16 Applications in Lung Cancer

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16.1 Non-Small Cell Lung Cancer

16.1.1 Introduction

For about two decades the development of multimodal treatment strategies in non-small-cell lung cancer (NSCLC) has led to some major, but often underestimated, progress in cure rates. This is especially the case for the locally advanced stages IIIA and IIIB, whereas in the early stages surgery continues to play the most dominant role and just recently the addition of chemotherapy became a therapeutic standard.

The presumed superiority of multimodal therapy in the advanced stages can now generally be disregarded. At the same time the sheer number of possible treatment options with respect to, for example, the choice of chemotherapeutic agents, the sequence of available therapeutic elements, radiotherapeutic fractionation schedules and emergence of "targeted therapy options" create a complex problem to find "the right" multimodal approach for the individual patient. The simple division of patients into stages IIIA (which is particularly heterogeneous) and stage IIIB alone does not satisfy the needs for deciding upon the appropriate differential therapy. Some crucial other factors, such as, for example, age, (potential) resectability, general health status and cardiopulmonary function, and availability and quality of staging methods have to be weighted against each other and evaluated as prognostic factors in the context of a multimodality approach; thus, the necessity for optimal selection criteria as well as a renewal of the staging system can be derived from such considerations.

16.1.2 Radiotherapy Regimens

In radiotherapy of NSCLC with curative intent tumour doses of 66 Gy in 2-Gy fractions can be considered as

standard of care. The Radiation Therapy Oncology Group (RTOG) 73-01 dose-escalation trial (Perez et al. 1980) could initially show higher response rates and a lower incidence of local failure in patients treated with 60 Gy compared with patients treated with 40 or 50 Gy. Still, in only 15% of patients undergoing radiotherapy alone local tumour control could be achieved with doses of 65 Gy (Le Chevalier et al. 1991). To improve local control both higher radiation doses and the combination with chemotherapy are mandatory (Emami 1996). The RTOG trial 9311 (Bradley et al. 2005) examined the possibility of further dose escalation using a state-of-the-art three-dimensional conformal radiotherapy. Depending on the percentage of the total lung volume that received >20 Gy [V(20)] patients were stratified at escalating radiation dose levels. For patients with V(20) values of <25% the radiation dose could safely be escalated to 83.8 Gy, and those with values of 25–36% could safely be escalated to 77.4 Gy, in conventional fractionation. Thereby locoregional control was achieved in 50–78% of patients. Excess mortality was oberserved at the 90.3-Gy dose level. The patients did not receive concomitant chemotherapy. If chemotherapy is being administered simultaneously, current indications suggest that the maximum tolerated dose is in the range of 70–74 Gy (Bradley 2005).

Another potential means to enable individual dose escalation is the implementation of positron emission tomography (PET) in radiotherapy planning, which has been increasingly used during the past few years. The more safely the planning target volume can be confined to morphologically and functionally visible tumour manifestations, the easier it might be to allow for an increase in dose. In a Dutch planning study (De Ruysscher et al. 2005a,b) the use of PET-CT led to a significant increase in tolerable total dose from 55.2 Gy (only CT-based planning) to 68.9 Gy. The maximum tolerable dose was determined by equivalent estimated toxicity levels of the lungs, oesophagus and spinal cord.

In a prospective clinical study by the same group (De Ruysscher et al. 2005a) 44 patients with NSCLC stages I–IIIB received an accelerated radiotherapy (without chemotherapy) exclusively of the primary tumour and the fluorodeoxyglucose (FDG)-PET positive mediastinal areas. The patterns of recurrence were thoroughly examined consecutively. The authors found a local recurrence in 11 patients (25%) after a median follow-up of 16 months, but only 1 patient developed an isolated nodal failure. Similar future trials with addition of chemotherapy will be needed to support the role of FDG-PET.

From a theoretical radiobiological viewpoint alternative fractionation regimens, i.e. especially a hyperfractionated accelerated radiotherapy, can be advantageous. By means of the reduction of the dose per fraction to less than 1.6 Gy, the late toxicity might be reduced while tumour response using twice-daily irradiation with at least 6 h interval should not be hampered. The shortening of total treatment time is supposed to antagonize the phenomenon of "accelerated repopulation" of clonogenic tumour cells during the course of radiotherapy. In this context the CHART study (continuous hyperfractionated accelerated radiotherapy) made an important contribution (Saunders et al. 1997). A total of 563 patients were accrued and received either CHART (three daily fractions of 1.5 Gy with 6-h interval on 12 consecutive days, i.e. weekends included) up to a total dose of 54 Gy, or a conventionally fractionated radiotherapy with 60 Gy in the control arm. The 2-year survival rate in the CHART arm was significantly increased to 30% compared with 21% in the control arm. This was due to an increased tumour control. In squamous cell carcinoma even a reduction in distant metastases could be observed.

As expected, the incidence of acute toxicity, especially oesophagitis, was significantly higher in patients treated with CHART, whereas no significant differences considering late toxicity were oberserved. Mature results of the German multicentre-study CHARTWEL-Bronchus that examined the effectiveness of CHART without treatment on weekends, in comparison with a conventional regime with an increase in dose to 66 Gy, are awaited (Baumann et al. 1997). A preliminary presentation suggests that CHARTWEL to 60 Gy in 2.5 weeks was not superior (Baumann et al. 2005). Acute toxicity of CHART protocols certainly limits the applicability of simultaneous chemotherapy. A combination of hyperfractionated-accelerated radiotherapy and full-dose chemotherapy is feasible only if the total radiation dose is reduced to a maximum of 45–50 Gy (Jeremic et al. 1996). This limitation makes such protocols suitable for a neoadjuvant treatment setting (see 16.1.4.2) but, for toxicity reasons, inappropriate for definitive radiochemotherapy regimens.

16.1.3 Chemotherapeutic Agents

The addition of chemotherapy in the treatment of non-metastasized NSCLC has to fulfil two major