Radiotherapy

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Introduction

Approximately 30–40% of all patients with non-small cell lung cancer (NSCLC) have unresectable stage IIIA and IIIB disease at diagnosis. Stage III NSCLC consists of a heterogeneous group of patients presenting with different patterns of locoregional tumour extension (N1 to N3, contralateral or supraclavicular), unresectable bulky lymph node involvement as well as apparently resectable disease containing unforeseen mediastinal lymph node metastasis. The treatment of T4 disease due to pleural or pericardial effusion is similar to stage IV disease and will not be discussed.

The 5-year overall survival for clinical stage III disease treated with radiotherapy alone is approximately 5%. The low cure rate and high metastasis rate have favoured the inclusion of chemotherapy in combination with radiotherapy, in particular for patients with good prognostic features (i.e. good performance status and limited weight loss) [1].

A meta-analysis of patient data from 52 clinical trials showed an absolute survival benefit of 4% at 2 years with the addition of platinum-based chemotherapy to radiation therapy [2]. This benefit translated into a minor improvement in the 5-year overall survival to approximately 8% [2]. The absolute gains are significant, albeit small, and most patients die of uncontrolled locoregional disease and/or distant metastasis. Conventional radiotherapy consists of 60 Gy delivered in 2 Gy per fraction (fx) during 6 weeks and has classically included all lymph node areas at risk for microscopic disease extension. Dose and volume have been criticised as they result in poor local control and considerable toxicity, in particular when concomitantly delivered with chemotherapy. As an uncontrolled primary tumour remains a source for continuous distant seeding, improvement of local tumour control may result in an increase in survival.

This article focuses on radiation dose and local control, issues of volume and fractionation and addresses several technological advances in radiotherapy that may contribute to an improvement in the outcome of patients with stage III NSCLC.

Importance of achieving local tumour control for survival

Control of intrathoracic disease is an important issue in both early and locally advanced disease. Local control is approximately 30–50% for early stage NSCLC treated with conventional radiotherapy doses of 60–66 Gy [3,4] but only 15–20% for locally advanced disease [5]. Forty-five percent of patients with locally advanced unresectable disease have an isolated local failure and as many as 90% of patients have a component of local failure [6,7].

Analysis of patterns of failure indicates a correlation between persistent or recurrent intrathoracic disease and the subsequent appearance of distant metastases [8,9]. Relapses in the thorax resulted in a death rate similar to the death rate of patients who developed distant metastases. As an uncontrolled primary tumour remains a source for continuous distant seeding, improvement of local tumour control may contribute to an increase in survival.

In the European Organisation for Research and Treatment of Cancer (EORTC) trial comparing radiotherapy alone versus radiotherapy plus daily low-dose cisplatin or weekly cisplatin the survival without local recurrence at 2 years was 31% in the combined arm versus 19% in the radiotherapy alone arm [10]. No differences were observed between the groups with regard to distant failure, indicating that improved local control alone was responsible for the improved survival. Saunders and colleagues [11] reported a similar correlation between improved local control and improvement in overall survival. They used a different approach and tested a continuous hyperfractionated accelerated radiation schedule (CHART, 54 Gy/36fx/12 d) versus a standard once a day (QD) schedule of 60 Gy/30 fx. In the subgroup of patients with squamous cell carcinoma there was a 27% reduction in the relative risk of local progression ($P=0.012$)

and an absolute improvement in 2-year survival of 13% from 20% to 33%. This study supported that an improvement in local control can increase survival [11, 12]. In addition, it confirmed earlier observations [13] that prolongation of treatment time (certainly beyond about 4 weeks) might contribute to radiation treatment failure because of cellular re-population during the course of radiotherapy.

Given the correlation between local tumour control and survival, improvement in local control is a major goal when designing therapeutic strategies to improve the outcome for patients with NSCLC.

Correlation between radiotherapy dose and local control in NSCLC

Inoperable lung cancers are often quite bulky at presentation. Therefore, it is not surprising that standard radiotherapy doses of 60–66 Gy result in poor local control. There is evidence for a direct relationship between the probability of achieving tumour control and radiation dose [9,14].

In 1973 Fletcher reported on the evidence for a dose-effect relation for local tumour control and estimated that to sterilise the size of tumours frequently treated in lung cancer, radiation doses up to 100 Gy might be necessary [15].

Meanwhile, data from the randomised Radiation Therapy Oncology Group (RTOG) trial 73-04, including four treatment arms, suggested a better local control as well as 3-year survival for 60 Gy/30 fx as compared with 50 Gy/25 fx and 40 Gy/20 fx, and a split course regimen (40 Gy/10 fx, with split of 3 weeks) [8]. The failure rate within the irradiated volume (as evaluated using chest X-rays) decreased from 52% at 40 Gy to 42% and 33% at 50 Gy and 60 Gy, respectively [8]. The results of this trial suggested that radiation treatment delivering 60 Gy in 30 fractions was optimal and to be recommended as standard.

Vijayakumar and colleagues [16] compiled literature data on local control as a function of radiation dose in NSCLC. In these studies, conducted in the 1970s and 1980s, local control was scored using chest X-ray or computed tomography (CT) scan [8,16]. The curve fitted to the data showed an increase in local control with increasing tumour dose. The fitted dose for 50% local control was 53 Gy and the projected dose for 90% local control about 80 Gy [16]. Arriagada and colleagues [2] used a rigorous assessment of local control including bronchoscopy and biopsies in patients with locally advanced NSCLC treated with 65 Gy in 26 fractions over 6.5 weeks. Local control at 1 year was achieved in only 15–17% of patients and was considerably lower than the local control rates of 40–60% reported when a presumably less strict non-invasive radiological evaluation was used.

More recently Martel and colleagues [14] analysed local control rates for 76 patients, where local control was defined clinical, bronchoscopic, and/or radiographic. A D50 (dose required for a 50% probability of tumour control) was estimated to be 62 Gy at 12 months and 84.5 Gy at 30 months, and the value of the steepness parameter γ of the sigmoid dose–response curve near D50 was estimated to be 1.5. A steepness parameter value of 1.5 suggests a 15% improvement in local control per 10 Gy increase in dose [17].

The study by Martel and colleagues [14] also indicated that doses higher than 85 Gy are required for local control longer than 30 months.

The volume of disease appears to have an impact on survival in patients treated with definitive radiotherapy. Bradley and colleagues [18] demonstrated by multivariate analysis that tumour volume rather than tumour-node-metastasis (TNM) stage was the most important predictor for overall and disease-free survival in 207 patients with locally advanced NSCLC treated with definitive radiotherapy. Etiz and colleagues [19] observed that increased local progression-free and distant failure-free survival were independently associated with a small total tumour volume (i.e. <80 ml). Willner and colleagues [20] retrospectively analysed local control as a function of dose and tumour volume and found that dose escalation beyond 60 Gy might be beneficial for small volume tumours (i.e. <100 ml). Higher dose levels did not improve local control for large volume (>100 ml) tumours. This is not unexpected, as with increasing tumour size there is a higher propensity for metastatic spread and in locally extended disease the potential survival advantage of improved local control will be offset by death due to distant metastasis. Martel and colleagues [21] reported that dose seems to be important for tumours <200 ml.

Rengan and colleagues [22] evaluated whether high-dose radiation improved local control in 72 patients with stage III NSCLC and large volume disease (>100 ml). They reported local failure rates at 1 and 2 years of 27% and 47%, respectively, for stage III patients treated to 64 Gy or higher and 61% and 76%, respectively, for those treated to less than 64 Gy. They estimated that a 10% increase in dose resulted in a 36% decreased risk of local failure.

From the available literature we concluded that thoracic radiotherapy delivering 60–66 Gy in classical fractionation is ineffective in ensuring persistent local

Table 1
Characteristics and doses attained in selected radiotherapy dose escalation trials

Institution	Fraction size (Gy)	Overall treatment time (weeks)	Tumour dose attained (Gy)		
			Low-risk	Intermediate	High-risk
RTOG 9311 [31]	2.15	6–10	83.8	77.4	[a]
University of Michigan [23,32,33]	2.10	6–10	102.9	75.6–84	65.1
NKI-AVL [25]	2.25	6	94–87.75[b]	81	74.25
MSKCC [26]	1.8–2	8–9	84	84	84

[a] Closed early due to poor accrual and perception of excessive risk of radiation pneumonitis (2 toxic deaths) [31].
[b] Updated (unpublished) analysis of [25].

control. With more intensive radiotherapy regimens improved local control and survival can be achieved in particular in low-volume disease.

Strategies designed to improve local control (and ultimately survival) include radiation dose escalation, altered fractionation schedules (hyperfractionated or accelerated thoracic radiotherapy) and combined chemoradiation approaches.

Radiation dose escalation

Modern radiotherapy techniques, such as three-dimensional conformal radiotherapy (3D-CRT), have resulted in a significant improvement in confining the high-dose volume to the tumour while sparing the surrounding normal tissue as much as possible. With the belief that higher than conventional dose radiotherapy may improve local control, several groups have initiated phase I radiotherapy dose escalation studies using 3D-CRT [23–26]. The maximum dose that can be delivered to a tumour is restricted by the tolerance of the surrounding normal tissues. For tumours located within the chest, these critical tissues include the lungs, the oesophagus and the spinal cord. Radiation pneumonitis is the primary dose-limiting complication with radiation alone. It has been recognised that the probability of developing severe radiation pneumonitis is related to the radiation dose, the amount of irradiated volume and the fractionation schedule [27].

Since the routine availability of 3D-treatment planning systems and 3D-dose calculation algorithms, lung dose-volume histograms can be easily generated. Several lung dose-volume parameters, such as the volume of lung receiving more than a threshold dose (Vth) of, for example, 20 Gy (V20) and the mean lung dose (MLD) can be derived from such dose-volume histograms. These parameters (which are often strongly correlated [28]) have been assessed for their association with the risk of radiation pneumonitis [28–30]. In the radiotherapy dose escalation studies [23–25], patients have been segregated into different risk groups based on their V20 or MLD and the dose has been escalated within each risk group. In general, patients with a low tumour volume (e.g. small peripheral tumours) were allocated to the low-risk group, while patients with stage III disease were allocated to the intermediate- or high-risk group, the latter in particular in case of bulky disease [26,31].

In the radiotherapy dose-escalation trials the lung dose limiting toxicity was generally defined as the development of radiation pneumonitis necessitating oxygen administration or assisted ventilation. With regard to oesophageal toxicity, severe dysphagia with dehydration or weight loss of >15% is considered dose-limiting.

In the selected trials (Table 1) the fraction size was rather ' standard' and the overall treatment time prolonged with increasing dose except for the Netherlands Cancer Institute (NKI) trial in which the overall treatment time was restricted to 6 weeks [25]. In none of the trials was concurrent administration of chemotherapy allowed. Table 1 summarises the dose levels attained in four published dose escalation trials [23,25,26,31–33] for the different risk groups.

The results of these four selected mature dose escalation trials suggest that for patients with locally advanced and ' intermediate' volume disease dose escalation up to 75–84 Gy can be safely achieved. For patients with a very large tumour burden, dose escalation is less attractive as volume restriction is often impossible. In this subgroup of patients induction chemotherapy should be considered as it may result in a reduction in tumour volume and consequently facilitate dose escalation.

Altered fractionation

Fractionation refers to how much radiation dose is delivered during each fraction and to the overall treatment time during which the total dose is delivered.

Standard fractionated radiotherapy delivers 1.8–2 Gy per fraction, once daily, 5 d a week, with an overall treatment time of 6 weeks for a prescribed tumour dose of 60 Gy. Repopulation is an important issue in the management of NSCLC and is hypothesised to be a factor that limits the success of conventional dose-escalation approaches [17]. Treatment prolongation has an adverse effect on survival. Cox and colleagues [13] analysed data from RTOG trials and found that without treatment delay the probability of 3-year survival was 56% compared with 17% with delay. Median loss in survival probability was calculated to be 1.6% per day of delay beyond 6 weeks. Very recently, Machtay and colleagues [34] evaluated data from three prospective RTOG trials in which immediate concurrent chemoradiation (cisplatin-based) was the primary therapy for good-performance status stage III NSCLC. They found that, even when concurrent chemotherapy was delivered, prolonged treatment time was significantly associated with poorer survival ($P = 0.02$), indicating a 2% increase in the risk of death for each day of prolongation in therapy.

Hyperfractionated and accelerated radiotherapy have been designed to prevent rapid tumour repopulation during a radiation treatment course. Acceleration of radiation treatment involves the delivery of the target dose in less time, and is analogous to the concept of ' dose-density' in chemotherapy [35]. To prevent the excessive late tissue toxicities that result from single large daily fractions (commonly used for palliation or in stereotactic radiotherapy) multiple smaller fractions are used each day (hyperfractionation). In hyperfractionated radiotherapy, doses of 1.1–1.6 Gy are delivered twice or three times daily with an interval of 4–8 h to allow normal tissue to repair sub-lethal damage. The use of small fraction sizes may permit an overall increase in tumour dose with less damage to late-reacting normal tissues. However, this approach may enhance adverse effects on acute-reacting tissue such as oral and oesophageal mucosa.

The RTOG 83-11 trial [36] tested multiple total tumour doses (60, 64.8, 69.6, 74.5 and 79.2 Gy) using hyperfractionated radiotherapy of 1.2 Gy fractions delivered twice daily. Although there was no decrease in late events such as radiation pneumonitis, the apparent survival benefit in these phase I/II trial was used to justify the inclusion of a hyperfractionated arm in the subsequent RTOG 94-10 trial [37]. This trial included stage III (and selected medically inoperable stage II) NSCLC and was designed to determine whether chemotherapy (vinblastine/cisplatin) concurrent with once daily radiotherapy or hyperfractionated radiotherapy resulted in improved survival over the same chemotherapy given sequentially before radiotherapy. The results showed a better median survival for the concurrent daily radiotherapy arm when compared with the sequential arm (17 versus 14.6 months, $P = 0.038$). The hyperfractionated arm had a median survival of 15.6 months, which was not statistically significantly different from the sequential arm [37].

The CHART trial [11] compared hyperfractionated accelerated radiotherapy (HART, 54 Gy/36 fx/12 d) versus a QD schedule of 60 Gy/30 fx. Overall, CHART produced a statistically significant improvement in survival of 10% at 2 years.

The ECOG 2597 trial [35] compared QD radiotherapy (64 Gy) with HART (57.6 Gy/36 fx/15 d) after induction chemotherapy in locally advanced stage III NSCLC. Not unexpectedly, the HART regimen resulted in a higher oesophagitis rate (25% for HART versus 16% for the conventional arm). Although there was a trend of improved survival (20.3 months for HART versus 14.9 months for the standard arm) the difference did not reach statistical significance. It should be noticed, however, that the ECOG 2597 trial did not meet its accrual goals. Trials investigating hyperfractionation are not popular in daily practice, as the logistics are inconvenient for patients and radiotherapy departments.

In conclusion, the CHART trial is the only trial proving that hyperfractionated radiotherapy is superior to the standard regimen of 60 Gy. However, this trial has been criticised because the hyperfractionated arm was compared with an outdated standard arm. There is currently consensus that the standard treatment in good performance stage III NSCLC is combined chemoradiation.

Combining chemotherapy and radiation

In the 1990s, the results of several phase III trials of chemotherapy followed by radiation versus radiotherapy alone emerged and showed a significant survival benefit with the addition of chemotherapy. The design and survival data of three major trials of induction chemotherapy followed by radiation versus radiation alone are summarised in Table 2 [5,6,38].

As a result of the meta-analysis of chemotherapy in NSCLC [2] showing a 13% reduction in the risk of death corresponding with an absolute improvement of 5% in 5-year survival, (sequential) platinum-based chemotherapy and radiotherapy became the standard of care in good-performance patients with stage III disease.

Simultaneously, a number of randomised trials (e.g. EORTC [10], Czech trials [39]) have evaluated the

Table 2
Design of selected trials of radiotherapy (RT) versus chemotherapy followed by radiotherapy in stage III NSCLC

Trial	Number of patients	Trial design	Survival	
			Median (months)	3 year (7 year)
CALBG 8433 [6]	155	Cisplatin + vinorelbine + 60 Gy versus 60 Gy	13.8 9.7 ($P = 0.007$)	23% (13%) 10% (6%) ($P = 0.012$)
RTOG, ECOG, SWOG [38]	458	Cisplatin + vinorelbine + 60 Gy versus 60 Gy versus 69.6 Gy hyperfractionated	13.2 $P = 0.04$ 11.4 12	17% 11% 14%
GETCB [5]	353	65 Gy versus VLCC[a] × 3 + 65 Gy + VLCC × 3	 Not available	4% 12% ($P = 0.02$)

[a] Vindesine/lomustine/cisplatin/cyclophosphamide.

Table 3
Trials of sequential versus concurrent chemoradiation in stage III NSCLC

Trial	Number of patients	Trial design	Survival	
			Median (months)	Year
Japan [42]	320			(5 year)
		Cisplatin + vindesine + mitomycin + 56 Gy (split) versus	16.6	15.8%
		Cisplatin + vindesine + mitomycin → 56 Gy (continuous)	13.3 ($P = 0.04$)	8.9%
RTOG 94-10 [37]	610			(4 year)
		Cisplatin + visblastine + 60 Gy versus	17 P = 0.046	21%
		Cisplatin + etoposide + 69.6 Gy hyperfractionated versus	15.6	17%
		Cisplatin + vinblastine → 60 Gy	14.6	12%
GLOT–GFPC [43]	212			(2 year)
		Cisplatin + etoposide + 66 Gy → cisplatin + navelbine versus	15	35%
		cisplatin + navelbine → 66 Gy	13.8 NS	23% NS

concurrent administration of radiosensitising platinum compounds in combination with standard [10] or hyperfractionated radiotherapy [39].

The use of concurrent chemoradiation might be seen as an approach of increasing the local effectiveness of radiotherapy (referred to as chemo-enhanced radiotherapy (CERT) [40]) at the same time as reducing the risks of metastatic disease by using chemotherapy.

Concurrent radiotherapy may increase the effectiveness of radiation by sensitising the tumour to radiation, but it can also increase the adverse effects, in particular oesophagitis.

In a recent Cochrane meta-analysis [41] of three trials of concurrent versus sequential chemoradiotherapy [37,42,43] (Table 3), there was a 14% reduction in risk of death at 2 years compared with sequential chemoradiotherapy and a 7% reduction compared

with radiotherapy alone. Concurrent chemoradiation resulted in an increase in acute oesophageal toxicity.

The authors warned about short follow-up, uncertainties in toxicity in the three trials and concluded that the optimal chemotherapy schedule remains unclear.

The EORTC 8972 trial was designed to address the dilemma of sequential versus concurrent administration of chemotherapy and radiation. In this trial, patients with low-volume stage I–III disease were randomised between induction chemotherapy (two courses of cisplatin/gemcitabine) followed by high-dose radiation (66 Gy/24 fx) versus concurrent daily low-dose cisplatin with the same radiation regimen. Unfortunately this trial closed prematurely because of poor patient accrual.

In conclusion, in patients with stage III NSCLC and good performance status, combined-modality therapy using platinum-based chemotherapy and thoracic radiotherapy results in a modest, albeit significant, improvement in survival and should be considered as the standard of care. The optimal sequencing of both treatment modalities remains to be determined.

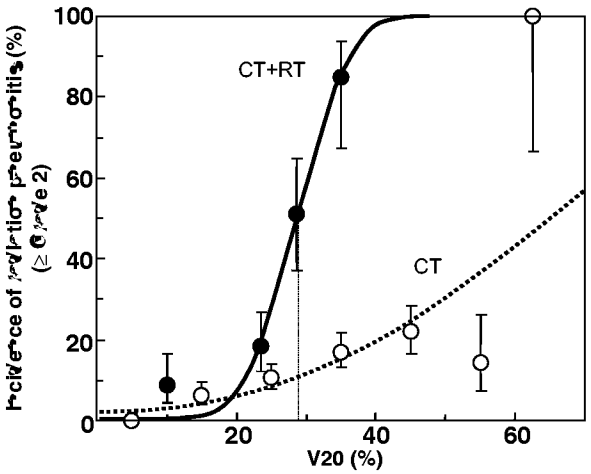

Fig. 1. Incidence of radiation pneumonitis (≥ Grade 2) as a function of the relative lung volume irradiated to more than 20 Gy (V20) of 71 lung cancer patients treated with concurrent chemoradiation (solid circles) and that of 382 patients treated with radiotherapy alone (open circles). The curves are calculated using the maximum likelihood model fit to the data. The error bars represent a 68% confidence interval. (Adapted from Seppenwoolde et al. 2003 [45].)

Radiation-induced lung toxicity

The dose-limiting normal tissues in thoracic irradiation include lung, oesophagus, spinal cord and heart. The most important acute complications of thoracic irradiation are radiation pneumonitis and oesophagitis.

Clinically significant radiation pneumonitis develops in approximately 13–37% of NSCLC patients treated with radical radiotherapy doses. The onset is typically between 1 and 6 months after completion of radiotherapy. Clinical symptoms range from shortness of breath, unproductive cough and occasionally mild fever to death from respiratory failure. Radiation pneumonitis usually responds well to treatment with steroids (40–60 mg prednisolone daily) followed by a slow taper to prevent rebound pneumonitis. Classically, radiation pneumonitis has been divided into an ' early' or acute pneumonitis phase and a ' late' fibrosis phase. Little is known about the exact mechanisms involved in the events leading to radiation pneumonitis. The current view is that radiation pneumonitis is a response of the complex tissue with multiple interactions between different cell populations (inflammatory, fibroblastic, endothelial and epithelial) via specific growth factors (e.g. transforming growth factor beta) and cytokines (e.g. tumour necrosis factor (TNF)-alpha, interleukin (IL)-1beta) forming a network of signals that modulate the function, differentiation and proliferation of those cells [44].

Several radiation pneumonitis scoring systems have been developed. The most frequently used scales include the Southwest Oncology Group (SWOG) scale, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and the EORTC/RTOG system. Radiation pneumonitis requiring steroids is usually assigned Grade 2, except for the EORTC/RTOG system, which considers the necessity to administer steroids a Grade 3.

Normal lung tissue complications are related to irradiated lung volume and radiation dose. The best models currently available for predicting radiation pneumonitis are the mean lung dose [28,29] and threshold dose model [30]. The latter relates the volume of lung receiving more than a threshold dose of, for example, 20 Gy (V20), to the risk for developing radiation pneumonitis with greater risk when V20 is >40% [30].

Concurrent administration of chemotherapy and radiation results in a higher probability of developing complications at the same dose. This synergistic effect translates in a shift of the dose-complication curve to the left, as illustrated in Fig. 1.

Radiation-induced oesophageal toxicity

In locally advanced stage III NSCLC the oesophagus often cannot be excluded from the radiation beams because of the proximity of this organ to the target volume, in particular in case of (bulky) mediastinal

lymph node involvement. Treatment with chemotherapy or radiotherapy, alone or administered concurrently, destroys the rapidly dividing basal epithelial cells. Cell death following exposure to chemotherapy and radiation decreases the renewal rate of the basal epithelium causing mucosal atrophy, ulceration of the mucosa and initiation of the inflammatory response [46]. Patients experience difficulty swallowing solids, which may progress to dysphagia, retrosternal chest pain and heartburn. These symptoms are acute side-effects and typically commence 2–3 weeks after the start of radiotherapy. The effects usually resolve within 2–3 weeks after completion of treatment. Late oesophageal toxicity may be seen 1–5 years after treatment and include stenosis, fibrosis and tracheo-oesophageal fistula due to mucosa necrosis.

Bruner and colleagues [47] have reported that of all toxic effects that can occur, oesophagitis has the greatest impact on the quality of life of patients.

The development of oesophageal toxicity depends mainly on the radiation dose delivered, and whether combined modality is given. Oesophageal toxicity is most pronounced with concurrent chemoradiotherapy or CHART radiotherapy. Synergy between chemotherapy and radiotherapy increases the effectiveness of radiation by sensitising the tumour to radiation, but it also increases the severity of adverse effects, in particular of oesophagitis.

There is no consensus as to which dosimetric parameters are most predictive for oesophageal injury. The length of irradiated oesophagus, maximum or mean oesophageal dose or percentage of oesophagus receiving more than a threshold dose have all been implicated as predictors for oesophageal toxicity [48–50].

The use of amifostine, a radioprotective compound, has been evaluated in randomised phase II and III trials in lung cancer. The results are mixed with regard to the ability of amifostine to reduce radiation-induced oesophagitis. Although it has never been demonstrated in a clinical study, experimental studies have suggested that amifostine may also protect tumour cells [51].

Technological advances, such as the use of involved field radiotherapy, and intensity-modulated techniques (IMRT), may minimise toxic effects of radiotherapy.

Technological advances

Radiation treatment volume

It has been realised that strategies to improve local control, such as the delivery of high-dose radiotherapy or concurrent chemoradiation, require restriction of treatment volume in order to minimise the risk of complications in the tumour-surrounding normal tissues (in particular oesophagus and lung). Elective nodal field irradiation (ENI) incorporating all lymph node areas at risk for tumour spread has long been standard practice in lung cancer radiotherapy. Nowadays, ENI has been abandoned as it hampers dose escalation and its benefits have never been demonstrated. Analysis of patterns of failure of phase I/II trials using involved field radiotherapy (including lymph nodes with a short axis diameter $\geqslant$1 cm on CT or showing fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)-scan [52,53]) showed an acceptable isolated regional nodal relapse at initial failure in approximately 0–6% of patients [25,53–56]. Hence, the value of ENI has been called into question and currently the standard of care has shifted from ENI towards the use of involved field radiotherapy.

Multimodality imaging to improve target volume delineation

There is now consensus that FDG-PET is superior to CT alone in mediastinal lymph node staging of NSCLC. As PET provides a better staging of the mediastinum, the integration of PET could assist the radiation oncologist to define the target volume more accurately. In treatment protocols in which ENI is omitted, in particular, the complementary information of PET might alter the nodal target volume [52,53].

When using CT as a sole imaging modality, large inter-observer variability in the definition and contouring of the tumour volume has been reported. Preliminary reports suggest that the incorporation of PET-CT fusion (Fig. 2) in treatment planning may lead to a more consistent definition of the gross target volume (GTV) [57].

The development of techniques for image correlation has facilitated the integration of information provided by different imaging modalities in the radiotherapy treatment planning process.

The impact of complementary PET data on changes in GTV, consecutive changes in planning target volume (PTV), radiation treatment plan and normal tissue complication probability, has been evaluated in several (retrospective and prospective) studies [52,57–60].

It is hypothesised that the integration of PET may lead to a better local control. Increases in target volume may limit the risk of a geographical miss, while decreases in target volume may facilitate dose escalation and concurrent chemoradiation maintaining toxicity acceptable.

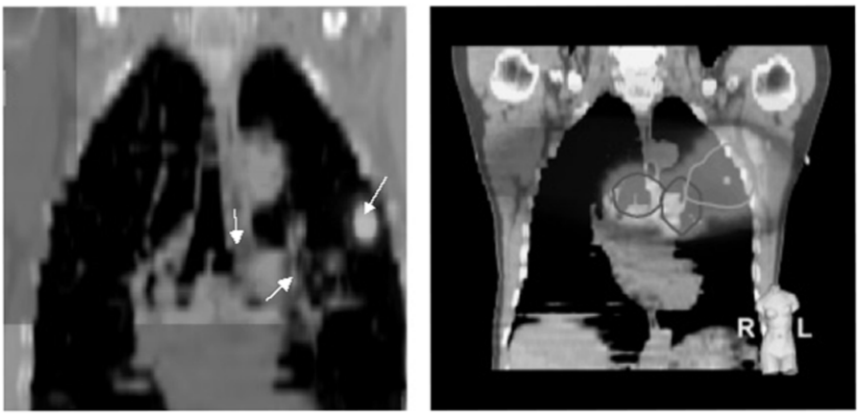

Fig. 2. Left panel: matched positron emission tomography-computed tomography (PET-CT) scan of a patient with left upper lobe T2N2 non-small cell lung cancer (NSCLC). Arrows indicate foci of FDG uptake. Right panel: Dose distribution (coronal view) of the involved radiotherapy plan for this patient.

Intensity-modulated radiotherapy – image-guided radiotherapy

Toxicity (in particular lung and oesophageal) limits dose escalation and strategies to improve local control should balance a potential gain against an increase in toxicity. Currently, 3D-CRT is the standard approach for radical treatment of NSCLC. In this approach, the beams are shaped to the planning target volume. Intensity-modulated radiotherapy (IMRT) is a rather novel development and allows the dose to be more precisely conformed to the target volume in order to spare maximally normal structures by using non-uniform beam intensity patterns. Algorithms are available that optimise the radiation intensity distribution (fluence) within each beam to achieve superior dose distribution and reduce dose to lung tissue and oesophagus [61,62].

The clinical introduction of IMRT has been delayed because of inaccuracy of dose calculation algorithms and complexity of lung radiotherapy, in particular in case of respiration-induced tumour motion, which can be considerable in lower lobe tumours.

Many strategies have been developed to cope with the problem of lung tumour motion, such as breath-holding (voluntary or forced using an apparatus), gating and respiration-correlated scanning [63,64].

Another new technology on the horizon is image-guided radiotherapy (IGRT). This approach uses imaging of the patient (e.g. using cone beam CT [65]) just before radiotherapy in order better to target the radiation dose in the tumour while reducing exposure of surrounding normal tissue. IGRT is a promising development and has the potential to significantly improve the accuracy of radiotherapy, thus facilitating safe dose escalation and, ultimately, local tumour control.

Role of postoperative radiotherapy

The role of postoperative radiotherapy in patients with NSCLC has been debated for many years.

Non-randomised, single institutional trials have suggested that postoperative radiotherapy to moderate doses of 45–55 Gy is able to eradicate microscopic residual disease and reduces the rates of local recurrence. However, whether or not the reduction in locoregional recurrence also leads to an improvement in survival has never been demonstrated in a prospective randomised trial.

The post-operative radiotherapy (PORT) meta-analysis of 2128 patients treated in nine randomised trials of postoperative radiotherapy showed a significant adverse effect of PORT on survival, with a hazard ratio of 1.21 or 21% relative increase in risk of death. This is equivalent to an absolute detriment of 7% at 2 years, reducing survival from 55% to 48% [66]. This decreased survival was related to an increase in radiation-induced lethal cardiac and pulmonary toxicity. Subgroup analysis has suggested that this effect was most pronounced for patients with stage I and II, N0–N1 disease, whereas for N2 disease there was no clear evidence of an adverse effect.

There has been a lot of criticism regarding the radiotherapy modalities of the studies included in this PORT meta-analysis. The studies used a wide range of doses, fraction sizes, volumes, old-fashioned techniques and equipment (e.g. Cobalt beams) and were conducted over a period of 30 years. Compared with current standards of treatment, it is likely that such postoperative radiotherapy would lead to excess deaths from cardiac and pulmonary toxicity. The increased risk of death was most pronounced in patients with stage I disease and was not significant in patients with

stage III disease. A few trials have demonstrated an improvement in local control, particularly in patients with stage II and III disease [67,68]. A potential survival benefit of modern radiotherapy for resected N2 patients cannot be excluded. In the absence of evidence for a survival benefit, postoperative radiotherapy should not be recommended. It should be considered in selected subgroups of stage III patients with increased risk of locoregional recurrence such as involvement of multiple lymph node areas, extracapsular extension or positive resection margins.

It was concluded that postoperative radiotherapy is detrimental to patients with early stage completely resected NSCLC. Further studies are needed to clarify the role of postoperative radiotherapy in patients with N2 disease.

Conclusion

Radiotherapy is an integral part of the treatment of patients with inoperable stage III NSCLC. For patients with good prognostic features the gold standard is to combine radiotherapy with chemotherapy. The optimal sequencing and regimen of both modalities is not determined. Although preliminary data suggest that concurrent chemoradiation yields better survival rates than sequential chemoradiotherapy administration, it should be realised that follow-up is still short and acute toxicity increased.

A myriad of technological advances, such as PET-CT imaging, IMRT, respiration-gating and image-guided radiotherapy, has become available. It is hypothesised that this high-tech radiotherapy will allow a better coverage of tumour volume (less geographical misses), better normal tissue sparing and safe dose escalation and that it will ultimately translate into better local control and survival of patients with NSCLC.

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