The role of radiotherapy in non-small-cell lung cancer

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Introduction

Radiotherapy has an important and established role in the treatment of patients with non-small-cell lung cancer (NSCLC). This overview will focus on the recent developments in combined modality treatment and technical advances in radiation delivery, both of which have led to significant improvements in treatment outcomes.

Medically inoperable stage I NSCLC

The 5-year overall survival in patients with stage I NSCLC after surgery is around 67% for T1N0M0 tumors and 57% for T2N0M0 tumors [1]. Significant co-morbidity in these patients can render them medically inoperable [2]. Untreated early-stage lung cancer has a poor outcome, with the majority of patients dying of lung cancer in the 5-year period following diagnosis [3, 4]. Outcomes after conventional radiotherapy are modest, with a literature review reporting 3- and 5-year disease-specific survivals of 39 ± 10% and 25 ± 9%, and overall survival around 34 ± 9% and 21 ± 8%, respectively [5]. Reasons for the poorer survival after conventional radiotherapy in comparison with surgery include suboptimal staging of patients, insufficiently high radiation doses and ‘geographical misses’ owing to tumor mobility.

Far superior local control rates have been reported with the use of hypofractionated extracranial stereotactic radiotherapy in stage I NSCLC, ranging from 85–95% for T1N0 lesions [6–8]. The high local control rates can be accounted for by the use of very high radiation doses (e.g., three fractions of 20 Gy) delivered with careful attention paid towards accurate positioning of patients, individualized assessment of tumor mobility, non-coplanar radiation beam arrangements (Figure 1) and short overall treatment times. Despite the delivery of biologically effective doses of up to 180 Gy [9], symptomatic radiation pneumonitis is observed in <5% of patients. While long-term follow-up data are awaited to confirm the low incidence of late radiation toxicity, stereotactic radiotherapy appears to be an effective alternative to surgery in high-risk patients with stage I NSCLC.

Treatment issues in stage III NSCLC

Key issues in the treatment of stage III NSCLC include (i) the role of surgery in local treatment, (ii) the role of concurrent versus sequential chemo-radiotherapy, (iii) use of computed tomography (CT)- and/or positron emission tomography (PET)-based involved-field radiotherapy, (iv) the role of advances such as use of 4-dimensional (4D) CT scans and gating, and (v) the implementation of combined modality treatment in daily practice.

Role of surgery in the local treatment

When comparing the outcomes of clinical trials, one should keep in mind the inclusion criteria, as well as the extent of mediastinal nodal disease and the staging procedures [e.g. CT scan only, histology/cytology, 18F-deoxyglucose PET (FDG-PET)], as these identify groups of patients with varying prognosis. Patients with nodal metastases identified only by invasive preoperative staging (e.g. mediastinoscopy; nodal biopsy by other means) have a far more favorable prognosis than those with bulky N2 disease or multi-station N2 disease. The majority of patients treated in trials evaluating definitive chemo-radiotherapy had bulky or fixed multi-station N2 disease [10], contrary to phase III trials evaluating surgery, which include only patients with limited N2 disease [11, 12].

In patients undergoing primary surgery and in whom mediastinal nodal metastases were detected preoperatively on CT scans, 5-year survivals range from only 8% (with single nodal level involvement) to 3% (nodal involvement at multiple levels) [13]. In the recent INT 0139 study, patients with pathologically confirmed, operable stage IIIA-N2 disease were randomized to either concurrent chemo-radiotherapy to 45 Gy followed by surgery, or definitive chemo-radiotherapy to 61 Gy [11]. The median and 3-year overall survivals in the two groups were not significantly different, and the median survival in the non-surgical arm of 22 months was the best ever reported for this approach in a randomized phase III trial. The INT 0139 study revealed that the benefits of surgery over chemo-radiotherapy alone are not apparent when comparable patients groups are evaluated. The question of best local treatment after induction chemotherapy was the subject of the European Organization for Research and Treatment of Cancer (EORTC) 08 941 study, where patients were subsequently randomized to either surgery or radiotherapy [12]. Results of the 08 941 study are keenly awaited, and are expected in 2005. Achieving tumor-free status in mediastinal lymph nodes with induction therapy appears to be the strongest predictor of long-term survival in patients undergoing surgical resection.
[11, 14], with 46% of patients in INT 0139 who were ‘downstaged’ to N0 disease having a median survival of 37 months. The use of techniques such as endoscopic ultrasound for restaging of the mediastinum following induction treatments are the subject of active research.

**Concurrent versus sequential chemo-radiotherapy**

For patients with ‘inoperable’ stage III disease, the overall survival is superior with sequential chemotheraphy and radiation versus only conventional radiotherapy [15]. However, the gains are modest, with median survivals being 13.2 months versus 11.4 months, and 5-year survivals of 8% and 5% after sequential chemo-radiotherapy and radiotherapy, respectively. Three completed phase III clinical trials have addressed the issue of sequential versus concurrent chemo-radiotherapy in stage III NSCLC, and two have reported a small improvement in median survival of ~2.5 months [10, 16], while the third trial did not show any survival benefit [17]. The Japanese trial was conducted in a highly selected patient population with a requirement that radiation fields be less than one half of a single lung [16]. The selection criteria may explain the low toxicity reported despite the use of concurrent mitomycin with thoracic radiotherapy (Table 1), a finding in marked contrast to the 48% incidence of acute grade 3–4 non-hematological toxicity observed in the Radiation Therapy Oncology Group (RTOG) 94-10 study [10]. A Cochrane meta-analysis of these three trials advised caution in adopting concurrent treatment as standard of care given the uncertainties about the true magnitude of benefit in comparison with sequential treatment [18]. The Cochrane analysis also concluded that the choice of optimal chemotheraphy schemes for concurrent treatments remain unclear.

Another point of concern is the suboptimal radiotherapy schemes used in sequential treatment arms of the two positive studies, namely 30 fractions of 2 Gy [10] and 28 fractions of 2 Gy [16]. ‘Standard’ fractionation schedules of 60 Gy in once-daily fractions of 2 Gy were clearly shown to be inferior in the continuous, hyperfractionated, accelerated radiotherapy (CHART) study [19]. The superiority of accelerated radiotherapy emphasizes the importance of tumor repopulation during treatment, and is supported by a retrospective analysis of patients treated for NSCLC that showed a 1.6% daily loss in survival when overall treatment times exceed 6 weeks [9]. The benefits of using accelerated radiotherapy schemes with induction chemotheraphy were also suggested by the findings of the Eastern Cooperative Oncology Group (ECOG) 2597 study, which was prematurely closed [20]. In ECOG 2597, induction chemotherapy was followed by sequential radiotherapy using either an accelerated scheme (HART 57.5 Gy in 2.5 weeks), which resulted in a median survival of 22.2 months, or by a ‘conventional’ scheme (64 Gy in 6.5 weeks), which resulted in a median survival of 13.7 months. Given the radio-biological evidence from randomized clinical trials such as CHART, the recommendations contained in the 2003 ASCO guidelines for ‘definitive dose’ thoracic radiotherapy to be ‘no less than the biologic equivalent of 60 Gy in 1.8-Gy to 2-Gy fractions’ [21] are suboptimal for sequential chemo-radiotherapy schemes. When using sequential chemo-radiotherapy, many departments in mainland Europe have adopted accelerated radiotherapy schemes using once-daily fractions of 2.6–3 Gy, and overall treatment time of ≤5 weeks. The published data suggest that toxicity of such hypofractionated schemes (i.e. use of a limited number of fractions with increased dose per fraction), if used in conjunction with involved-field radiotherapy, is acceptable.

![Figure 1. Screenshot of a stereotactic plan for stage I NSCLC. Seven non-coplanar beams were used to achieve a sharp dose fall-off so that the adjacent chest wall received <40% of the prescription dose.](https://academic.oup.com/annonc/article-abstract/16/suppl_2/ii223/160820)
Clinical implementation of chemo-radiotherapy

Superior sulcus tumors (Pancoast’s tumors)

When technically operable, these relatively uncommon tumors are now widely treated with cisplatin-based concurrent chemo-radiotherapy to 45 Gy, followed by surgical resection. This practice has been supported by the findings of two phase II studies conducted in North America [22] and Japan [23]. Patients in the North American study were treated with a cisplatin–etoposide combination and 36% of resected cases had a pathological complete response, an identical figure to that observed in the INT 0139 study where an identical scheme was used [11]. A cisplatin–mitomycin C–vindesine combination was used in the Japanese study, where a pathological complete response rate of only 15% was observed. In the light of these findings, the cisplatin–etoposide–radiotherapy scheme is recommended for clinical use for NSCLC of the superior sulcus.

Avoiding concurrent chemo-radiotherapy in high-risk patients

As the survival benefit from concurrent chemo-radiotherapy is limited, patients who are at high-risk for toxicity should preferably be treated in only well-controlled clinical trials. The incidence of high-grade radiation pneumonitis correlates with the total lung volume treated to a dose of 20 Gy or more (i.e. the V20), and it has been recommended that patients with a V20 >35% should not be treated with concurrent treatment outside clinical trials [24]. Such caution is justified, as grade 2 or higher radiation pneumonitis has been reported in >50% of such patient who were treated with concurrent chemo-radiotherapy. Furthermore, patients with a V30 <37% have been reported to develop grade 3 late pulmonary toxicity, despite having manifested no acute grade 3 pulmonary toxicity [25]. A radiotherapy-planning CT has to be performed in order to determine a V20, but the following clinical scenarios generally predict high V20 values: patients with metastases in the contralateral hilus, peripheral lower lobe lesions with contralateral upper mediastinal nodes and large retrocardiac tumors with nodal metastases.

Use of CT- and/or PET-based involved-field radiotherapy

The high incidences of high-grade esophagitis, and to a lesser extent radiation pneumonitis, reported in previous trials of concurrent chemo-radiotherapy are partly related to the use elective nodal irradiation. Future studies will show less toxicity as current EORTC guidelines recommend omission of elective nodal irradiation in NSCLC [24]. Studies that have evaluated patterns of disease recurrence following involved-field radiotherapy have not observed a significant incidence of recurrences in thoracic nodal regions outside the planning target volume [26]. FDG-PET is superior to conventional techniques for nodal staging such as CT scans and esophageal ultrasound for NSCLC [27]. In view of the high negative predictive value of PET in excluding mediastinal N2 or N3 disease, PET-positive mediastinal regions are being incorporated into radiotherapy planning. However, there are at present insufficient data to support the use of only PET information for defining the target volume for primary tumors. Nevertheless, use of elective nodal irradiation remains widespread in North America and Japan in spite of the absence of evidence showing that it improves either local control or survival.

Minimizing delays between induction chemotherapy and radiotherapy

ASCO guidelines recommend that in patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of initial platinum-based chemotherapy should be no more than four cycles [21]. In one report, tumor progression following the completion of induction chemotherapy resulted in nearly 41% of potentially ‘curable’ patients being considered ineligible for high-dose radiotherapy [28]. In the latter, the mean interval between post-chemotherapy diagnostic scans and radiotherapy planning...
scans was 80.3 days (range 29–141). The resulting relative increase in tumor volumes ranged from 1.1% to 81.8%, with calculated tumor doubling times of 8.3–171 days (mean 46 days). Tumor volumes have been shown to inversely correlate with radiocurability [29], and progression prior to radiotherapy is disadvantageous. Undesirable delays can be minimized if all patients are discussed in multidisciplinary teams prior to initiating treatment, thereby allowing for radiation oncologists to schedule radiotherapy to start at around 3 weeks following the last of cycle of chemotherapy.

Role of radiation dose escalation

The best survival reported in a phase III trial of concurrent chemo-radiotherapy was achieved with a dose of 61 Gy with concurrent cisplatin–etoposide [11]. Despite a local recurrence rate of 26%, there is no evidence to suggest that higher (and potentially more toxic) doses are beneficial in this setting. With sequential chemo-radiotherapy, accelerated radiotherapy delivering doses of between 50 and 66 Gy is recommended for stage III NSCLC in order to minimize the adverse impact of accelerated tumor repopulation. The maximally tolerated dose of irradiation (twice-daily fractionation) following induction chemotherapy was estimated to be ∼80 Gy [30]. However, doses exceeding 70 Gy have been evaluated within clinical trials in patients with relatively favorable tumor geometries and pulmonary function. Unexpected radiation-induced late toxicity includes symptomatic bronchial stenosis with a 4-year actuarial rate of stenosis of 38% [31], mediastinal fibrosis and stenosis of the pulmonary artery [30]. Such late toxicity manifesting in selected study populations indicate that dose escalation must not be pursued outside the context of prospective trials.

Post-operative radiotherapy

A meta-analysis found a deleterious effect for post-operative radiotherapy in patients with resected N0–1 disease, and no survival benefit in patients with completely resected N2 disease [32]. No single randomized trial included in the meta-analysis showed an improvement in overall survival. Nevertheless, this procedure continues to be performed in many countries owing to institutional preferences and tradition. Well-designed randomized clinical trials addressing the role of post-operative radiotherapy for completely resected stage III are awaited.

Advances in radiotherapy planning and delivery

FDG-PET scans

Survival after radiotherapy is reported to be superior in patients who have undergone a staging FDG-PET scan, a finding that can be explained by the ability of PET to exclude up to 30% of patients who have otherwise unsuspected distant metastases [33, 34]. PET scanning may be useful in treatment planning, but this has not been formally evaluated in clinical trials. However, significant changes in the definition of target volumes have been reported in between 30–60% of patients with NSCLC (reviewed in [34]). Nevertheless, false-positive PET scans for mediastinal nodes can be as high as 39%, depending on the patient population studied. Consequently, histological confirmation is preferred, and can be achieved using endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in up to 70% of patients in whom FDG-PET scans indicate nodal metastases [35]. The combination of PET and EUS-FNA qualifies as a minimally invasive staging strategy for defining involved-fields for radiotherapy planning.

4D CT scans and respiratory gating

A major recent breakthrough is 4D radiotherapy, which is defined as the explicit inclusion of the temporal changes in anatomy during the imaging, planning and delivery of radiotherapy [36]. The mobility of lung tumors can be visualised using the technique of 4D, or respiration-correlated, CT scanning [37]. 4D CT permits the use of individualized margins for treatment planning and the safe delivery of respiration-gated radiotherapy, in which irradiation is limited to a predetermined window (or ‘gate’) in the respiratory cycle where the tumor is relatively immobile [38]. Gating permits the use of smaller treatment portals, which in turn reduces the risk of radiation-induced toxicity. Clinical data on local control after gated-radiotherapy has yet to be published.

Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) is based on the use of optimized non-uniform radiation beam intensities. Treatment planning studies suggest that IMRT can be beneficial for patients with N2 disease, and for centrally located tumors [39]. IMRT is, however, characterized by steep dose gradients, and both geographical misses and unexpected toxicity can arise in the presence of patient set-up errors or organ mobility. IMRT is considered as investigational in lung cancer in view of the complexity of tumor and normal organ mobility in the thorax, as well as the limitations of commonly used dose-calculation algorithms. Alternative measures, e.g. omission of elective nodal irradiation, can achieve significant reduction in normal tissue irradiation without the need for IMRT [39].

Palliative radiotherapy for thoracic disease

Short courses of external beam radiotherapy (between 2 and 10 fractions) offer a quick and effective means to palliate symptoms such as hemoptysis (in 72–86% of patients), chest pain (59–80%), cough (48–65%) and breathlessness (41–57%) [40]. Owing to comparable levels of palliation being achieved with different radiation fractionation schemes, very short schemes of one to five fractions have gained popularity in NSCLC, particularly as such schemes can achieve quicker palliation [41, 42]. A recent randomized clinical trial found
that patients who received five fractions survived on average 2 months longer (P=0.03) than patients who received one fraction [43]. However, this finding remains to be confirmed by other trials, particularly in patient populations that are eligible for, and receive, palliative chemotherapy.

Trials of single-agent chemotherapy (gemcitabine or paclitaxel) plus supportive care versus supportive care alone in advanced NSCLC have reported significant improvements in the quality of life when chemotherapy is added [44], and in both quality of life and survival [45]. In both these trials, the utilization rates of palliative radiotherapy were reduced from nearly 80% to 50%. If the above-mentioned finding of a survival benefit for higher dose palliative radiotherapy is confirmed, clinical trials to determine the optimal integration of palliative radiotherapy with systemic therapy will be of interest in this patient population.

Palliation of brain metastases

The natural course of patients with untreated brain metastases is one characterized by rapid neurological deterioration, with a median survival of only 1–2 months. Whole-brain radiotherapy (WBRT) is the standard treatment for brain metastases in NSCLC, but it results in a median survival of only 3–6 months [46, 47]. Recursive partitioning analysis (RPA) of prognostic factors in patients treated with WBRT within successive RTOG studies led to the identification of three prognostic subgroups [46]. In RPA class 1 (i.e. Karnofsky performance status ≥70, age <65 years, controlled primary tumor and no extracranial metastases), the median survival after WBRT is 7–10 months [47]. In contrast, survival in RPA class 3 (Karnofsky performance status <70) was only 2 months, and that for RPA class 2 was 3–5 months following WBRT.

In the absence of systemic tumor activity, surgical excision of a solitary metastasis followed by WBRT can result in good local control, and long-term survival is possible [48]. In patients with a single non-resectable brain metastasis, the combination of WBRT and stereotactic radiotherapy improves functional autonomy and survival in comparison with WBRT alone [49]. In patients with up to three metastases, the addition of stereotactic radiosurgery to WBRT also results in a significant improvement in performance score and decreased steroid use at 6 months [49]. However, many patients present with multiple brain metastases and/or uncontrolled extracranial disease, and as such are not candidates for either surgery or stereotactic radiotherapy.

Summary

Technical advances in stereotactic radiotherapy have resulted in marked improvements in local control for medically inoperable stage I NSCLC. A better integration of chemo-radiotherapy in stage III NSCLC can improve survival for these patients. Although concurrent chemo-radiotherapy appears to be superior, it is clear that this approach is not suitable for all patients. Patients are likely to derive maximal benefit from these recent advances in the treatment of thoracic malignancies when close collaboration exists within multidisciplinary teams involved in the treatment of NSCLC.

References


