New American College of Chest Physicians guidelines on mediastinal staging and management of stage IIIA-N2 non-small cell lung cancer: a European perspective

Kurt G. Tournoy, Jan P. van Meerbeeck
Ghent University Hospital – Thoracic Oncology, Ghent, Belgium

Four years after the 1st edition [1], the American College of Chest Physicians (ACCP) has published its 2nd edition of their evidence based clinical practice guidelines on the diagnosis and management of lung cancer [2]. The goal of these guidelines is to assist chest physicians in achieving the best outcomes possible for their patients taking into account the new evidence based knowledge and techniques available.

The ACCP guidelines incorporate all evidence recently published about lung cancer diagnosis and treatment, and represent the most comprehensive summary currently available. The document is over 400 pages and provides the reader also with systematic summaries of the recommendations in each chapter. The authors of these guidelines have to be commended for this truly herculean task, which will set the stage for the approach to the patient with (presumed) lung cancer in the next years.

Compared to the previous 2003 edition [1], a number of changes have occurred. It would be helpful for the reader with some background in the matter to include an overview of those changes that were implemented since, in order to quickly get informed of the novel evidence. Not unexpectedly, the emphasis is largely put on US evidence and approach as this is the main target audience of the journal. However, compared to the previous issue, more non-US and specifically European authors were involved, making the guidelines breathe a more worldwide view than before. The editors have to be credited for this approach.

In this editorial, we will only address the issues of mediastinal staging and approach of stage IIIA non-small cell lung cancer (NSCLC) and will not comment on other topics which are also discussed thoroughly in the new ACCP guidelines [2]. The large amount of new evidence, especially on invasive mediastinal staging and treatment of stage IIIA NSCLC obliged the guidelines to be profoundly updated on these issues. This will affect current thoracic oncology practice and challenges several European guidelines, for example the National Institute for Clinical Excellence (NICE) guideline [3] which will be updated in 2009 at the earliest.

The non-invasive mediastinal staging of non-small lung cancer

Patients with NSCLC should be staged with great care and accuracy because the treatment options and prognosis differ significantly by stage. When there is no evidence for extra-thoracic metastasis, the mediastinum should be investigated. In the new ACCP guideline, the test characteristics for non-invasive mediastinal staging by means of CT and FDG-PET were updated [4] from the first iteration of lung cancer guidelines. The sensitivity of CT and PET is 51 vs. 74% respectively, while the specificities are 85% for both techniques. These values are lower but still comparable with those from the former guidelines and confirm that PET is more accurate than CT for detecting malignant mediastinal lymph node disease. A CT scan with contrast enhancement remains the cornerstone of the initial diagnostic strategy in a patient with (suspected) NSCLC but is inaccurate for the differentiation of benign and malignant lymph nodes. The clinician should remain cautious to interpret the mediastinum based only on the CT images because of the risk of both over- and understaging the lung cancer patient. The only situation where a CT scan alone is acceptable to evaluate the mediastinum remains the patient with a peripheral T1 lesion without enlarged lymph nodes on the CT-scan. These patients might not require invasive staging prior to thoracotomy because the probability to have mediastinal invasion is as low as 6%.

The implementation of a PET-scan in the clinical staging of a patient with NSCLC in whom no malignant pleural fluid or distant metastasis are present, is stimulated and better incorporated in the new guideline. The PET-scan helps the clinician to guide the invasive mediastinal staging besides the

Correspondence to:
Professor Jan P. van Meerbeeck, MD, PhD, Ghent University Hospital – Thoracic Oncology, De Pintelaan 185, 9000 Ghent, Belgium, phone/fax: +32-09-332-3862, e-mail: jan.vanmeerbeeck@ugent.be
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fact that unexpected distant metastasis are found in 10–15% of the patients. Unfortunately, there is no recommendation on the place and the implication of the newer generation integrated FDG-PET/CT that allows a more accurate fusion of CT and PET images. This is related to the relative scarce publications on this subject, however it is reasonable to predict there will be no major changes in patient management upon implementation of integrated FDG-PET/CT systems. The new ACCP guideline is in line with current European practice about the use of magnetic resonance (MR) to stage the mediastinum. There is no place for routine mediastinal MR in lung cancer staging although there might be a benefit for the selected patient with a superior sulcus tumour for the exact delineation and extent of malignant invasion.

The invasive mediastinal staging of non-small lung cancer

The ACCP guideline has adopted extensively the need and the methods for invasive mediastinal staging [5]. With the introduction of minimally invasive diagnostic and staging techniques such as transoesophageal endoscopic ultrasound with fine needle-aspiration (EUS-FNA) and endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), the role of surgical mediastinal staging (mainly by means of a cervical mediastinoscopy) is redefined. It is noteworthy this is the first guideline on lung cancer that gives a clear place to these novel techniques, besides the update on the test-characteristics. Other guidelines, for example the British NICE guideline [3] do not report on these techniques but will have to at the time of revision.

A clear definition of 4 patient groups with NSCLC with a suspicion for mediastinal involvement is proposed (Fig.). The guideline proposes the most accurate invasive approach for each situation. Patients in group A are defined as patients in whom the tumour mass directly invades the mediastinum such that discrete lymph nodes cannot be distinguished or measured. In these patients, radiographic assessment of the mediastinal stage is sufficient, and no invasive confirmation is warranted ("obvious T4"). This holds also for patients in whom vocal cord paralysis is found during bronchoscopy, indicating the direct invasion of the recurrent laryngeal nerve. In case of doubt, the selected patient might be proposed an exploratory thoracotomy to objectify the resectability.

Patients in group B have discrete enlarged (short axis ≥10 mm) mediastinal lymph nodes. In this group, invasive confirmation is recommended and many techniques (EUS-FNA, EBUS-TBNA, mediastinoscopy) are equally reasonable. Negative fine needle aspirates should however always be confirmed because the negative predictive value of these techniques does not warrant immediate thoracotomy. An important difference with the NICE guideline is also that this recommendation is unrelated to the PET findings and takes into account the data of two studies that showed a PET false negative rate of 20–28% in patients with enlarged mediastinal lymph nodes [6,7].

Patients in group C have either a central lung tumour (within the proximal one third of the hemithorax) or clinical N1 tumour (enlarged or with FDG uptake) but a normal mediastinum (no enlarged lymph nodes, no FDG uptake). In these patients, invasive staging of the mediastinum is needed and in general a mediastinoscopy is suggested although EUS-FNA and/or EBUS-TBNA may be reasonable alternatives if non-diagnostic results are followed by mediastinoscopy. The latter relates to the negative predictive value of the minimally invasive fine needle techniques, but it is to our opinion not clear at this point if the negative predictive value of mediastinoscopy after a negative EUS-FNA or EBUS-TBNA really contributes to a better clinical staging in this particular patient. On the other hand, ruling out malignant mediastinal invasion is important in these patients, and a thorough preoperative mediastinal lymph node sampling is the only valid way to achieve this. Both fine needle techniques are as single procedures not suited to do a systematic sampling, and by consequence, it seems logic to propose a mediastinoscopy in these situations. Whether combined procedures (EUS-FNA + EBUS-TBNA) are an alternative is currently under investigation.

The patients in group D have a peripheral lung lesion (outer two thirds of the hemithorax) and both a normal mediastinum and hilar lymph nodes (<1cm). The false negative rates for mediastinal invasion are 9% for T1 tumours, and are as low as 5% in case a PET shows no FDG uptake in the mediastinal nodes. By consequence, invasive staging of the mediastinum is not recommended for these patients.

The merit from these guidelines is the formulation of evidence based recommendations that can be implemented in daily practice. However, it is clear that patients sometimes do not fit within the tight guideline frame. For example, what is the best approach for a patient with a contralateral enlarged or FDG avid hilar lymph node, in the absence of suspect mediastinal lymph nodes? One could argue to approach the node by means of EBUS-TBNA, however, there are no data at all about the negative predictive value of this technique for this particular situation. Furthermore, the recommendation to perform a mediastinoscopy after a negative fine needle aspiration is based on a clinical feeling rather than on hard evidence since the negative predictive value of a mediastinoscopy is only 88% as compared with 82% for EBUS-TBNA; making a mediastinoscopy after a negative EBUS-TBNA probably of limited value. It is also remarkable to note that no guideline is given for patients with discrete small mediastinal lymph nodes that however show FDG-uptake. Although one could suggest that the minimally invasive techniques such as EUS-FNA or EBUS-TBNA might be prone to yield a negative result because it could technically be more difficult to puncture small lymph nodes, the available data suggest this is not the case. So to our feeling, these patients can be categorized in group B. With these comments,

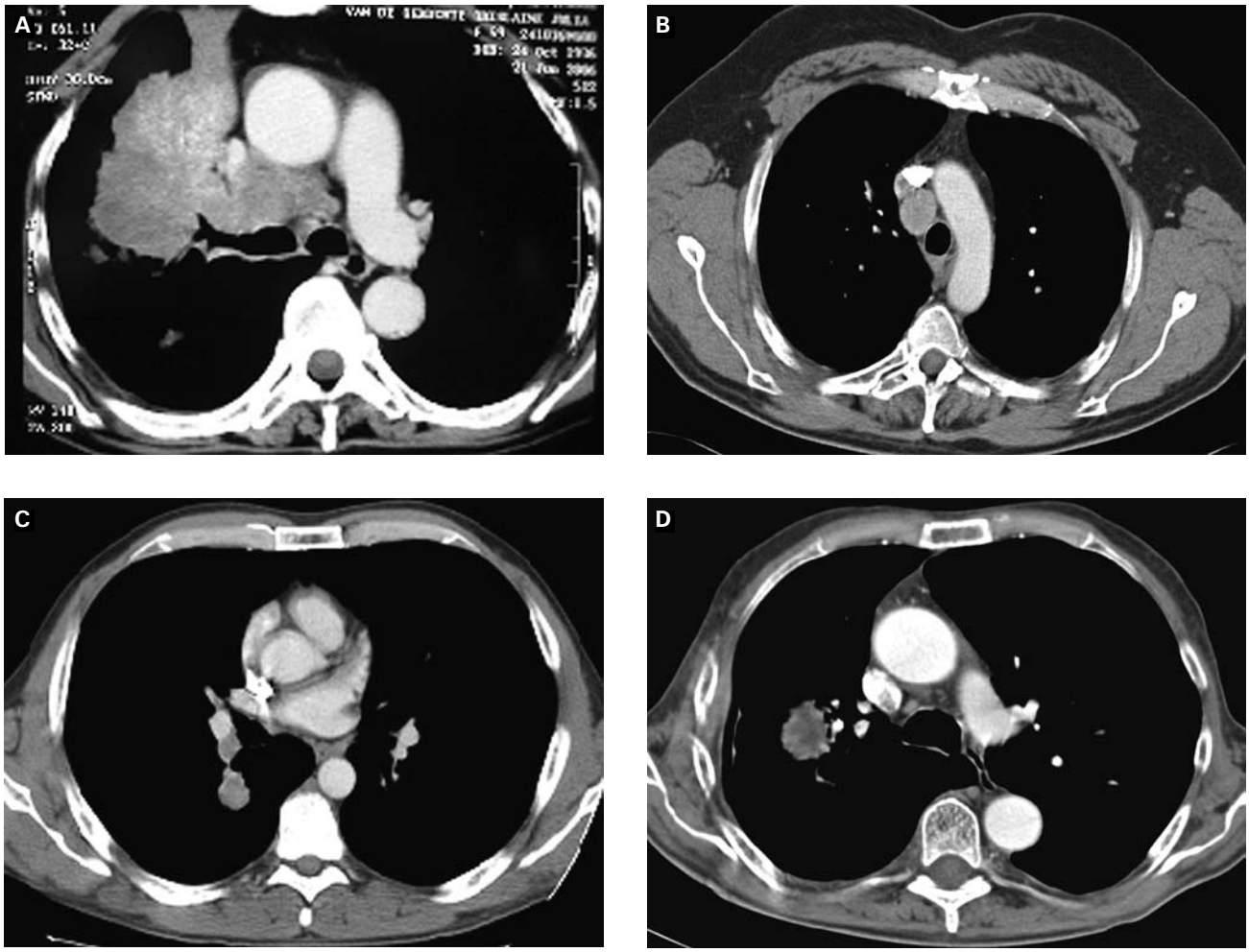

Fig. Categories of mediastinal lymph node involvement in NSCLC patients (see text)

it becomes clear that additional research is needed to investigate these issues in order to provide a further refinement of the recommendations.

Therapeutic issues: what's new about stage IIIA-N2 NSCLC?

It is recognized that patients with IIIA N2 NSCLC constitute a substantial heterogeneity in clinical presentation, treatment and prognosis. Four previously defined subsets of N2 tumours are used (Tab.), on which the available evidence was analysed and translated into an update of the ACCP guideline [8]. Patients in whom incidental nodal metastasis are found in the resection specimen ($IIIA_1$) or with a single node metastasis recognized intraoperatively ($IIIA_2$) are now, in contrast to the earlier recommendations, proposed to receive adjuvant platinum based chemotherapy and radiotherapy, the latter only for very selected patients with a high risk of local recurrence. Although the recommendation of adjuvant chemotherapy is based on large randomized controlled trials [9], it should be acknowledged that these studies are heterogenous with the fraction of patients that were really $IIIA_{1-2}$ but not $IIIA_{3-4}$ remaining ill defined. Moreover, that recommendation is also based on descriptive subanalysis of these trials. Looking from the other direction, limited data are available that directly address the question of survival advantage of adding adjuvant radiotherapy to adjuvant chemotherapy in the completely resected $IIIA_{1-2}$ patient, though new trials are underway [10].

Patients with $IIIA_3$ N2 NSCLC, with prethoracotomy recognized single or multiple discrete nodal metastasis, represent an area of even larger controversy. These patients have N2 disease identified preoperatively. The current ACCP guideline has been adapted profoundly based on large prospective randomized trials that compared the role of surgery *vs* radiotherapy after neoadjuvant chemotherapy. Whereas formerly, surgery was recommended after neoadjuvant therapy, the guideline now explicitly states that this strategy is not the first choice anymore. In addition, primary surgical resection followed or not by any adjuvant therapy is also not recommend-

Table. Categories of biopsy proven N2 NSCLC IIIA

Category	Description
$IIIA_1$	Incidental nodal metastasis found in the resection specimen
$IIIA_2$	Nodal (single station) metastasis found intra-operatively
$IIIA_3$	Nodal metastases recognized preoperatively (mediastinoscopy, EUS-FNA, EBUS-TBNA)
$IIIA_4$	Bulky multistation N2 disease

EUS-FNA – endoscopic ultrasound with fine needle-aspiration, EBUS-TBNA – endobronchial ultrasound with transbronchial needle aspiration

ed. The strategy for these patients is now platinum based combination chemoradiotherapy. This treatment is in selected patients delivered concurrently. Although it was already known that progression to surgery in patients with biopsy proven residual tumour in the mediastinal nodes was harmful [11], the currently available evidence suggests that there is probably no place at all for surgery in $IIIA_3$ N2 NSCLC patients [12].

$IIIA_4$ or bulky N2 disease represents a group of patients characterized by mediastinal nodes of at least 20 mm (short axis), multistation nodal disease and/or groupings of multiple biopsy proven smaller lymph nodes. Although this is a fuzzy definition, most experts agree this implies tumour unresectability. For these patients, the combination of chemotherapy and high dose radiotherapy was already recommended in the former American and European guidelines. Based on the newly available evidence, concurrent therapy strategies are now recommended for those patients with a good performance status. Despite this clear recommendation, several questions remain. For example, there is no clear answer on the role of consolidation chemotherapy or targeted therapies. Further clinical trials are certainly needed to define the role of these strategies for treating patients with N2 IIIA NSCLC.

Conclusion

The publication of the new evidence based ACCP guidelines on the diagnosis and management of lung cancer provides us with updated recommendations to ensure the best care is provided for our patients. Staging and treatment issues, especially of patients with IIIA N2 NSCLC, are two of the most intriguing and quickly evolving areas where the recommendations have been adapted profoundly. The more data available, the more it is clear that were are faced with important diagnosis and treatment uncertainties. A lot of work has still to be done to ensure a further improvement in the quality of management. In view of the diversity in health care systems between many different countries that make up Europe, the task of implementing guidelines in each country is still left up to the responsibility of the local health authorities and doctors. With this guideline, these local actors however are now provided with a firm and evidence based document to reconsider some of their diagnosis and treatment strategies.

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