REVIEW SERIES

Lung cancer • 5: State of the art radiotherapy for lung cancer

A Price

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Radiotherapy has a key role in curative and palliative treatments of patients with lung cancer. Important advances are described in the technique of treatment delivery and its integration with chemotherapy.

Radiotherapy is the most commonly used treatment modality for patients with lung cancer in the UK, with established, although frequently ignored,[1] indications. It has a role in early, medically inoperable, and locally advanced unresectable non-small cell lung cancer (NSCLC), where some patients are cured, in the palliation of advanced lung cancer of all types, and in the adjuvant treatment of limited stage small cell lung cancer (SCLC) where meta-analyses have shown it increases survival.[2 3] Each of these indications will be reviewed, with discussion of recent meta-analyses, the impact of technical advances in radiotherapy physics, integration of chemotherapy with radiotherapy, and studies of radiotherapy scheduling in radical and palliative treatments. The review is based on a Medline search of "radiotherapy and lung cancer" from 1996 to 2001 (1549 hits) and hand searches of the Abstracts of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology since 1999.

CURATIVE RADIOTHERAPY IN MEDICALLY INOPERABLE NSCLC

Radical radiotherapy

No randomised trial has compared radical radiotherapy with active supportive care. A Cochrane review[4] identified only one acceptable phase III trial in this setting—the CHART study—which showed an increase in 5 year survival for all patients (60% of whom had stage III disease) from 7% to 12% with 54 Gy in 36 fractions over 12 days.[5] The review identified 26 retrospective surveys reporting 5 year survival of 0–42%, 5 year cancer specific survival of 13–39%, and local failure rates of 6–70%. Outcomes were better with smaller tumours and higher radiation doses.

Dose escalation

Attempts to improve these results focus on radiation dose escalation above the longstanding international standard dose of 60 Gy,[6] since the co-morbidities which preclude surgery often preclude high dose chemotherapy while the use of low dose chemotherapy as radiosensitisation has not been explored in randomised trials. Dose escalation has been facilitated by advances in radiotherapy physics, particularly the techniques for beam shaping and treatment verification described below.

In an ongoing phase I trial at Ann Arbor the radiotherapy dose has been increased using the estimated risk of radiation pneumonitis based on the lung volume irradiated.[7] To date, the dose delivered to the largest volumes has been increased by less than 10%, but with the smallest volumes it has been possible to almost double the radiation dose to 102.9 Gy. Other groups are exploring doses from 77.4 to 94.5 Gy,[8–11] having established that lower doses appear safe.

Importantly for dose escalation, it is becoming apparent that elective nodal irradiation is unnecessary. Failure in unirradiated mediastinal nodes has not been a problem in the Ann Arbor series, while a Dutch series reported 2% isolated regional relapse.[12] If the dose escalation studies ultimately show improved local control, isolated nodal failure may become more important and the issue of elective nodal irradiation will need to be readdressed.

Unfortunately, increasing the radiation dose in these studies has often required increased overall treatment time, and current estimates suggest that tumour repopulation during treatment necessitates an extra 0.2–0.4 Gy for each additional treatment day. CHART was designed to overcome this repopulation by shortening overall time to 12 days. In the North of Britain, fraction sizes of 2.75–3 Gy delivered to small volumes have been standard for radical treatments for over 50 years, allowing 3–4 week treatments rather than the 6–7 weeks used in the United States, Europe, and the South of Britain. Such fractionation schemes are now being explored in dose escalation trials to avoid the problems of increased time[13] and in a current EORTC chemoradiotherapy trial.

Radiotherapy planning and treatment delivery

Multi-leaf collimation uses 0.5–1 cm tungsten leaves in the linear accelerator jaws which can be moved incrementally into set positions at the start of, or dynamically during, treatment to allow shaping of the radiation portal to spare normal tissues and deliver dose gradients across the radiotherapy volume.

Patient immobilisation and portal imaging during radiotherapy to monitor set up accuracy allow tolerances of 5 mm or less in the day to day variation of field position.[14 15] Unfortunately these tolerances are substantially less than the movements of tumour and normal structures due to breathing, and this has to be incorporated into the target volume around the tumour and tissues at risk of involvement with the cancer. Studies

Correspondence to:
A Price, Department of Oncology, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; A.Price@ed.ac.uk

Table 1 Trials of neodjuvant chemoradiotherapy in NSCLC

Reference	No	Sample	Treatments	Median survival	p value
NSCCLCCG[35]	1780	Various	C-R, R	HR 0.87	0.01
Cullen[36]	446	Unresectable	C-R	12 months	0.14
			R	10 months	
Sause[37]	327	Inoperable (CS II–IIIB)	C-R	13 months	0.04
			R	11 months	

C-R=sequential chemoradiotherapy; R=radiotherapy.

Table 2 Trials of full dose concurrent chemoradiotherapy in NSCLC

Reference	No	Sample	Treatments	Median survival (months)	p value
Blanke[73]	240	Unresectable or inoperable	CR	10	0.35
			R	11	
Furuse[38]	314	Unresectable CS III	CR	17	0.04
			C-R	13	
Curran[39]	611	CS II–III	CR	17	0.08
			ChfR	16	
			C-R	15	
Mornex[74]	212	CS IIIAN2–IIIB	CR	16	0.55
			C-R	14	

C-R=sequential chemoradiotherapy; CR=concurrent chemoradiotherapy; R=radiotherapy; hfR=hyperfractionated radiotherapy.

measuring this movement have shown it to be maximal in the craniocaudal direction, with a mean of 12 (2) mm in one study[16] and of 8 (9) mm in another.[10] More accurate delineation of the extremes of tumour movement is being developed as part of the planning process using slower CT scans with altered pitch and slice thickness.[17]

Attempts have been made to limit tumour movement by breath holding or to make allowance for it by gating radiotherapy. Significant reductions in the lung volume receiving more than 20 Gy (V_{20})[18] and in the average lung dose delivered[19] have been reported when patients held their breath in deep inspiration, but the mean breath holding time was only 23 seconds which may be too short for image acquisition for planning, and two out of 10 patients were unable to perform this manoeuvre. Gating techniques, such that the linear accelerator stops irradiation when a marker has moved more than a certain distance, have been described but no clinical data have been published.[20 21]

PET scanning may also improve radiotherapy outcomes, both by identifying patients with occult metastatic disease[22] and allowing more precise definition of the target volume, decreasing the risk of geographical miss of the tumour and, in a few patients, reducing the target volume with lower risk of complications. One study using PET reported target volume reduction in four patients but increases in seven to encompass occult nodal disease.[23]

Radiation morbidity

The dose limiting normal tissues are lung, spinal cord and oesophagus, with the first being most important with radiation alone and the third with combined modality treatment. The risk of acute radiation pneumonitis is related to performance status,[24 25] underlying lung function,[24] the lung volume irradiated, and the radiotherapy dose. The best models currently available for predicting this are the mean lung dose, where the risk of pneumonitis increases above 20 Gy[26] and the V_{20} with greater risk when this is above 40%.[27] Data on the long term effects of radiotherapy on lung function are limited. One study suggested that patients with good initial lung function had significant long term impairment in lung function (15–20%), particularly in gas transfer, but that patients with poor initial lung function (<50% predicted) showed little long term change or even improvements in lung function.[28 29] A third study of 31 patients reported a nadir in lung function at 9 months with forced expiratory volume in 1 second (FEV_1) 90% and carbon monoxide transfer factor (TLCO) 70% of baseline, but recovery of FEV_1 to original values and TLCO to approximately 90% of baseline 18 months after treatment.[30]

Oesophageal toxicity is more severe when synchronous chemoradiotherapy or multiple daily fractions are given,[31 32] but the importance of the length of oesophagus irradiated is the subject of debate.[31 33 34]

CURATIVE RADIOTHERAPY IN SURGICALLY UNRESECTABLE NSCLC

Chemoradiotherapy

There is little doubt that chemotherapy added to conventionally fractionated radical radiotherapy produces a small improvement in survival. No data support the addition of chemotherapy to CHART. Both a large meta-analysis[35] and two subsequent randomised studies[36 37] have shown a small survival benefit (2–3% at 5 years) for full dose cisplatin-based combination chemotherapy before radical radiotherapy (table 1). These studies included a wide range of chemotherapy and radiotherapy regimes, many of which would now be considered inadequate. It remains unclear whether chemotherapy should be given prior to or synchronously with radiotherapy and, if the latter, whether at cytotoxic or radiosensitising doses (tables 2 and 3). Chemotherapy after radical radiotherapy has never been formally assessed.

As a result of two studies comparing synchronous full dose chemotherapy with sequential chemotherapy which indicated a survival benefit for the former,[38 39] this is becoming the standard of care, particularly in the USA. However, one of these two studies[38] was compromised by suboptimal radiotherapy, a feature of many such studies where radiotherapy dose or fractionation is modified to accommodate chemotherapy. Moreover, there is also one negative study with an inferior chemotherapy regime, single agent cisplatin. An important EORTC study is currently comparing sequential

Table 3 Trials of low dose concurrent chemoradiotherapy in NSCLC

Reference	No	Sample	Treatments	Median survival	p value
Soresi[75]	95	Unresectable locally advanced	CR R	16 months 10 months	NS
Schaake-Koning[76]	331	Non-metastastic inoperable	CR CR R	26% 2 years 19% 2 years 13% 2 years	0.01
Trovo[77]	173	Inoperable	CR R	10 months 10 months	NS
Jeremic[43]	169	CS IIIA–B	ChfR ChfR hfR	13 months 18 months 8 months	0.003
Jeremic[78]	131	CS III	ChfR hfR	22 months 14 months	0.02
Clamon[79]	283	Inoperable stage III	C-CR C-R	13 months 13 months	0.74
Ball[80]	160	Unresectable or inoperable	CR R ChfR hfR	17 months 14 months 15 months 14 months	0.76

C-R=sequential chemoradiotherapy; CR=concurrent chemoradiotherapy; R=radiotherapy; hfR=hyperfractionated radiotherapy.

chemoradiotherapy at cytotoxic doses and concurrent chemoradiotherapy at sensitising doses, delivering 66 Gy in 24 fractions over 4.5 weeks. The safety data accumulating with this regime suggest that, far from needing to reduce the radiotherapy dose to accommodate chemotherapy, it may be possible to dose escalate radiotherapy even when synchronous chemotherapy is given.

Innumerable phase I and II studies have been carried out with the third generation chemotherapy agents (taxanes, topoisomerase I poisons, gemcitabine, and vinorelbine) given concurrently with radiotherapy, but no phase III studies have been reported to date.

Radiotherapy alone

In patients who are not fit for chemotherapy CHART is the treatment of choice, but it is currently available in only nine of the 56 radiotherapy centres in the UK. This regime has been modified to exclude weekend irradiation (CHARTWEL) to make it logistically easier to deliver. A dose of 60 Gy in 40 thrice daily fractions over 18 days is safe and appears worth pursuing as an alternative to CHART,[40] although this will require further randomised trials to prove equivalence. A meta-analysis of hyperfractionation found three trials in patients with NSCLC with a significantly reduced odds ratio of death of 0.69.[41] Trials of increased radiation dose without altered fractionation have not shown any benefit to date. It will be important to find out from the ongoing phase I dose escalation studies whether any meaningful increase above the 10% seen so far for the largest volumes is possible for bulky stage III disease. If, for different reasons, neither dose escalation nor altered fractionation are possible in the UK, then low dose synchronous chemotherapy may be worth exploring as a radiosensitiser,[42 43] avoiding the side effect profile of conventional high dose chemotherapy, as may the role of the newer biological agents such as epidermal growth factor antagonists or farnesyl transferase inhibitors and agents which exploit hypoxia such as mitomycin or tirapazamine.[44]

Survival and quality of life

A Canadian study of 129 patients included radiotherapy as a covariate in a Cox proportional hazards model of prognostic and treatment factors.[45] Radical (>50 Gy) radiotherapy increased median survival by 302–488 days with a relative risk of death of 0.24, while high dose palliative radiotherapy (30–50 Gy) increased median survival by 31–106 days with a relative risk of death of 0.53.

A Dutch study examined quality of life prospectively in 164 patients receiving 60 Gy for NSCLC.[46] Symptomatic responses were seen in more than 60% of patients for haemoptysis, pain, and anorexia, but in fewer than 40% for dyspnoea, cough, and fatigue. Overall quality of life assessed using EORTC scales improved in 36%, was unchanged in 40%, and deteriorated in 24%.

POSTOPERATIVE RADIOTHERAPY IN NSCLC

A meta-analysis of 2128 patients treated in nine randomised trials of postoperative radiotherapy reported a 7% decrease in survival at 2 years in irradiated patients.[47] This effect was apparent in patients with stages I and II disease but not stage III. These studies used a wide range of doses, volumes, and techniques over a 30 year period, and their applicability to contemporary practice has been debated.[48] Radiotherapy does produce an improvement in local control, particularly in patients with stage III disease.[49 50]

This effect on local control is likely to be revisited when the current generation of adjuvant chemotherapy trials is complete. Some of those already published report local failure rates as high as 20%, which may mask the benefits of increased control of metastatic disease.[51] The techniques which allow higher doses of radical radiotherapy are also pertinent to postoperative treatment. However, to allow high doses of radiotherapy to be focused on sites at high risk of recurrence, it will be necessary to collect much better data than are currently available about precise sites of relapse—whether local at the bronchial resection margin or regional at nodal sites and, if the latter, which nodal levels are involved for each primary site. Simply recording failure as locoregional (somewhere in the chest) is inadequate.

PALLIATIVE RADIOTHERAPY

Radiation dose

A Cochrane review[52] identified 12 trials in which two different palliative radiation doses were compared. No evidence of a radiation dose response for palliation was apparent, supporting current UK practice of delivering this treatment in one or two fractions, but there was evidence for a modest survival advantage in fitter patients with higher radiation doses.

However, three trials do suggest that such a benefit exists. Two of these were not available for the Cochrane review. An MRC trial reported a 7 week increase in median survival with 39 Gy in 13 fractions over 2.5 weeks compared with 17 Gy in two fractions over 1 week in patients otherwise deemed suitable for radical radiotherapy but whose tumours were considered too big, comparable to the benefit seen with combination chemotherapy.[53] Indeed, the only direct comparison of high

dose palliative radiotherapy (42 Gy in 15 fractions over 3 weeks) with chemotherapy (cisplatin, etoposide) reported no survival difference but double the response rate with the former.[54] A trial in Edinburgh comparing 30 Gy in 10 fractions with a 10 Gy single fraction found better physician reported palliation of cough, pain, and dyspnoea with the fractionated regime.[55] A Canadian study comparing 20 Gy in five fractions over 1 week with a 10 Gy single fraction reported a survival advantage with the former in patients with better performance status.[56]

Radiation morbidity

Significant toxicity which is not ameliorated by steroids but may be helped by anti-emetics[57] has been reported with hypofractionated palliation.[58] While single fraction radiotherapy remains the palliation of choice in patients with a poor prognosis, anti-emetic prophylaxis should be routine and additional studies are required to define the mechanism of and methods to prevent the associated systemic morbidity. In patients with stage III or bulky stage II disease which cannot be radically irradiated, higher radiation doses are appropriate. The relative roles of chemotherapy and radiotherapy in this situation have not been defined.

Palliative benefit

An Italian study of hypofractionated palliation reported clinical palliation in 77% of patients with improved performance status in 73%. The median duration of palliation ranged from 28% to 57% of patient survival.[59] A Dutch study using the EORTC quality of life scales in 65 patients receiving palliative radiotherapy reported relief of haemoptysis in 79%, of pain and cough in 50%, dyspnoea in 40%, fatigue in 22%, and anorexia in 11%.[60]

Endobronchial radiotherapy

Endobronchial radiation was compared with palliative external beam radiotherapy in a randomised trial in Manchester. Survival was better and retreatment less frequent but toxicity greater with external beam therapy.[61] The addition of endobronchial therapy to external beam treatment increased the re-expansion rate of collapsed lungs (57% *v* 35%), but there was no difference in the palliation of dyspnoea.[62] With potentially curative radiotherapy the addition of endobronchial radiation had no effect on survival but improved local control in the subgroup with squamous carcinoma.[63] Endobronchial therapy may have a role in patients with symptomatic local recurrence after external beam therapy. Hernandez and colleagues[64] treated 29 patients with re-expansion in 28%, palliation of haemoptysis in 69%, and improved performance status in 24%.

RADIOTHERAPY IN SCLC

Thoracic irradiation

The role of radiotherapy in SCLC has recently been well reviewed.[65] Current controversies relate to the timing of thoracic radiotherapy, with the balance of evidence favouring early concomitant therapy with radiation and cisplatin + etoposide. In the UK this practice will be heavily influenced by the recently completed London Lung Cancer Trial replicating the earlier National Cancer Institute of Canada study, the results of which can be expected in 2–3 years.[66] US practice currently favours twice daily radiotherapy based on one positive[67] and one negative[68] study. The benefit observed in the first study reflects the 2 week difference in treatment time between the two regimes, equivalent to a dose differential of over 10% given the likely effect of accelerated repopulation in SCLC. In the second study overall treatment time was kept constant.

Twice daily radiotherapy is not standard practice in Europe. The question is further complicated by a recent phase I study suggesting that, while the twice daily radiation dose was at tolerance, the once daily dose could be escalated by over 50%.[69] Moreover, the issues of dose, timing, and radiation volume are not independent. Since the radiation dose that can be delivered will be higher if the volume treated is smaller, there may be advantages to late rather than early synchronous therapy if the residual rather than original tumour is regarded as the target volume. This hypothesis has never been tested in a randomised trial.

A Norwegian phase II trial has reported the safe addition of paclitaxel to cisplatin, etoposide and thoracic irradiation, although only five of 39 patients remained in remission with a median follow up of 36 months.[70]

The role of adjuvant thoracic radiation in extensive disease is controversial. Some studies of adjuvant thoracic irradiation included these patients, but the 433 patients were excluded from the meta-analysis of this therapy.[3] A randomised trial of adjuvant radiotherapy and chemotherapy versus further chemotherapy alone in patients with a good response to chemotherapy for extensive disease reported an increased survival for the former (9% *v* 4% at 5 years).[71]

Prophylactic cranial irradiation

A meta-analysis of 987 patients in seven randomised trials of prophylactic cranial irradiation (PCI) reported a survival advantage of 5% at 3 years for this treatment with a halving of the incidence of cerebral metastases, a suggestion of a dose response which is being tested in a current international trial, and a trend for benefit with earlier treatment .[2] An earlier analysis of published trials also favoured early PCI within 60 days of initiating chemotherapy—that is, before cycle 4 of conventional chemotherapy regimes.[72] Future trials exploring this issue will need to pay careful attention to late neuropsychological toxicity. This is not a problem with current sequential chemotherapy-PCI regimes, but there are too few data to comment on the safety of concurrent PCI and chemotherapy with modern regimes (which do not contain methotrexate or alkylating agents).

Summary

- High dose thoracic radiotherapy is indicated for good performance status patients with medically inoperable or surgically unresectable non-metastatic NSCLC. This should be CHART in patients who are not fit for chemotherapy and conventionally fractionated chemoradiotherapy in patients fit for this treatment. Research is ongoing to define the maximum radiation dose which can be delivered and to determine the best way of integrating chemotherapy and radiotherapy.
- In patients for whom radical treatment is inappropriate, palliative radiotherapy will relieve symptoms. In unfit patients or those with stage IV disease, hypofractionated regimes with anti-emetic cover are indicated. In patients with stage I–III disease higher doses of radiation prolong survival.
- In patients with SCLC, adjuvant thoracic and cranial irradiation both prolong survival. The optimum dose and timing of these treatments is the subject of ongoing research.

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LUNG ALERT

Long term functional limitations in survivors of ARDS

▲ Herridge MS, Cheung AM, Tansey CM, *et al*. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;**348**:683–93

One hundred and nine survivors of ARDS (mean age 45 years) were assessed at 3, 6 and 12 months after discharge from ICUs in Toronto. Patients had a mild restrictive pattern on lung function testing with mild to moderate reduction in carbon monoxide transfer factor at 3 months and, although this improved slightly (by 9%), it only reached 72% of predicted values.

Of the other end points assessed, the distance walked in 6 minutes improved over the 12 months but still remained lower than predicted (66%). The persistent functional limitation was largely a result of muscle wasting and weakness and, to a lesser extent, to entrapment neuropathy, heterotopic ossification, and intrinsic pulmonary morbidity. These sequelae were not compared with a control group of ICU survivors who did not have ARDS, so the consequences may not be specific to the syndrome but upshots of any severe critical illness. The absence of systemic corticosteroid treatment, the absence of illness acquired during the ICU stay, and rapid resolution of the lung injury and multiorgan failure were associated with a better outcome at 1 year.

Survivors of ARDS thus have persistent functional disability and reduced carbon monoxide transfer factor at 1 year after discharge from ICUs. However, these features may not be specific to ARDS.

S Cooper
Whittington Hospital, London
samanthacooper@hotmail.com