues to increase in women [2]. In the last ten years, the epidemiology has changed [3]. The incidence of this disease is increasing in non-smokers (11% of LC in France) and in women. Ten years ago squamous cell carcinoma was more frequent than adenocarcinoma (39% vs 29%). Today, the distribution has changed with 46% of adenocarcinomas, 26% squamous cell carcinomas 10% large cell carcinomas and 13% small cell carcinomas. The ATS/ERS/IASLC classification of adenocarcinomas was modified in 2011 [4], and now includes four new entities: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant non-mucinous adenocarcinoma, and invasive mucinous adenocarcinoma. Because of the strong anatomoradiological correlation, this new classification also has implications for the radiologist [5]. This classification, which was developed for biopsy samples, has been adapted to small tissue specimens [6].

Cytological and biopsy tissue specimens for diagnosis

More than half LC is diagnosed at the metastatic stage [3]. In this case, the physician performing the biopsy, whether s/he is an endoscopist or a radiologist, s/he must obtain specimens that are quantitatively large enough and qualitatively good enough to obtain a precise diagnosis and identify biomarkers to help determine the treatment strategy. Today, the histological type and the molecular profile are determining factors of the therapeutic strategy. The IASLC recommends searching for an EGFR mutation and an ALK translocation [7] in all metastatic adenocarcinomas, whatever the clinical features, because there are targeted therapies for these two molecular anomalies that have obtained French marketing (AMM) approval. Since 2006, INCa has organized molecular genetics platforms to determine molecular profile of tumors and identify new therapeutic targets to help develop targeted treatments and make personalized medicine a reality for patients. Biomarqueurs France is a database that includes all molecular analyses performed in INCa approved platforms since 2012. In one year, 10,000 LC have been tested [8]. It is interesting to note that a team from Grenoble [9] has shown that the reliability of transthoracic needle biopsies to determine the histological subtype and the molecular profile of adenocarcinomas has significantly improved in just two years (72% of the biopsy specimens were adequate for molecular analyses during the first period vs 92% during the second period). The number as well as the length of the biopsies has increased. Radiologists have improved their practices along with pathologists and biologists to adapt to new guidelines. New techniques, such as radial probe endoscopic ultrasound (EBUS) have also been developed in bronchoscopy to improve results [10] and electromagnetic navigation [11] has helped improve biopsy specimens, especially of peripheral lesions. However, very few centers have these technologies.

Initial evaluation

When cancer seems to be localized, the challenges are elsewhere. The histological subtype and the molecular profile are not needed, because they do not affect the therapeutic strategy. On the other hand, disease extension should be precisely determined. Contrast-enhanced thoracic CT Scan and PET scan are recommended by the INCa [12] and the ACCP [13]. Brain imaging should be systematically performed according to the INCa (CT scan or MRI) and the “guide to good practices of imaging tests” (gbu.radiologie.fr) and is recommended in stage III or IV disease by the ACCP (MRI). To obtain reliable mediastinal staging, in the absence of distant metastases, imaging should be associated with mini-invasive procedures (EBUS, Endoscopic ultrasound (EUS) or mediastinoscopy) in the following cases [12, 13]: mediastinal lymph nodes ≥ 10 mm, high tracer uptake on PET scan whatever the size of the lymph node, the presence of suspicious hilar lymph nodes or central location of the tumor. Results of EUS staging seem to be better than mediastinoscopy [14], which is why it is now recommended as the first imaging test [13]. The effectiveness of whole body MRI or combined with PET scan is being studied to evaluate disease extension in LC [15, 16].

Advances in treatment strategies

Treatment depends on the TNM stage. A lobectomy and lymph node dissection is the standard treatment for stages I and II. Video assisted surgical techniques are being developed. Infra-lobar resections, in particular segmentectomies can be discussed [13] in certain cases: tumors less than 2 cm predominantly ground glass opacity-type, or pulmonary function preventing resection of an entire lobe. Approximately 25% of patients with local stage LC have a major surgical contraindication. Stereotactic radiotherapy is an option if the tumor is less than 5 cm [13]. Radiofrequency can also be considered if the tumor is less than 3 cm but there...
are fewer results in the literature [13]. Results of local disease control (83%–89% vs 58–68% at 5 years), overall survival (38–85% vs 47–74% at 3 years) and the rate of complications (3–38% vs 33–100%) seem to be better with stereotactic radiotherapy than with radiofrequency [17]. However, in the absence of randomized trials, these results should be taken with caution. Two phase III clinical trials (ACOSOG Z4099 and RTOG 1021 trial) comparing partial resection to stereotactic radiotherapy in high risk patients are ongoing. The best patient postoperative follow-up protocol must be determined. The IFCT phase III study comparing a protocol of a clinical examination associated with thoracic radiography to a clinical examination and thoracic and upper abdominal CT Scan and pulmonary fibroscopy in case of a squamous cell tumor, including 1775 patients operated for LC, should provide a response.

Platinum-based adjuvant chemotherapy is indicated in stage II surgical patients [13]. Neoadjuvant chemotherapy is an option.

Treatment of stages IIIA-N2 is the subject of debate. The ACCP recommends combined radiochemotherapy [13]. Surgery as first-line treatment followed by adjuvant chemotherapy is not recommended [13]. Chemotherapy as first-line treatment followed by surgery can be considered if the N2 is small [13]. Adjuvant chemotherapy may be indicated in patients with a tumor in whom mediastinal invasion is not known before surgery (cN0 or N1 and pN2). ESMO [18] guidelines are slightly different. If the tumor is resectable, radiochemotherapy and neoadjuvant chemotherapy followed by surgery are two options.

Radiochemotherapy is indicated in stage IIIB tumors, if the size of the tumor permits curative radiation.

Treatment of stage IV tumors is supportive, except for rare cases of resectable pulmonary tumors with pulmonary (M1a), adrenal or cerebral metastases alone. The goal is not a cure but to improve patient survival and quality of life. The benefits of chemotherapy are real and the meta-analysis published in 1995 [19] showed better results with combination platinum and a third generation drug compared to supportive care alone. Progress has been made in the last ten years.

Today the choice of chemotherapy can be adapted to tumor histology (for example, by limiting pemetrexed to non-predominantly squamous cell NSCLC). Bevacizumab, the monoclonal antibody acting on VEGF, improves progression-free survival and probably overall survival [20]. It can be combined with chemotherapy in case of non-squamous NSCLC. Indeed, during the development of bevacizumab, cases of mortality from hemoptysis were described in phase II studies in patients with squamous cell carcinomas, which is why this histological type has been excluded from this option. Nevertheless, the risk of hemoptysis persists and predictive radiological criteria have been developed [21]. The evaluation of risk by a radiologist is therefore important.

First-line therapy includes 4 to 6 cycles of chemotherapy. Before the notion of maintenance therapy was introduced, there was a pause in treatment then second line treatment was begun at tumoral progression. Today this approach has been validated because maintenance therapy [22] has been shown to improve progression-free survival and overall survival. This may include real maintenance therapy or continuation maintenance (the treatment used for induction is maintained when platinum therapy is stopped until progression or toxicity) or switch maintenance (induction chemotherapy is stopped and another type of treatment is begun). The predictive factors of effective maintenance therapy are still a subject of debate. Response to induction therapy may play a role. This hypothesis is being tested in France in a phase III trial (IFCT-GFPC 1101).

New chemotherapies, the association with bevacizumab and maintenance therapy has improved median progression-free survival (approximately 7 months) and overall survival can reach up to 17 months [23].

Major progress has been made in the management of metastatic NSCLC with the identification of oncogenic addictions [24]. Tyrosine kinase inhibitors EGFR (ITK-EGFR) were initially developed in a non-selected population. Clinical criteria of response to ITK-EGFR were rapidly identified (female gender, non-smokers, Asian and adenocarcinoma). EGFR gene mutations were found to be the best predictive factor of response to treatment. Today EGFR gene mutations are systematically searched for in metastatic adenocarcinomas. In the presence of an activating mutation (approximately 10% of the adenocarcinomas in France), the patient can receive ITK-EGFR as first-line therapy. Progression-free survival was better than with chemotherapy and reached 9 months in one Caucasian population [25]. The prognosis of patients with an EGFR mutation is better than others. The median overall survival reached 19 months in the Caucasian population [25]. In the absence of a mutation, ITK-EGFR (only erlotinib has an AMM for this indication) can be administered as a second line therapy or at later cycles. At tumoral progression, new tissue specimens can be obtained to determine the mechanism of resistance to ITK (appearance of a resistance mutation, histological transformation…) and to adapt patient management. In 2007, the ALK translocation [26] was described in NSCLC (approximately 4% of NSCLC) and in 2011, crizotinib was validated for this indication, resulting in progression-free survival of between 7 and 9 months. Other biomarkers [24] have been discovered including certain that are associated with targeted therapies.

Clinical research in immunotherapy in NSCLC seems promising [27]. Last year, two phase I trials were published in the New England Journal of Medicine, one with anti-PD-1 antibodies [28], the other with an anti-ligand antibody to PD-1 [29]. Although included patients had received multiple treatments, several of them presented with objective responses. With immunotherapy, the evaluation of response-to-treatment can be difficult because the immune cascade set off by treatment can induce an initial increase in the size of targeted lesions, or the appearance of new lesions. The RECIST criteria are not adapted which is why specific immunotherapy criteria were published [30]. Today numerous trials are underway in immunotherapy.

**Conclusion**

In conclusion, the management of NSCLC in particular at the metastatic stage, has changed significantly in the past few years, both for diagnosis (necessity of having a large enough tissue specimen to identify oncogenic addictions) and...
treatment with the availability of personalized medicine. Despite progress, the prognosis is still poor and the fight against tobacco as well as diagnostic campaigns should be a priority.

**TAKE-HOME MESSAGES**

- Biopsy specimens should be adequate for diagnosis and the search for biomarkers.
- The physician performing the biopsy and the pathologist must therefore optimize their technique.
- In localized stages, precise staging must be obtained. A lobectomy associated with lymph node dissection is the standard therapy.
- In metastatic stages, treatment is determined by the histological subtype and the presence of mutations, in particular EGFR.
- Despite progress the prognosis is still poor. The fight against tobacco is a priority.

**Disclosure of interest**

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

**References**


