Paradigms in chemoradiotherapy

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Abstract

The efficacy of radiation in locally advanced non-small cell lung cancer (NSCLC) is limited. In a search for improving the outcome, particular attention has focused on the possibility of combining radiation with chemotherapy. The two most frequently used combined modality strategies include induction chemotherapy (chemotherapy preceding radiation) and concurrent chemoradiation. The former allows for drug delivery in full doses and in principle aims at a reduction of micrometastatic disease, whereas the latter is believed to improve locoregional control by making tumour cells more vulnerable to radiotherapy. The results of phase III trials of induction chemotherapy were equivocal; nevertheless, three large trials using platinum-based regimens demonstrated significant survival benefit. The role of single agent platinum compounds (believed to be radiosensitising agents) applied concurrently with radiotherapy is controversial. Improved survival with this strategy was demonstrated in two studies, but several other studies were negative. Concurrent application of multidrug platinum-based chemotherapy in conventional schedules has been found relatively toxic yet feasible in selected patients. The direct comparison of sequential versus concurrent use of chemotherapy and radiation demonstrated the superiority of the latter, but at the expense of higher acute in-field toxicity. More recently, several new agents, including taxanes, vinorelbine and gemcitabine, have appeared promising in NSCLC. Their role in combined modality regimens warrants further clinical research. Chemotherapy as an adjunct to radiation has become a standard in fit patients with locally advanced NSCLC. The gain from the combined modality approach, however, is modest on average and should be weighted against increased early and late toxicity. Further studies built upon recent positive results should focus on identifying the means of optimal interactions between the two modalities. This research should define the most effective types and doses of anti-cancer agents as well as the optimal features of radiotherapy. Additionally, the knowledge of the biological characteristics of individual tumours, in particular their expected response to therapy, may contribute to further progress.

Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Non-small cell lung cancer (NSCLC), including adenocarcinomas, squamous cell and large cell carcinomas, accounts for more than 75% of all lung cancer cases. About one-third of patients will present with locally advanced non-metastatic disease [2]. Until the late 1980s, thoracic radiation therapy was considered the mainstay of treatment in inoperable stage III disease, even though 5-year survival rates with this method were in the range of only 3–10%. Subsequently, several refinements of radiation techniques, such as sophisticated three-dimensional computerised planning systems, dose-intensity modulation and image-guided radiotherapy allowing an escalation of the total radiation dose, have been introduced. Although some progress has been made, the majority of patients with locally advanced NSCLC still die either from locoregional or distant disease progression.

In locally advanced inoperable NSCLC, the addition of chemotherapy to radiation, as opposed to local therapeutic approaches, may potentially increase the cure rate not only by improving tumour control in the thorax, but also by eliminating or delaying the emergence of metastatic disease. Nevertheless, until recently, the role of chemotherapy in locally advanced NSCLC has been questioned. Only a metaanalysis published in 1995, including 22 randomised clinical studies and 3033 patients, demonstrated some benefit of sequential chemotherapy combined with definitive radiation [3]. The overall hazard ratio was 0.90 in favour of chemotherapy, or a 10% reduction in the annual risk of death, corresponding to absolute benefits of 3% and 2% at 2 and 5 years, respectively. The hazard ratio for the trials using cisplatin-based chemotherapy was 0.87. The absolute survival benefit

Table 1
Phase III studies of sequential chemotherapy and radiation versus radiation alone in NSCLC

Authors, year	No. of eligible patients	Therapy	Median survival (months)	Two-year survival (%)	Difference
Mattson *et al.*, 1988 [4]	238	RT	10	17	
		CT-RT-CT[a]	11	19	NS
Morton *et al.*, 1991 [5]	114	RT	10	16	
		CT-RT-CT[b]	10	21	NS
Le Chevalier *et al.* 1991 [6], 1992 [7]	353	RT	10	14	
		CT-RT-CT[c]	12	21	<0.05
Dillman *et al.*, 1990 [8], 1996 [9]	155	RT	10	13	
		CT[d]-RT	14	26	0.012
Sause *et al.*, 1995 [10], 2000 [11]	458	RT	11	22	
		HFX RT[e]	12	24	NS
		CT[d]-RT	13	29	0.04
Brodin *et al.*, 1996 [12]	302	RT	11	17	
		CT[f]-RT	11	21	NS
Cullen *et al.,* 1999 [13]	446	RT	12	20	
		CT[g]-RT	10	16	NS

[a] Cyclophosphamide, doxorubicin, cisplatin. [b] Methotrexate, doxorubicin, cyclophosphamide, CCNU.
[c] Cisplatin, vinblastin, CCNU, cyclophosphamide. [d] Cisplatin, vinblastin. [e] Hyperfractionated radiotherapy. [f] Cisplatin, etoposide.
[g] Mitomycin, ifosfamide, cisplatin.

was relatively small though (4% after 2 years and 2% at 5 years) and there was concern about whether it was large enough to offset the increased toxicity of therapy.

Since then, several randomised phase III studies using various radiotherapy and chemotherapy schedules and sequences have been performed. The two most frequently used strategies were primary (induction) chemotherapy followed by radiation (sequential treatment) and concurrent application of both methods. Other approaches included concurrent chemoradiotherapy followed or preceded by chemotherapy. The clinical experience that emerged from these studies will be addressed in this review.

Induction chemotherapy

Induction chemotherapy allows for drug delivery in full doses without the additive toxicity that occurs with concurrent therapy. This strategy principally aims at the eradication of occult micrometastases, but it may also reduce primary tumour volume. The latter may allow smaller field radiotherapy, with less normal tissue toxicity, permitting higher radiation doses. Finally, it is hoped that tumour shrinking with chemotherapy may reduce radioresistant hypoxic areas present in bulky tumours. The disadvantages of primary chemotherapy are prolonged total treatment time, postponed irradiation and a possibility of accelerated repopulation of tumour cells.

The results of phase III trials comparing radiation alone to radiation preceded by chemotherapy have been inconsistent (Table 1). Most of the early studies performed in the 1980s failed to show an ultimate advantage for combined modality treatment. Subsequently, however, three large phase III studies, all using short-term cisplatin-based chemotherapy administered before radiation, demonstrated increased median survival of about 3 months [8,7,11]. In the study performed by the Cancer and Leukaemia Group B (CALGB), patients were randomised to radiotherapy alone (60 Gy over 6 weeks) or the same radiotherapy preceded by two cycles of a relatively low-toxic combination of cisplatin and vinblastine. Three-year survival in the combined modality and radiotherapy-alone arms was 23% and 11%, respectively [8]. Importantly, this benefit was of long duration, with a survival probability of 13% and 6% at 7 years in the combined modality and radiotherapy only arms, respectively [9]. In the confirmatory US Intergroup Study, patients were randomised to the same two treatments used in the CALGB study, and to a third arm of hyperfractionated radiotherapy (two daily fractions of 1.2 Gy for a total dose of 69.6 Gy) [11,10].

Table 2
Phase III studies of concomitant chemoradiation versus radiation alone in NSCLC

Authors, year	No. of eligible patients	Therapy	Median survival (months)	Two-year survival (%)	Difference
Schaake-Koning *et al.*, 1992 [15]	308	RT	12	13	0.009
		RT+DDP[a] (daily)	14	26	NS
		RT+DDP[a] (weekly)	12	19	
Trovo *et al.*, 1992 [16]	169	RT	10	13	NS
		RT+DDP[a] (daily)	10	13	
Ball *et al.*, 1999 [17]	204	RT	14	26	NS[d]
		HFX RT[b]	14	28	
		RT+CBDCA[c]	17	29	
		HFX RT[b]+CBDCA[c]	15	20	
Clamon *et al.*, 1999 [18]	250	RT[d]	13	26	NS
		RT+CBDCA[c,d]	13	29	
Blanke *et al.,* 1995 [19]	215	RT	10	13	NS
		RT+DDP[a] (q. 3 weeks)	11	18	
Trovo *et al.*, 1990 [20]	111	RT	12	17	NS
		RT+CT[e]	10	19	
Jeremic *et al.*, 1995 [21]	169	HFX RT[b]	8	25	0.003
		HFX RT[b]+CT[f]	18	35	NS
		HFX RT[b]+CT[g]	13	27	
Jeremic *et al.*, 1996 [22]	131	HFX RT[b]	14	26	0.021
		HFX RT[b]+CT[h]	22	43	
Groen *et al.,* 2004 [23]	160	RT	11.7	28	NS
		RT+CT[i]	11.8	20	

[a] cisplatin. [b] hyperfractionated radiotherapy. [c] carboplatin.
[d] factorial analysis: CBDCA versus no CBDCA; patients in both arms also received induction chemotherapy consisting of vinblastine and cisplatin.
[e] methotrexate, doxorubicin, cyclophosphamide, CCNU. [f] carboplatin + etoposide (low-dose, weekly).
[g] carboplatin + etoposide (higher dose, biweekly). [h] carboplatin + etoposide (daily). [i] carboplatin administered continuously.

Overall survival for patients who received chemotherapy was improved compared to those who received conventional irradiation alone, whereas the survival of patients treated with hyperfractionated radiotherapy was between the results of the two other arms. Patients who received primary chemotherapy had significantly fewer distant metastases (other than in the brain) [14]. However, despite preselection of patients for favourable prognostic factors, 5-year survival was disappointing in all study arms: 5% for standard radiotherapy, 6% for hyperfractionated radiotherapy and 8% for chemotherapy followed by radiotherapy. In the French study, patients were randomised to irradiation alone (65 Gy in 26 fractions) or the same radiotherapy preceded by three cycles of vindesine, lomustine, cyclophosphamide and cisplatin [7,6]. Patients whose disease did not progress after primary chemotherapy were administered three additional cycles of the same regimen after completion of radiotherapy. The combined modality approach was associated with survival benefit (3-year survival of 12% and 4% in patients who did and did not receive chemotherapy, respectively). This effect was due to a reduced distant-failure rate in the combined modality arm (1-year failure rate of 22%, as compared to 46% in the control arm), whereas the local tumour control in both arms was relatively poor and virtually the same.

Concomitant chemoradiation

Chemotherapy used concomitantly with radiation, apart from its distant action, is believed to improve locoregional control by making tumour cells more vulnerable to radiotherapy (radiosensitisation). On the other hand, concomitant chemoradiation is generally more toxic and may necessitate reductions in chemotherapy dose-intensity.

Table 3
Randomised studies comparing concomitant versus sequential radiotherapy and chemotherapy

Author	*N*	Median survival (months)		Two-year survival (%)		*P*	Grade 3–4 oesophageal toxicity (%)	
		C	S	C	S		C	S
Furuse *et al.*, 1999 [28]	320	16.5	13.5	37	29	0.04	23	4
Curran *et al.*, 2003 [29]	402	17.0	14.6	37	31	0.046	25	4
Zatloukal *et al.*, 2004 [30]	102	16.6	12.9	34	14	0.02	28	4
Fournel *et al.*, 2005 [31]	205	16.3	14.5	35	23	NS	32	3
Belderbos *et al.*, 2007 [32]	158	16.5	16.2	39	34	NS	17	5

C, concomitant; S, sequential.

In NSCLC studies, concomitant chemoradiation included either single-agent platinum compounds or platinum-based multidrug regimens (Table 2). The possible mechanisms responsible for the enhancement of the response by platinum salts include an increased induction of DNA double-strand breaks, inhibition of DNA repair after irradiation, cell cycle redistribution and induction of apoptosis. Several studies used daily or weekly chemotherapy administered at low doses, a strategy believed to provide a radiosensitising effect rather than efficient systemic exposure. Most of the numerous single-agent platinum studies were negative or inconclusive, and only two studies, both using low daily doses of cisplatin, showed a superiority of concomitant therapy [15,24]. In the study performed by the European Organisation for Research and Treatment of Cancer (EORTC), patients were randomised to one of the three regimens: irradiation alone (30 Gy in 10 fractions, followed by a 3-week rest period and then 25 Gy in 10 fractions), the same radiotherapy preceded by daily cisplatin (6 mg/m^2), or radiotherapy combined with weekly cisplatin (30 mg/m^2). Survival was significantly improved in the daily-cisplatin arm (2-year survival of 26% and 13% with and without cisplatin, respectively) due to highly significant improvement in loco-regional control in the daily-cisplatin arm. The outcome in the weekly-cisplatin arm was intermediate and not significantly different from either of the other arms. Survival benefit in the daily-cisplatin arm was due to improved local tumour control ($P = 0.003$). It was, however, postulated that the addition of chemotherapy might only have compensated for the suboptimal radiotherapy schedule used in that study (55 Gy with a 3-week rest period after 30 Gy). Indeed, the 3-year survival in the irradiation-alone arm was only 2%. No survival benefit has been demonstrated in studies utilising single-agent carboplatin [18,25,23].

Survival benefit was demonstrated in two phase III studies of platinum-based multidrug chemotherapy combined with hyperfractionated radiotherapy, albeit with higher incidence of acute and late toxic reactions [22,21]. A recent meta-analysis, based on nine trials including 1764 patients, showed that combining radiotherapy with concomitant platinum-based chemotherapy is associated with reduced risk of death (hazard ratio 0.89; 95% CI 0.81–0.98; $P = 0.02$) compared to radiotherapy alone [26]. This corresponds to an absolute benefit of chemotherapy of 4% at 2 years, an effect similar to that of the meta-analysis[3] comparing sequential chemoradiotherapy to radiotherapy alone in NSCLC (4% at 2 years, 2% at 5 years). However, due to considerable clinical heterogeneity between particular studies in terms of frequency of administration and total chemotherapy doses, and a large inconsistency of the results, this metaanalysis should be interpreted with caution. Survival benefit (hazard ratio 0.93; 95% CI 0.88–0.98; $P = 0.01$) from concomitant chemoradiation was also demonstrated in the recent Cochrane review [27]. Subgroup analysis suggested the possibility of a greater benefit from regimens which incorporated conventional fractionation of radiotherapy or a higher total chemotherapy dose. The incidence of acute oesophagitis, neutropenia and anaemia were significantly increased by concurrent chemoradiotherapy.

Sequential versus concomitant chemotherapy and radiation

A series of randomised trials directly compared concomitant versus sequential administration of cisplatin-based chemotherapy and radiation (Table 3). In the Japanese study, patients with unresectable stage III disease were randomly allocated to the concurrent treatment arm including split-course radiotherapy (56 Gy) combined with MVP chemotherapy, vindesine and cisplatin [28]. In the sequential arm, two induction cycles of MVP every 4 weeks were followed by

radiotherapy (56 Gy). Median survival in the concurrent and sequential arms was 16.5 and 13.3 months, respectively ($P = 0.04$) and 5-year survival rates were 16% and 9%. Oesophagitis and myelosuppression were more common in the concurrent therapy arm but were at an acceptable level, most probably due to the planned interruption of radiotherapy. The phase III trial performed by the Radiation Therapy Oncology Group (RTOG) enrolled 611 patients to one of the three arms: induction chemotherapy using cisplatin and vinblastine followed by radiotherapy (60 Gy), concurrent chemoradiotherapy using cisplatin and vinblastine plus standard radiation (60 Gy, 2 Gy daily), or concurrent chemoradiotherapy using cisplatin and orally administered etoposide, combined with hyperfractionated radiotherapy (69.2 Gy, 1.2 Gy twice daily) [29]. The median survival with concurrent conventional radiation and chemotherapy was 17.0 months compared to 14.6 months with sequential treatment ($P = 0.046$). The hyperfractionated arm did not improve overall survival (median 15.2 months), whereas it was associated with excessive acute oesophageal toxicity. Long-term survival favoured concurrent chemoradiation using conventional radiotherapy, with 21% of patients surviving 4 years versus 12% in the sequential treatment arm. This benefit was achieved at the expense of more severe acute grade 3 and 4 oesophagitis (25% and 4%, respectively).

In the Czech randomised phase II study, 102 patients with locally advanced stage IIIA or IIIB NSCLC were randomised to cisplatin and vinorelbine administered prior to or concurrently with conventionally fractionated radiotherapy at a dose of 60 Gy [30]. Overall survival in the sequential and concurrent arm was 12.9 and 16.6 months, respectively ($P = 0.023$). Concurrent schedule was associated with higher systemic and in-field toxicity (severe oesophagitis 18% versus 4% in the sequential arm).

In the French trial, 205 patients were randomly assigned to sequential therapy (three cycles of induction chemotherapy consisting of cisplatin and vinorelbine followed by thoracic radiotherapy at a dose of 66 Gy in 33 fractions), or the same radiotherapy with two concurrent cycles of cisplatin and etoposide followed by two cycles of consolidation chemotherapy including cisplatin and vinorelbine [31]. Median survival was longer in the concurrent arm (16.3 months compared to 14.5 months in the sequential arm) but due to low statistical power the difference was not significant ($P = 0.24$). The 4-year survival favoured concurrent arm (21% compared to 14% in the sequential arm). Similar to other studies, oesophageal acute toxicity was significantly more frequent in the concurrent compared to sequential arm (32% and 3%, respectively).

In the most recent study, performed by the European Organisation for Research and Treatment of Cancer (EORTC), inoperable stage I-III NSCLC patients were randomised to receive two courses of cisplatin and gemcitabine prior to radiotherapy or concurrent chemoradiation using low-dose daily cisplatin [32]. Both arms used accelerated high-dose conformal radiotherapy (66 Gy in 24 fractions; 2.75 Gy per fraction). The study was prematurely closed due to poor accrual, therefore survival data are inconclusive. The median survival for the sequential and concurrent arm was 16.2 months and 16.5 months, respectively. Acute haematological toxicity, mainly severe granulocytopenia, was more pronounced in the sequential arm, whereas severe acute oesophageal toxicity was more pronounced in the concurrent arm. Severe late pulmonary toxicity was similar in both treatment arms.

In conclusion, the majority of studies demonstrated either a trend to or a significant improvement in survival with the concomitant therapy. A superiority of concurrent versus sequential chemoradiotherapy (RR 0.86; 95% CI 0.78–0.95; $P = 0.003$) was also demonstrated in a recent Cochrane review [27]. However, this benefit was achieved at the expense of increased rate of acute in-field toxicity, in particular oesophagitis, with associated nutritional problems.

Sequential and concomitant chemotherapy and radiation

With the goal of improving systemic control, several studies using induction or consolidation chemotherapy combined with the concurrent chemoradiotherapy have been pursued. Two studies showed no benefit from the application of carboplatin concomitantly with radiotherapy over radiotherapy alone following two cycles of induction chemotherapy [18,33]. In a recent study comparing concomitant chemoradiation versus radiotherapy alone, both following induction chemotherapy, the former approach increased time to progression but overall survival was not significantly longer [34]. Similarly, no survival benefit was found from adding induction chemotherapy to concurrent chemoradiation [35]. The role of consolidation chemotherapy following chemoradiation remains to be established.

Table 4
The impact of sequencing of chemotherapy and radiation on local and distant control

Authors, year	Strategy	Better local control	Better distant control
Schaake-Koning *et al.*, 1992 [15]	Concomitant	0.03	NS
Jeremic *et al.*, 1996 [22]	Concomitant	0.015	NS
Cakir *et al.*, 2004 [24]	Concomitant	0.001	NS
Furuse *et al.*,1999 [28]	Concomitant	0.04	NS
	Sequential	NS	NS
Le Chevalier *et al.*, 1992 [7]	Sequential	NS	<0.001
Komaki *et al.*, 1997 [14]	Sequential	NS	0.045

The role of new drugs

Within the last decade several new agents, including taxanes, vinorelbine and gemcitabine, have demonstrated activity and acceptable toxicity in the advanced NSCLC setting. These agents warrant testing, as they proved to be active in advanced disease [36] and showed radiosensitising properties in preclinical models. For example, taxanes (paclitaxel and docetaxel) were shown to enhance the cytotoxic effect of radiotherapy by accumulating cells in the G_2/M phase, the most radiosensitive phase of the cell cycle [37–42]. Phase II trials using these two compounds concomitantly with radiation determined the feasibility and encouraging activity of the approach [43,44]. Gemcitabine is a potent radioenhancer but standard weekly doses of 800 mg/m^2 were associated with unacceptable pulmonary toxicity [45,46]. As a consequence, in more recent studies radiotherapy was combined with low cytotoxic doses (300 mg/m^2) or radiosensitising doses (50 mg/m^2). Finally, vinorelbine was found to be a promising agent used both in primary chemotherapy regimens and concomitantly with radiation [30,31,47].

In the Cancer and Leukaemia Group B (CALGB) phase II trial, locally advanced inoperable NSCLC patients were randomised to receive two cycles of induction chemotherapy, including paclitaxel, gemcitabine or vinorelbine in combination with cisplatin, followed by two additional cycles of these drugs with concurrent standard chest radiotherapy [48]. All regimens could be safely combined with radiotherapy and showed similar activity but had different patterns of toxicities. The superiority of novel over traditional regimens in combined modality treatment of NSCLC remains to be confirmed in prospective randomised trials.

Conclusions

With the positive results of numerous randomised studies, combined modality therapy became the standard of care in unresectable locally advanced NSCLC patients with good performance status. However, the available data are insufficient to accurately define the optimal schedule of combining both modalities. Increased survival in the studies using induction chemotherapy seemed to be primarily due to a reduction of systemic failure rates without affecting local control, whereas the concomitant approaches provided increased local and regional control (Table 4). Of the two strategies, concomitant therapy was found to be more effective, albeit at the expense of higher early toxicity. Studies using low-dose platinum compounds suggest that cisplatin is a more potent radio-sensitiser than carboplatin. Despite these positive results, the recent Cochrane overview advises caution in adopting concurrent chemoradiotherapy as the standard of care because of uncertainties about the true magnitude of benefit in comparison with sequential chemoradiotherapy and increased treatment-related morbidity [27]. Induction chemotherapy may still be considered in fragile patients who are not candidates for more intensive concomitant chemoradiotherapy approaches or for those in whom the tumour cannot be initially encompassed within an appropriate treatment volume.

Several factors may impact the outcomes of combined sequential chemoradiation. For example, the efficacy of sequential treatment seems to be highly dependent on the interval between the end of induction chemotherapy and the start of radiotherapy. The gain related to tumour volume reduction may be lost owing to fast regrowth of NSCLC as a result of accelerated tumour cell proliferation. Indeed, the mean tumour doubling time after chemotherapy seems to be far shorter than that of untreated tumours [49]. Delayed

radiotherapy following induction chemotherapy may also allow for tumour progression, the effect seen in one study comparing sequential versus concomitant therapy [30]. It is also possible that accelerated repopulation may render tumours more resistant to subsequent irradiation, further decreasing the efficacy of sequential chemoradiotherapy. It is likely that protracted radiotherapy schedules may be particularly vulnerable to accelerated repopulation. This effect may further be aggravated by gaps in treatment due to toxicity, owing to the well-known negative impact of treatment interruptions on the effectiveness of radiotherapy in NSCLC [50]. Thus, shortening the period between chemotherapy and radiation and shortening the overall treatment time may potentially improve the outcomes of sequential chemoradiation to the level obtained with concomitant treatment, while avoiding the toxicity of the latter. These issues should be addressed in future studies.

Importantly, the gain from a combined modality approach is modest on average and should be balanced against enhanced early and late toxicity. It should also be noted that patients in clinical studies had favourable prognostic factors and underwent careful staging procedures. Thus, extending this aggressive strategy to patients with poor performance status or severe comorbidities may not be appropriate. It should also be remembered that a clinical benefit of similar magnitude has been achieved by the application of continuous hyperfractionated accelerated radiotherapy (CHART) [51]. Thus, future therapeutic strategies in locally advanced inoperable NSCLC should integrate most effective chemotherapy regimens with optimal schedules of irradiation.

Although a survival benefit related to combined modality therapy has clearly been demonstrated, many questions remain. These include the most effective drugs and the optimal mode of their administration (systemic versus merely low-dose radio-sensitising doses), the role of induction or consolidation chemotherapy and the most effective parameters of radiotherapy (total dose, fractionation, overall treatment time and treatment volume).

There is also an obvious need for a continuous search for more effective strategies. In further studies, selection of anti-cancer agents should be based on their mechanism of action and potential to increase the cell-killing effect of radiation. This search should also include the knowledge of the characteristics of individual tumours, in particular their expected response to therapy. Hopefully, recently developed molecular assays, particularly micro-array technology, will provide long-awaited reliable predictive tests. This should allow the selection of most suitable treatment for each individual patient. Classical radiochemotherapy approaches might soon be supplemented by novel molecular biological response modifiers. Of the substances that have been demonstrated to enhance the radiation response in experimental models, particularly interesting seem to be monoclonal antibodies directed against epidermal growth factor receptors, farnesyl transferase inhibitors, and inhibitors of angiogenesis. Developments in systemic therapy should be accompanied by defining the optimal features of radiotherapy used in combined modality strategies. At present, there is no evidence that hyperfractionated radiotherapy applied concurrently with chemotherapy is superior to chemotherapy combined with concurrent conventional radiotherapy in terms of local control and survival. However, dose escalation may contribute to better local control. Given the increased toxicity of combined modality approaches, restriction of the volume of irradiated lung should always be attempted. This may be realised with the use of sophisticated conformal radiation techniques and image-guided radiotherapy. As the benefit from the addition of chemotherapy to radiation is modest on average, quality of life issues should also be addressed. Finally, due to increasing financial constraints, future trials should evaluate the economic implications of the addition of chemotherapy to radiation. This issue may become particularly relevant with the use of relatively expensive new-generation compounds.

Conflict of interest statement

None declared.

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