11.1 Intensity-Modulated Radiation Therapy for Lung Cancer

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11.1.1. Introduction

In the 1980s, Brahme (1982) demonstrated the unique potential of intensity-modulated (IM) beams to create homogeneous concave dose distributions. Inside IM beams, the radiation fluence (intensity) was not equal at all sites inside the beam i.e. the beam was not flat (unmodulated) but had a value that was function of its location across the field (Lax and Brahme 1982). Brahme (1988) also proposed the concept of inverse planning as a possible strategy to make the design of IM beams feasible. Intensity-modulated radiation therapy (IMRT) remained a research topic in physics laboratories until 1993, when Carol et al. (1996) proposed a novel planning and delivery system (NOMOS MiMiC) as a comprehensive solution for clinical IM tomotherapy. Since 1993, the three major vendors of linear accelerators have developed multileaf collimator (MLC) technology capable of delivering IMRT, and smaller companies have developed micro-MLCs with IMRT capability. IMRT research is intense, and clinical results have been published for various tumour sites, including the prostate, head and neck, and base of the skull. A PubMed search on 25 March 2004 using “intensity modulated lung cancer” as keywords yielded 45 publications, most of which were on physics issues. None reported on the clinical outcome of IMRT in lung cancer.

Against this background, a chapter on the use of IMRT in lung cancer remains largely speculative. Our aims are to formulate the clinical objectives of IMRT to treat lung cancer; to discuss the anatomical challenges of IMRT, the choice of beam directions, and the potential of intensity-modulated beams to spare lung, oesophagus, and spinal cord; to describe the potential clinical benefit of biological image-guided IMRT optimisation; to discuss specific planning issues, including the problem of heterogeneities in tissue density for IMRT optimisation; and finally to discuss the implementation and quality assurance problems that have delayed clinical trials.

11.1.2 Clinical Objectives

In limited-disease (LD) small cell lung cancer (SCLC), randomised trials comparing early versus late accelerated radiation therapy concurrent with chemotherapy showed a significant increase in 5-year survival from 13-20% for the late arm to 22-30% for the early arm (Jeremic et al. 1997; Takada et al. 2002; Murray et al. 1993). A large difference in survival between early and late thoracic radiation as well as survival...
rates above 20% were seen in randomised trials using a dose intensity of about 15 Gy/week (Perry et al. 1998; Work et al. 1997) instead of the standard of 9-10 Gy/week. Using early thoracic radiation, a randomised trial (Turrisi et al. 1999) comparing 45 Gy in 3 weeks (group 1) with 45 Gy in 5 weeks (group 2) confirmed the advantage of a high dose intensity, with a 26% 5-year survival rate for group 1 and 16% for group 2 (p=0.04). A 50-66% local control rate that was achieved with the best schedules (Knoos et al. 1995; Murray et al. 1993; Turrisi et al. 1999) using 40-54 Gy in 3-3.5 weeks indicates the existence of a window for improvement with more efficient local treatment. A phase I dose and dose-intensity escalation study showed that the maximum tolerated radiation dose intensity is limited by acute oesophageal toxicity at 45 Gy in 30 fractions over 3 weeks (Choi et al. 1998). An analysis of patients with LD-SCLC treated with doses ≥50 Gy suggests further increase of dose response above 50 Gy (Roof et al. 2003). These results direct us to a design of IMRT studies with further dose and dose-intensity escalation at the tumour, respecting isotoxicity at the oesophagus by selective underdosage. The hypothesis that such use of IMRT can improve the therapeutic result should be tested.

In patients with locally advanced (LA) non-small cell lung cancer (NSCLC), combined treatment with radiotherapy and second-generation chemotherapy drugs was extensively studied over the past 20 years, and it became the standard over radiotherapy alone in patients with good performance status. Cisplatin seems the drug of choice but results in significant increase of oesophageal toxicity. In LA-NSCLC, the maximum dose of radiotherapy with or without concurrent chemotherapy is most often restricted by pulmonary toxicity (radiation pneumonitis). For further improvement in survival, the two components of the treatment need to be improved. An effective treatment of micrometastatic disease through full-dose delivery of cytotoxic drugs could be obtained by adding at least one more active drug in conjunction with cisplatin. To further improve loco-regional control of the disease, radiotherapy dose escalation seems a logical strategy. Clinical data regarding the magnitude of dose escalation that can be achieved by IMRT are inexistent. In planning studies, the Rotterdam Oncological Study Group (Van Sornsen de Koste et al. 2001) showed a reduction of 20.3% in the mean lung dose using three-dimensional (3D) missing tissue compensators, as well as a reduction in the total lung volume exceeding 20 Gy (V20). Derycke et al. (1997) compared a three- or four-beams conventional 3D technique (3D-CRT) and two techniques involving, respectively, seven and five non-coplanar beam incidences with intensity modulation and showed an improvement both in tumour control probability (TCP) and lung normal tissue complication probability (NTCP) for the IMRT plans, with a window for 20-30% dose escalation. Marnitz et al. (2002) showed a reduction of the irradiated lung volume using non-coplanar IMRT fields.

Randomised trials have shown an improved outcome of combined radiation therapy and chemotherapy over radiotherapy alone, with the concurrent radio-chemotherapy schedules being the most efficient (Lara et al. 2002). Accelerated radiotherapy schedules were shown to be superior to schedules using conventional fractionation (Saunders et al. 1996). The design objectives of IMRT for LA-NSCLC seem very similar to those of IMRT for LD-SCLC, namely to obtain an accelerated radiation treatment that can be delivered simultaneously with chemotherapy. For both pathologies, IMRT needs to address at least three objectives: limiting oesophageal toxicity, limiting the risk of radiation pneumonitis, and increasing dose and dose intensity selectively to the tumour. Dose intensity escalation seems to be more important than physical dose escalation for LD-SCLC, whereas both types of dose escalation seem important for LA-NSCLC. As a result of improved survival and enhanced local control, most of the present radiochemotherapy studies show a significant increase in the incidence of brain metastases (Reboul 2004). Addressing the question of prophylactic cranial irradiation might be a 4th objective in future IMRT trials.

11.1.3 Challenges Related to Anatomy and Preservation of Organ Function

Safe delivery of high doses to lung tumours is prohibited most often by risk of toxicity to lung, spinal cord, and oesophagus. Lung can be considered as an organ that consists of functional units organised in a parallel architecture. The probability of life-threatening radiation pneumonitis can be estimated from the percentage volume of lung irradiated above a critical dose – for example, 20 Gy (V20) (Graham et al. 1999) – or from the mean (biological) lung dose (MLD) (Kwa et al. 1998; Seppenwoolde et al. 2003). With a fixed constraint on V20 or MLD, the maximum prescription dose decreases for larger planning target volumes (PTVs) and is dependent on the location of the PTV. For equal PTV size and doses above 50 Gy