Treatment options in stage IIIB non-small cell lung cancer: Making the proper choice

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Introduction

Lung Cancer is the second most frequent malignancy in man and its incidence is rising in women. Despite many years of research and development of new treatments, this disease remains the number one in cancer death rate [1]. Worldwide 1.2 million cases of lung cancer are diagnosed yearly and 85% of them die within 5 years. In Europe, 386,300 cases of lung cancer (12.1% of total cancer incidence) were reported and 334,800 died [1]. Of these new cases 80% are non small cell lung cancers (NSCLC) which can be subdivided into adenocarcinoma (40%), squamous cell carcinoma (35%) and large cell carcinoma (25%). Although lung cancer occurs more often in males, the incidence in females has increased over recent years. Since there is a direct relationship between stage of disease and survival, many attempts are now being made to identify patients in an earlier stage of disease. Therefore, groups of persons at risk are being screened with low dose CT scan and regular visits. The data are now emerging from large cohorts of patients with adequate follow-up, and the results are currently debated [2].

Unfortunately, the majority of patients present with locally advanced disease. In this stage, therapy provides disappointing outcomes and is associated with considerable toxicity. It is therefore of importance to carefully select patients for treatment. In the most recent studies, the median survival for patients with stage IIIB is 8 to 10 months from the time of diagnosis and the 1-year survival rate is 33–37% [3,4].

For the physician dealing with lung cancer patients, the major challenge is to find the balance between the toxicity and benefits for a patient. This requires a full knowledge of both patients' related factors and the success and toxicity of the available therapies. In the following paragraphs, the issues related with the choice of therapy in patients with locally advanced NSCLC are discussed.

Patients

Patients with lung cancer present with a variety of symptoms which are seldom typical for the disease. They can complain of dyspnoea, recurrent pneumonia, a change in coughing pattern, haemoptysis, pain, fatigue and loss of appetite. Even with limited signs or symptom of the disease, more than half of these patients have advanced disease at first presentation.

When examined by the physician, the patient's history, general performance, weight loss, chest movements and the appearance of lymph nodes in the supraclavicular fossa are considered important. In addition to the physical examination, laboratory and radiological examinations are required to stage the patient and to determine which treatment is best fitted. Since lung cancer often occurs in patients over 65 years of age, co-morbidity is also an important issue. Smoking is not only the causative agent in lung cancer, it also leads to cardiovascular disease and COPD which have to be taken into account in choosing the optimal treatment.

At presentation, different predictive and prognostic factors will determine the treatment outcome. Prognostic factors will give information on the survival of the patient while predictive factors will translate into the chance of success of a particular treatment. Determinants like race, molecular make-up (EGFR mutation, ERCC1 expression etc.) are important predictive factors but since they depend on the choice of therapy, no general guidelines can be given for a particular patient [5]. Of the prognostic factors, performance status is considered to be the most important factor for survival, followed by stage and weight loss (Table 1). The performance status was examined in a large study that encompassed 893 patients. The 1-year survival rates were 36%, 16% and 9% for patients with an initial WHO performance status of 0, 1 and 2, respectively ($P < 0.001$) [6]. A performance status of 2 can therefore be considered to be a negative prognostic factor and this has been

Table 1
Prognostic factors in NSCLC

Stage of disease
Performance status
Weight loss
Laboratory: Anaemia, hypercalcemia
Tumour related factors: Histology, molecular analysis-like mutation status of EGFR, VEGF, ERCC1 RRM1 etc.

confirmed in a review of recent therapeutic studies. Weight loss has not always been confirmed as a negative prognostic sign but many studies exclude patients with >10% weight loss because of decreased tolerance for an aggressive treatment. The age of the patient is not considered to be a clear prognostic factor since most studies have only a very limited proportion of patients over 70 years and no strong conclusions can be drawn [7]. In stage IV disease, special studies for the frail and elderly patients have recently indicated that some types of chemotherapy or radiation therapy can be given with acceptable toxicity [8]. Less data are available for the combination treatments.

Staging procedures

For this educational review we will focus on stage IIIB. In Fig. 1 the staging for this group is defined using the current International Association on the Study of Lung Cancer (IASLC) classification [9]. In 2009, the IASLC will report an updated analysis of 26,000 patients who were staged over the last 20 years. It is expected that this update will result in some stage shifts.

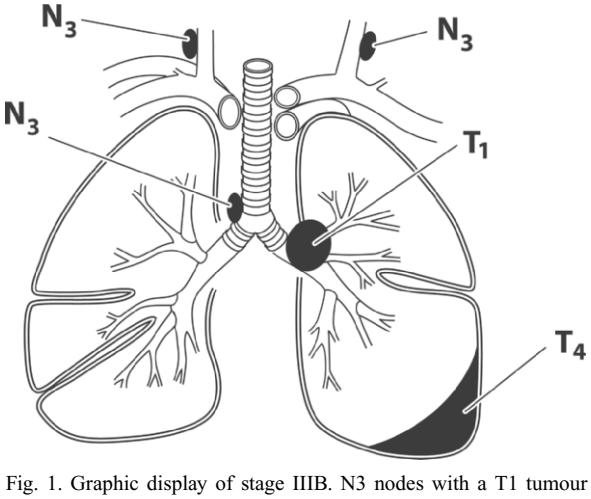

Fig. 1. Graphic display of stage IIIB. N3 nodes with a T1 tumour or a malignant pleural effusion which is now still considered a T4 tumour.

In stage IIIB, two important large subgroups can be identified. Those with malignant pleural effusion and those with extended lymph node metastases (Fig. 1). Although these groups are both considered stage IIIB, it is imperative to make this distinction for the choice of treatment. Patients with a malignant pleural effusion are candidates for standard (systemic) chemotherapy, whereas other treatment modalities or combinations can be given to the latter group. The survival figures of patients with malignant pleural effusion are comparable with patients with stage IV NSCLC.

For staging purposes CT scans are now widely available and give a reasonable impression of the extent of the disease. In recent years, positron emission tomography (PET) scanning with a glucose tracer has become available and is now used in many countries. When the primary tumour is PET avid, the negative predictive value of PET is high. However, when positive results are obtained, the involvement by the malignancy must be confirmed since the specificity is approximately in the range of 85–89% [9,10]. Nowadays a combination of both PET and CT scan has further improved the staging efficacy (Fig. 2).

T-Status

The T status stands not only for the size of the tumour but also for the location and type of growth (invasion). For the T1 and T2, the size of the tumour is inversely related to survival [11]. Larger tumours have more frequent lymph node involvement or distant metastases. T3 tumours can grossly be divided in those that are located centrally in the main bronchi and those that are growing into the mediastinum or chest wall. In the chapter by Grunenwald, more details are presented. Many studies suggest that radical surgical treatment can lead to 5-year survival rates of 16 to 56% in patients whose tumours have grown through the parietal pleura or into the thoracic wall when no lymph nodes are involved [12]. A special subgroup of T3 tumours are the sulcus superior tumours that often benefit from an aggressive treatment involving radio-

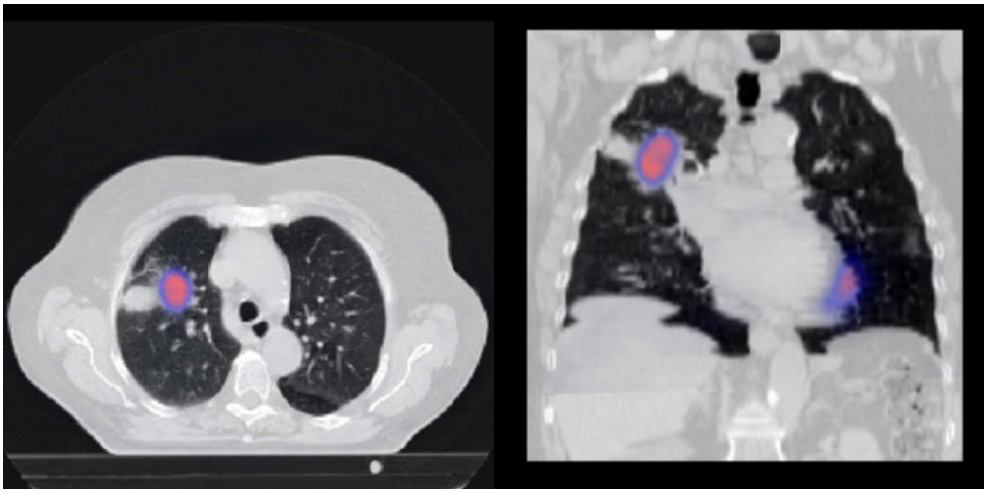

Fig. 2. Merging images of PET and CT scan. The metabolic active tumour is clearly delineated from the post-obstructive atelectasis.

therapy and surgery. They are considered stage IIIA tumours [13].

For T4 tumours the survival figures are poor except for highly selected patients. The type of invasion and the involvement of lymph nodes clearly determine the survival [14]. Standard treatment is chemotherapy and/or radiotherapy with a 9–14% 5-year survival [15]. One of the reasons for these dismal figures is the inability to perform a R0 resection, and the involvement of major organs is associated with a high post-operative mortality rate. The T4 tumours may also include multiple tumours of the same kind in only one lobe. These can be synchronous tumours or primary lung tumours with intra-lobar metastases. In both cases, the prognosis after complete resection with N0 status can be compared to stage II survival figures [16]. It remains to be seen if the annotation T4 in these cases will remain in the future [16]. Pleural spread of tumour (pleuritic carcinoma) however, is considered not resectable. These patients are candidates for chemotherapy. Occasionally multimodality studies, including surgical resection, are performed but no improvement in survival has been reported.

N-Status

The N-status is another important factor for the staging and the prognosis of patients with NSCLC. As described, stage IIIB is a combination of the T- and N-status. Histological evaluation of the supra-clavicular and mediastinal lymph nodes more frequently determines the stage IIIB than the T status alone. The N3 status in the supra-clavicular region can well be explored by ultrasound and safely confirmed by needle aspiration. The level of the lymph nodes in the neck is also considered important. The higher the level of involved lymph node, the worse the prognosis. The level also determines whether radiation will be possible or not.

Which treatments are available?

Surgery

It is generally accepted that surgery is the cornerstone for resectable NSCLC. However, survival figures of patients with early stages of NSCLC (stage I-IIIa) in the last decades of the 20th century have been disappointing with 5-year survival of 22–61% [12]. Despite improvements in anaesthesiology and thoracic surgical techniques, the majority of patients will die from distant recurrences.

For stage IIIB, surgery is only considered an option is selected patients, as a part of a multimodality management, and no relevant randomised studies addressing the role of this method have been performed. The number of patients included in phase II studies cannot be compared easily due to the different combinations of chemotherapy and radiation doses and fields.

Chemotherapy

In the early 1990s it was recognised that for patients presenting with stage IV disease, chemotherapy showed some activity and it was postulated that in earlier stages, with less tumour load, this effect would be more pronounced in patients presenting with stage IIIA disease.

Although chemotherapy had been reserved for ‘irresectable’ cases of lung cancer, the approach

of induction chemotherapy was first considered in patients with good performance status and locally advanced disease. Patients with proven stage IIIA (N2) or IIIB (T4/N3) were entered in feasibility and safety studies. In subsequent phase III studies the impact of induction chemotherapy with surgery versus surgery alone were investigated. A series of studies [17–20] showed a possible advantage of induction chemotherapy before surgical resection. In patients with locally advanced disease, even complete pathologic responses were observed. Furthermore, the introduction of the preoperative chemotherapy did not result in a significant increase in operative mortality. For patients with localised disease who are not primarily considered suitable for surgical intervention (stage IIIB, no pleural effusion), the impact of induction chemotherapy has also been investigated. In the SWOG 8805 study, a platinum based induction regimen was followed by 45 Gy radiation therapy [21]. A 3-year survival of 27 and 24% for the IIIA and IIIB stage was observed. In the group of patients also treated with resection, 21% had a pathological complete response and in 37% of the patients with residual radiological disease, only scattered tumour foci were observed. The observed operative mortality rate in this study (5%) was increased but acceptable. Other investigators have also noticed an increase in the operative mortality rate [22].

These randomised studies initiated new phase II studies to optimise the schedules of chemotherapy in this group of patients. Based on preliminary results, randomised phase III studies comparing surgery versus radiation therapy after induction chemotherapy, are now in progress or being evaluated in Europe and the USA. It is important to notice that in most of these studies hardly any patients over 70 years of age with stage IIIB are included. It is therefore difficult to make assumptions on the exact place and indication of surgery with or without chemotherapy in this stage.

Radiotherapy

There are different indications for the use of radiotherapy. This modality can be used with curative intent or for symptom relief. The use of radiotherapy is indicated, especially in patients who present with symptoms of superior vena cava syndrome. Locoregional radiation will result in symptom improvement and tumour shrinkage in two thirds of the cases. Many changes have occurred in the field of radiation therapy. New irradiation units (linear accelerators), 3D and 4D planning, intensity modulated radiation therapy and stereotactic radiation are important improvements compared to the planning before 2000. From a biological point of view it is now accepted that elective nodal irradiation is not mandatory in all cases which has allowed the radiation dose to be increased. Although in general a total dose of 60–70 Gy is given, patients with small tumours might even be treated with a higher dose. In the chapter by Price and colleagues, the new approaches and schedules are presented. Especially for the stage IIIB, a high dose of radiation, preferably with concurrent chemotherapy, is considered standard treatment.

When initially the field of radiation is considered too large, induction chemotherapy can be used to shrink the tumour allowing the planning of a radical radiation schedule (see also Chapter ‘Paradigms in Chemoradiotherapy’ by Jassem [23]).

The combination studies were piloted in the 1990s and meta-analyses were published in 1995 and 1996. An increase in median survival of 2 months and a 4% increase in 2 years survival was noted. In nearly all studies cisplatin-containing chemotherapy was given. The dose of radiotherapy with 50–60 Gy was lower than currently advised.

In the multidisciplinary meetings, a decision must be taken as to whether the planned radiation field allows immediate combined chemo–radiation therapy or whether the volume of the tumour should be reduced to allow higher doses of radiation (with or without concurrent chemotherapy). For stage IIIB with pleural effusion there is no place for radiotherapy. These patients are primarily treated with chemotherapy.

A new field of clinical research is the combination of radiotherapy with the targeted agents like VEGF and EGFR inhibitors. For stage IIIB it is not expected that very high biological doses of radiation therapy, as given by stereotactic hypofractionation, will be feasible due to the dose limiting adjacent tissues like spinal cord, oesophagus and the heart. The issue of sequential versus concurrent administration of chemotherapy in stage III disease has been addressed in detail in the chapter by Jassem [23].

Conclusions

For the treatment of stage IIIB not as much data as in stage IIIA or IV are available. The standard approach for this disease is concurrent chemo-radiotherapy when field size of the radiation portal is not too large. For larger fields, induction with two or three courses of chemotherapy followed by high dose of (chemo) radiation therapy could be considered. In the near future the implementation of targeted agents in

this approach will likely lead to other schedules and toxicity profiles.

It must be kept in mind that the primary goal of treatment in locally advanced inoperable NSCLC is to preserve quality of life and to avoid unwanted serious side effects of treatment.

Conflict of interest statement

None declared.

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