Non-small Cell Lung Cancer

12

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IMRT • Non-small cell lung cancer

12.1 Introduction

In 2013, a statistical fact sheet from the US Surveillance, Epidemiology, and End Results reported that an estimated 228,190 new cases of lung cancer would be diagnosed and that an estimated 159,480 people would die of this disease [1]. Non-small cell lung cancer (NSCLC) remains the predominant variant and the leading cause of mortality worldwide; it represents 13.7 % of all new cancer cases in the United States [1]. Treatment for NSCLC often requires multimodality therapy including surgery, systemic chemotherapy, novel targeted agents, and radiation therapy. High doses of radiation therapy (i.e., those above 60 Gy) have been investigated in attempts to control both local and regional treatment failures in NSCLC. However, delivering higher radiation therapy doses, particularly in combination with chemotherapy, increases the risk of treatment-related toxicity. With the emergence of technologies such as intensity-modulated radiation therapy (IMRT) and particle beam therapy, the goal in radiation therapy is to effectively treat NSCLC while simultaneously minimizing clinically relevant treatment-related toxicity.

The availability of advanced techniques such as IMRT and image-guided radiation therapy has greatly improved the precision of delivering radiation treatments

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for patients with lung cancer. IMRT is thought to enhance the therapeutic ratio by using beams of nonuniform intensities to tightly conform the dose to the target. Through inverse treatment planning, a combination of carefully chosen beam arrangements, optimization parameters, and strict adherence to dose limits for normal structures allows the delivery of tightly conformal dose distributions to targets of complex shapes. Because each field contributes a nonuniform intensity pattern, combining the fields can create a uniform target dose distribution. Another advantage of IMRT for treating lung cancer is the potential for dosimetric improvements in terms of delivering high, tightly conformal doses to the tumor while sparing surrounding normal structures such as the healthy lung and spinal cord, in this way improving the therapeutic ratio for lung cancer. This chapter summarizes the current state of the art in the use of IMRT for treating NSCLC.

12.2 Treatment Planning for Thoracic Tumors

12.2.1 Treatment Simulation, Treatment Planning, and Dosimetry

At the authors' institution, treatment planning for all patients involves treatment simulation that is based on the findings from four-dimensional computed tomography (4D CT). Patients are positioned in the intended treatment position on a CT couch and immobilized through the use of a customized, indexed immobilization vacuum device around the upper torso. A respiratory monitoring system is placed on the patient's abdomen, and a series of ten CT datasets representing different points of the respiratory phase are reconstructed. The acquired CT dataset is imported into the treatment planning system, where the average intensity projection is used as the primary dataset for dose calculations, but all datasets are used to determine the internal target volume.

For patients undergoing 4D CT-based treatment simulation, a 5–8 mm margin is added to the internal target volume to create the clinical target volume (CTV), and an additional 5–7 mm margin is added to the CTV to create the planning target volume (PTV) in patients being treated for NSCLC. Treatment plans for IMRT are designed using the inverse planning component of the Pinnacle treatment planning system's software with an optimization algorithm (Philips Healthcare, Inc.). The goals of IMRT planning are to deliver the prescribed dose to the PTV, with a minimum of 95 % of the prescribed dose and a maximum of 110 % of the prescribed dose. The beam configuration for the IMRT plans depends on the location and size of the tumor; however, generally 5–7 beams are sufficient, with gantry angles separated by a minimum of 25–30° (Fig. 12.1).

Normal tissue constraints for radiation therapy used to treat thoracic malignancies are summarized in Table 12.1. At the authors' institution, we attempt to minimize the total lung volume that receives >5 Gy (i.e., the V_5) to the greatest extent possible; we further restrict the mean lung dose (MLD) to 20 Gy or less and the volume of lung that receives >20 Gy (V_{20}) to <40 %. Other dose constraints include

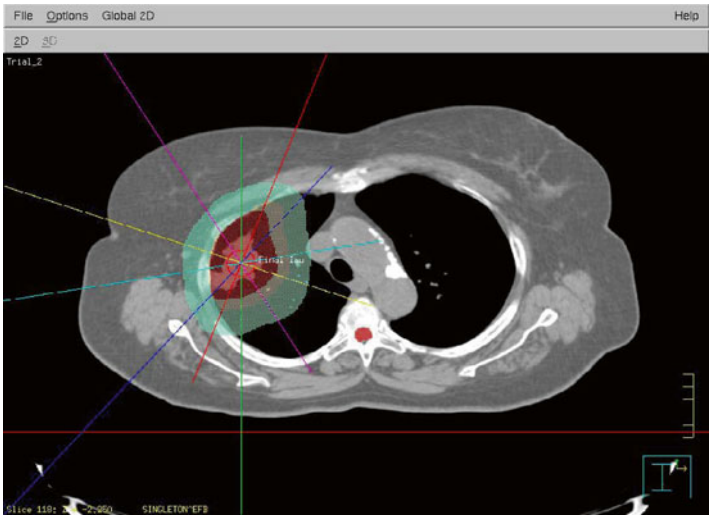

Fig. 12.1 Beam configuration for an intensity-modulated radiation therapy plan to treat a patient with non-small lung cancer. The beams are separated by 25–30° so as to avoid parallel opposed beams

Table 12.1 Dose-volume constraints for normal tissues during standard fractionation radiation therapy

	Radiation only	Radiation with chemotherapy	Radiation with chemotherapy before surgery
Spinal cord	D_{max} <45 Gy	D_{max} <45 Gy	D_{max} <45 Gy
Lung	MLD ≤20 Gy	MLD ≤ 20 Gy	MLD ≤20 Gy
	$V_{20} \leq 40$ %	$V_{20} \leq 35$ %	$V_{20} \leq 30$ %
		$V_{10} \leq 45$ %	$V_{10} \leq 40$ %
		$V_5 \leq 65$ %	$V_5 \leq 55$ %
Heart	$V_{30} \leq 45$ %	$V_{30} \leq 45$ %	$V_{30} \leq 45$ %
	Mean dose <26 Gy	Mean dose <26 Gy	Mean dose <26 Gy
Esophagus	D_{max} ≤80 Gy	D_{max} ≤80 Gy	D_{max} ≤80 Gy
	$V_{70} < 20$ %	$V_{70} < 20$ %	$V_{70} < 20$ %
	$V_{50} < 50$ %	$V_{50} < 40$ %	$V_{50} < 40$ %
	Mean dose <34 Gy	Mean dose <34 Gy	Mean dose <34 Gy
Kidney	20 Gy <32 % of bilateral kidney	20 Gy <32 % of bilateral kidney	20 Gy <32 % of bilateral kidney
Liver	$V_{30} \leq 40$ %	$V_{30} \leq 40$ %	$V_{30} \leq 40$ %
	Mean dose <30 Gy	Mean dose <30 Gy	Mean dose <30 Gy

minimizing the mean dose and V_{50} to the esophagus, restricting the cardiac V_{30} to <45 %, and limiting the dose to the spinal cord to <45 Gy. We closely follow these and other dose-volume constraints based on summary QUANTEC recommendations for standard fractionation treatment.

12.2.2 Radiation Dose

Principles of basic radiobiology suggest that doses of 80–100 Gy are required to sterilize lung cancer [2]. The Radiation Therapy Oncology Group (RTOG) and other institutions have conducted randomized trials evaluating radiation doses of 60 Gy or more in combination with chemotherapy to treat inoperable NSCLC [3–7]. The optimal dose for definitive radiation therapy for patients with inoperable NSCLC at diagnosis is still controversial. At MD Anderson Cancer Center, such patients are treated with definitive radiation doses of 60–74 Gy with concurrent chemotherapy, if they can tolerate this therapy.

12.2.3 Radiation-Induced Toxicity

12.2.3.1 Radiation Pneumonitis

Patients receiving radiation therapy to the thorax are at risk for developing radiation pneumonitis (RP), which typically manifests within 3–9 months after the completion of radiation therapy. Many studies have demonstrated that MLD [8–15] and the percentage of lung volume receiving more than some threshold dose [8, 11, 13, 16–18] can predict the development of RP; however, other studies have shown that some of these factors are not linked with RP [16, 19, 20], but rather that only a history of smoking [11, 17], chronic obstructive pulmonary disease [9], and receipt of induction chemotherapy with mitomycin [10] predict RP.

Variables typically used in the evaluation of lung dose and risk of RP include the volume of both lungs receiving more than a threshold dose (V_{dose}), the MLD, the lung V_{20}, and normal tissue complication probabilities (NTCPs) given various combinations of dose-volume variables. We and others also evaluate the lung V_5.

In general, in radiation therapy for lung cancer, the total tolerable radiation dose depends on the volume irradiated. In a retrospective analysis, the MLD (Fig. 12.2) and relative V_5–V_{65} in increments of 5 Gy were all found to be associated with the incidence of grade ≥3 RP according to the Common Terminology Criteria for Adverse Events v3.0. Investigators at MD Anderson [21] showed that V_5 was also a significant predictor of RP (Fig. 12.2); in that study, the 1-year incidence of grade ≥3 RP for patients with a relative $V_5 \leq 42$ % was 3 % compared with 38 % for those with $V_5 > 42$ % ($P = 0.001$). This finding suggests that damage to the lung, which has functional subunits in parallel, may depend more on the volume irradiated than on the radiation dose. Gopal et al. similarly demonstrated that exposing normal lung to as little as 13 Gy led to a pronounced decrease in diffusion capacity for carbon monoxide (DLCO), and a loss of DLCO of >30 % was associated with grade ≥2 pulmonary symptoms ($P = 0.003$). Those investigators concluded that such a low threshold for deterioration of DLCO (13 Gy) indicates that it is better to treat a small amount of normal lung to a high dose rather than treating a large volume to a low dose [22]. Similarly, Yorke et al. reported that in patients with NSCLC treated with dose-escalated radiation therapy, the incidence of grade ≥3 pneumonitis correlated with

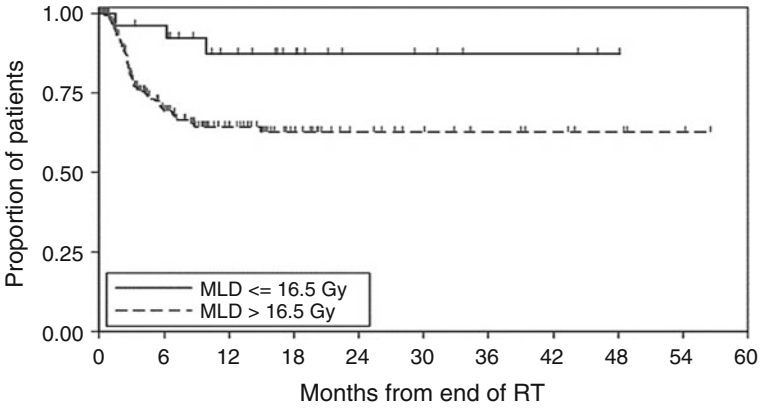

Fig. 12.2 Effect of mean lung dose (MLD) on freedom from grade ≥3 treatment-related pneumonitis. *RT* radiotherapy (Figure republished (with permission) from Wang et al. [21])

MLD ($P \leq 0.05$). The dose response as a function of mean dose to the total lung rises steeply, beginning at approximately 10 Gy [10]. In clinical practice, V_{20} is often used as a surrogate to evaluate total dose to the lung in radiation treatment planning. Graham et al., in their analysis of V_{20} for predicting RP, stratified patients into risk groups and found that the incidence of RP increased steeply when V_{20} levels were 40 % or higher [16].

12.2.3.2 Esophagitis

Another form of radiation-induced toxicity, acute esophagitis, typically occurs within 90 days after the start of radiation therapy, whereas chronic esophagitis occurs after that time. Chronic esophagitis can result in the development of esophageal stricture requiring dilation and, in rare cases, esophageal fistula. Grade 1–2 radiation-related esophagitis is relatively common after treatment for lung cancer, and rates of grade >3 esophagitis range from 10 to 50 % [23–25]. A recent analysis of acute esophagitis in four RTOG trials involving 528 patients reported that 75 % of patients had grade >2 acute esophagitis and 34 % had grade >3 acute esophagitis after radiation therapy. Nineteen percent of these cases had developed within the first month of treatment, 32 % by the second month, and 33 % by the third month [26]. At the authors' institution, we closely monitor acute esophagitis weekly during treatment, and we use aggressive supportive care measures to avoid the need for hospitalization and treatment interruptions.

Reports of potential clinical and dosimetric predictors of esophagitis are many, with substantial variation among studies. Esophagitis has generally been found to be associated with the volume of the esophagus receiving a specific dose, the mean esophageal dose, and the maximum esophageal dose (D_{max}), having a history of esophageal morbidity, having nodal involvement, and receiving twice-daily rather than once-daily irradiation [27–32]. At the authors' institution, we adhere closely to the following dose constraints for patients receiving high-dose radiation for thoracic

malignancies: mean esophageal dose <34 Gy, V_{70} < 20 %, and D_{max} of 80 Gy. These dose constraints were based in part on the reported experience at Washington University [33]. A group at MD Anderson investigated the potential of IMRT for reducing the volumes of irradiated lung and esophagus during the treatment of NSCLC in a retrospective treatment planning study and found that IMRT produced lower lung V_{20} and MLD than did three-dimensional conformal radiation therapy (3D CRT) in all cases. Notably, IMRT also led to smaller volumes of the esophagus and heart being exposed to radiation doses in excess of 45 Gy [34]. In a similar analysis, Gomez et al. tested the ability of a variety of factors to predict radiation-induced esophagitis in 652 patients with NSCLC treated with 3D CRT, IMRT, or proton beam therapy. In that study, the rate of grade ≥3 esophagitis was highest among patients who had been treated with IMRT (28 % vs. 8 % for 3D CRT and 6 % for proton therapy), leading the authors to conclude that the Lyman-Kutcher-Burman statistical model used in that study seriously underestimated the risk of severe esophagitis among patients treated with IMRT [35].

12.2.3.3 Cardiac Toxicity

Most of the posited effects of radiation-induced cardiotoxicity have been extrapolated from studies in which thoracic irradiation was delivered with older, 2D radiation techniques for breast cancer or lymphoma [36–40]. Findings from these studies, in which patients had been treated many years ago with techniques that could not minimize dose to the heart, are generally not applicable to current technology. Moreover, the reported rates of long-term cardiac morbidity varied considerably across studies, from <1 % to >15 %, although the rates do seem to continue to increase over time.

Several studies have compared the putative dosimetric advantages of IMRT over 3D CRT for sparing normal critical structures such as the heart. In one retrospective treatment planning comparison, Liu et al. investigated whether IMRT could reduce the volumes of lung and other critical structures relative to 3D CRT during radiation therapy for NSCLC. In addition to producing a lower MLD, IMRT led to smaller volumes of the esophagus and heart being exposed to high-dose radiation (>45 Gy). IMRT further allowed an additional safety margin around normal structures including the spinal cord, heart, and esophagus to account for uncertainties related to variations in setup, thereby minimizing the risk of radiation-associated cardiomyopathy [34]. Others at MD Anderson found similar results in their evaluations of IMRT versus 3D CRT for patients with stage III–IV NSCLC. Again, IMRT led to smaller lung V_{10} and V_{20} values as well as smaller MLD and a 10 % absolute reduction in risk of RP; IMRT also reduced the volumes of the heart and esophagus receiving >40–50 Gy. Those investigators concluded that IMRT could significantly improve target coverage and reduce the volume of normal lung irradiated to low doses; they further stated that the extent of low-dose exposure of normal tissues can be controlled in IMRT by choosing appropriate planning parameters [41].

12.3 Clinical Use of IMRT

As noted previously within this chapter, concurrent chemoradiation therapy is usually recommended for patients with locally advanced, inoperable stage IIIA or IIIB NSCLC. Nevertheless, treatment failures are relatively common, and overall survival rates remain relatively low at 5 years. Several studies have demonstrated that improving local disease control can improve overall survival for patients with stage III NSCLC [42–45]. Using IMRT rather than 3D CRT is thought to provide both dosimetric and clinical advantages when sufficiently high doses can be given for locally advanced NSCLC. IMRT enables tighter sculpting of high-dose regions around the target volume; the steep gradients created can reduce the radiation dose to surrounding normal tissues, which presumably could facilitate dose escalation [46].

Govaert et al. assessed survival outcomes and acute pulmonary and esophageal toxicity in 86 patients who received IMRT for stage III NSCLC. The median survival time was 29.7 months after delivery of 66 Gy, with or without chemotherapy. Esophageal toxicity was more pronounced in the group that received concurrent chemoradiation, but no differences were noted in pulmonary toxicity [47]. Long-term clinical outcomes for 165 patients with inoperable stage III–IV NSCLC treated with IMRT to doses >60 Gy were recently reported from MD Anderson; the 3-year overall survival rate was 30 %, the rate of grade ≥3 RP was 14 % at 12 months, and the median time to maximum (grade 3) esophagitis was 6 weeks. Those investigators concluded that IMRT led to low rates of pulmonary and esophageal toxicity and favorable clinical outcomes in terms of survival [48].

The use of 4D CT-based treatment simulation and then IMRT instead of 3D CRT for NSCLC became routine at the authors' institution in 2004. In 2010, Liao et al. published findings on disease control, survival, and toxicity for 496 patients who had been treated with IMRT or 3D CRT, both with concomitant chemotherapy, to a median radiation dose of 63 Gy. Toxicity was considerably lower among patients treated with IMRT, specifically in smaller lung V_{20}, lower rates of grade 3 RP, and improved overall survival, leading the authors to conclude that IMRT was associated with therapeutic gain. Rates of locoregional progression-free and distant metastases-free survival rates were no different between those who received IMRT and those who received 3D CRT (Fig. 12.3). Nevertheless, the advantage of lower toxicity, which presumably would allow effective doses of systemic therapy to be given concurrently, may have been a factor in the improved overall survival in this study [49].

A phase I/II protocol involving the use of image-guided, dose-escalated IMRT for patients with stage II–III NSCLC receiving concurrent chemoradiation is currently underway at MD Anderson. The goal of the study is to determine the maximum tolerated dose to the gross tumor volume, starting at 72 Gy and escalated to the highest dose level of 84 Gy, while keeping the dose to the PTV at 60 Gy (Fig. 12.4). This nonuniform delivery of different radiation dose distributions is

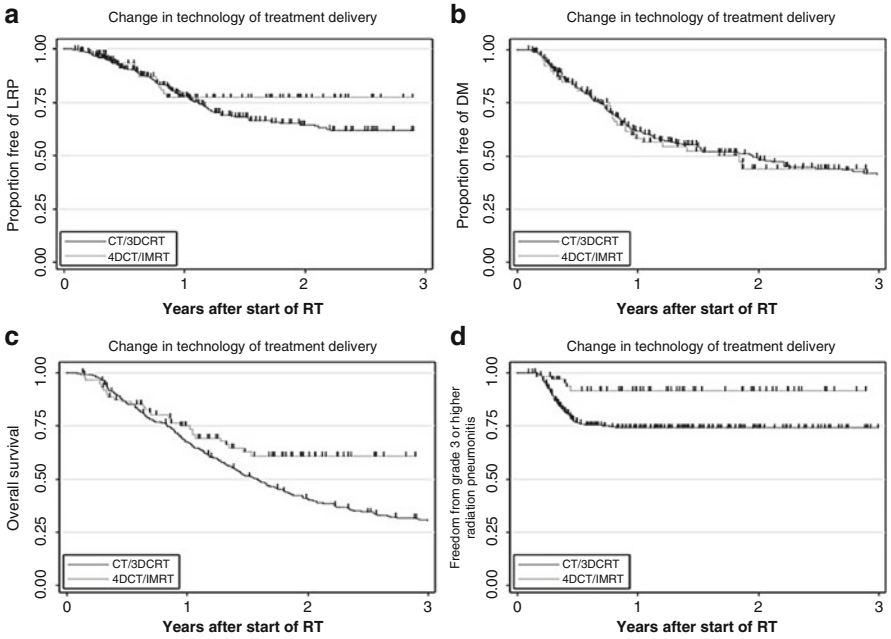

Fig. 12.3 Comparison of (**a**) freedom from locoregional progression (LRP), (**b**) freedom from distant metastases (DM), (**c**) overall survival, and (**d**) freedom from grade ≥3 radiation pneumonitis in patient treated with three-dimensional conformal radiotherapy (3D CRT) or intensity-modulated radiotherapy (IMRT) based on 4D computed tomography simulation (4D CT) (Figure republished (with permission) from Liao et al. [49])

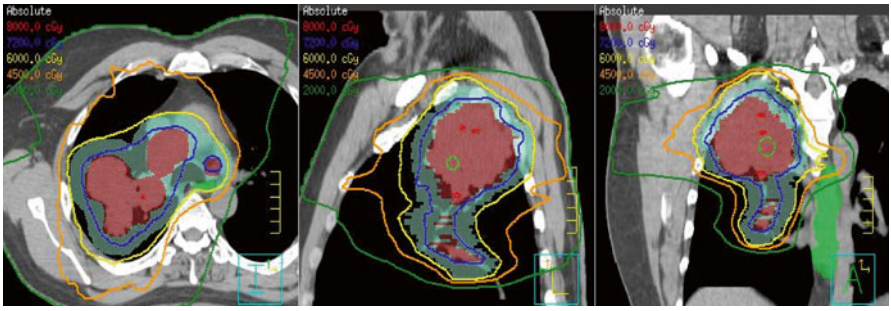

Fig. 12.4 Axial, sagittal, and coronal slices of a treatment plan designed to deliver 72 Gy to the gross tumor volume and 60 Gy to the planning target volume via intensity-modulated radiation therapy with a simultaneous integrated boost

possible with the use of IMRT. The hypothesis of this study is that using a simultaneous integrated boost technique will permit accelerated radiation therapy, with the ultimate goal of improving tumor control without the expected increase in risks of normal tissue toxicity.

12.4 Conclusions

Technologic advances in IMRT and image-guided radiation therapy over the past decade have significantly changed the field of radiation oncology. The availability of daily imaging and more sophisticated treatment delivery systems have allowed the delivery of higher radiation doses to the target volume with tighter conformality, minimizing the dose to normal thoracic structures and thereby improving the therapeutic ratio. Minimizing treatment-related toxicity could expand the number of patients with locally advanced NSCLC who could tolerate concurrent chemotherapy or novel molecular targeted agents, which in turn could lead to improved clinical outcomes.

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Conflict of Interest The authors declare no conflicts of interest.

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