Platinum-based chemotherapy with thoracic radiotherapy in stage III good performance status non-small cell lung cancer patients

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Introduction

Patients with stage III non-small cell lung cancer (NSCLC) comprise about one-third of the NSCLC population. The stage III group is heterogeneous, consisting of patients with differing prognoses, even within the surgically resected N2 subgroup. In general, clinical trials have not distinguished adequately between the stage III subgroups and have also included stage I and II patients as ' early stage' potentially resectable disease. There are currently 11 possible T,N combinations within stage III, indicating the heterogeneity of the group and the future need to define the study population more precisely. Furthermore, the trial evidence is based on patients with good performance status often including other favourable prognostic factors e.g. weight loss <5%. These considerations in addition to the use of a variety of radiotherapy (RT) and chemotherapy (CT) regimens has added to the complexity of data interpretation.

Patients with early stage NSCLC treated with single modalities are at high risk for loco-regional recurrence and distant relapse. The aim of decreasing both failure patterns led to combined chemoradiotherapy (CTRT) studies. Sequential CT–RT allows full doses of each modality to be given without the additional toxicity that occurs with concurrent therapy. Induction CT can reduce tumour volume allowing smaller field RT, with less normal tissue toxicity, allowing the use of potentially higher doses of both modalities. Furthermore tumour reduction with CT could reduce radioresistant hypoxic areas present in bulky tumours [1]. However, there is no radiosensitising effect and CT insensitive disease can continue to grow before RT is eventually given. Concurrent CT/RT does provide potential synergy but with increased toxicity. The chemotherapy dose it is possible to deliver may be suboptimal for systemic control and there is no pre-RT cyto-reduction to facilitate smaller field RT. Two other approaches to improve the concurrent CT/RT alone approach are induction CT then CT/RT, and CT/RT followed by more CT as consolidation. The effective CT regimens featured in the clinical trials have used platinum (usually cisplatin) combinations. The RT fractionation has included standard once daily schedules and more recently hyperfractionated (HFRT), e.g. twice daily (bd) treatment.

The three main areas in stage III disease where combined CT and RT have been used are for adjuvant treatment post-resection, for neoadjuvant or pre-operative treatment followed by surgery, and for unresectable tumours.

Adjuvant chemotherapy and radiotherapy

The largest meta-analysis that included patients in all stages of NSCLC, examined six trials of cisplatin-based CT followed by post-operative radiotherapy (PORT) after complete surgical resection, and demonstrated a non-significant survival gain for sequential CT–RT. In a planned subgroup analysis the survival of stage III patients who received CT–RT tended to be better ($P = 0.07$) than for stages I, II [2]. A subsequent meta-analysis of PORT in 2218 patients from 9 trials of surgery plus RT versus surgery alone revealed a 7% survival detriment at 2 years, and 6% at 5 years particularly in stage I, II, N0 N1 but with neither a beneficial or detrimental effect in stage III [3,4]. This meta-analysis was updated to include a randomised trial of 104 patients with stage I NSCLC that suggested a possible survival advantage with PORT, but this did not alter the original conclusion [4,5]. A subsequent trial in stages II, IIA and IIB confirmed the failure of PORT to increase overall survival [6]. Attempts to explain the poorer survival have included inferior radiotherapy techniques and some trials being underpowered [7]. More recently a trial randomised patients following resection to thoracic radiotherapy or concurrent CT/RT using a standard cisplatin–etoposide

(PE) combination [8]. There was no difference in survival even though concurrent CT/RT is considered a standard approach in more advanced disease. The Adjuvant Lung Cancer Project Italy (ALPI) study randomised patients to three courses of triplet MVP (mitomycin, vindesine, cisplatin) chemotherapy with investigator choice to give RT after the CT and there was no survival difference [9]. However, a somewhat larger study (International Adjuvant Lung Cancer Trial, IALT), which allowed a variety of cisplatin regimens (commonest being PE 56% and cisplatin + vinorelbine PVi 27%) followed by RT according to investigator choice did show a survival benefit of 4.1% at 5 years. An interaction analysis showed no influence of RT on survival [10]. The pragmatic trial (Big Lung Trial, BLT) in which RT and stage III patients were included did not find a survival difference. However, the confidence intervals of the ALPI, IALT and BLT and the meta-analysis overlap and are consistent with a hazard ratio (HR) of 0.79–0.98 indicating a survival benefit [11]. A summary of these four adjuvant CT trials, which included PORT for some patients, is displayed in Table 1. The Cancer and Leukemia Group B (CALGB) 9734 trial attempted to determine the value of adjuvant PORT following resection with adjuvant CT, but was closed due to poor accrual and the results did not reveal a role for PORT [12]. More recently, in two trials, which did not include stage III, PORT with adjuvant platinum-based CT did not show a survival benefit [13,14]. The meta-analysis of 11 trials of 5716 patients reported after the NSCLC Collaborative group 1995 publication found that both cisplatin-based CT and single agent tegafur-uracil (Uftoral®) (UFT) gave a survival benefit with 0.6% CT-related deaths [15].

It could therefore be reasoned that there is no evidence that PORT in the adjuvant setting is of survival benefit. However, this may change if systemic treatment becomes more effective in controlling distant metastases, with loco-regional recurrence becoming the major survival determinant.

Table 1
Adjuvant chemotherapy-postoperative radiotherapy (PORT) trials

Trial [ref.]	% of stage III patients	% of patients given RT per arm[a]		Survival difference *P*-value
		Adjuvant CT arm	No CT arm	
ECOG [8]	58	82	86	0.56
ALPI [9]	28	65	82	0.59
IALT [10]	39	70	84	0.03
BLT [11]	26	14	13	0.90

[a] RT, radiotherapy; CT, chemotherapy.

Pre-operative chemotherapy and radiotherapy

Multiple non-randomised studies have demonstrated the feasibility of combining pre-operative CT and surgery with or without RT, reporting survivals beyond 3 years [16]. Nevertheless two main questions remain: does neo-adjuvant CT in resectable, low volume, minimal N2 disease improve survival, and for more bulky tumours (not normally considered for resection) that are sufficiently downstaged by pre-operative CT, is surgery better than RT? Unfortunately the definition of resectable, marginally resectable, unresectable, minimal stage III, bulky stage III is unclear in many of the reports to date [17]. The distinction therefore between initially resectable and potentially resectable after induction therapy is somewhat arbitrary. There are no phase III data definitively proving that RT increases survival over induction CT followed by surgery or that surgery adds to the survival of an initial bimodality CT-RT approach.

Neo-adjuvant treatment for resectable stage III NSCLC

Trials of early-stage or minimum N2 (negative CT of the mediastinum with either no or minimal N2 involvement at mediastinoscopy) for patients eligible for surgery and PORT are summarised. Only two trials out of several randomised trials recruited over 100 patients and the other trials were stopped early. Neo-adjuvant cisplatin-based CT was given in all trials. RT was given sequentially after surgery in seven trials, before surgery in two and concurrently with CT in three trials. In six trials PORT was given for particular subgroups of patients that varied among the trials. In six trials, postoperative CT was also given (Table 2) [18–29]. Moreover, there was considerable diversity in eligibility criteria, e.g. variable TN subsets, disease volume and need for pathological staging. In the Spanish study of N2 patients PORT was planned for all patients. The induction CT consisted of three cycles of MIP (mitomycin, ifosfamide and cisplatin) CT [19,20]. Neo-adjuvant CT and PORT produced a significant improvement in survival over surgery and PORT, which resulted in the early stopping of the trial. Another study was again stopped early after inclusion of 60 patients, as there was a survival improvement with peri-operative PEC (cisplatin, etoposide and cyclophosphamide). Patients received three courses of CT and a further three if there was tumour regression. Patients who were not completely resected could receive RT at the discretion of the treating

Table 2
Randomised trials of pre-operative, neo-adjuvant (induction) therapy and surgery versus surgery with radiotherapy in stage III non-small cell lung cancer[a]

Trial [ref.]	Patients (*n*)	Induction arms	Median survival, months	Survival, %
Pass *et al.* (NCI) [18]	27	PE – S – PE	29	42 (3 year)
		S – PORT	16	12 (3 year)
			($P = 0.095$)	
Rosell *et al.* [19,20]	60	MIP – S – PORT	26	20 (3 year)
				17 (5 year)
		S – PORT	8	5 (3 year)
			($P < 0.001$)	0 (5 year)
Roth *et al.* [21,22]	60	PEC – S – (PEC, PORT)	21	43 (3 year)
				36 (5 year)
		S – PORT	14	19 (3 year)
			($P = 0.048$)	15 (5 year)
Wagner *et al.* (LCSG) [23]	67	MVP – S – (PORT)	12	27 at 4 years for both arms
		RT – S	12	
Yoneda *et al.* [24]	83	PVd concurrent RT–S	14	40 (2 year)
		S – (PVd-PORT)	15	37 (2 year)
Elias *et al.* (CALGB) [25]	57	PE – S – PE-PORT	18	NR
		RT – S – PORT	23	NR
Depierre *et al.* [26]	373	MIP – S – (MIP, PORT)	37	52 (3 year)
		S – PORT	26	41 (3 year)
Nagai *et al.* (JCOG) [27]	62	PVd – S – (PORT)	17	23 (3 year) 10 (5 year)
		S – (PORT)	16	26 (3 year) 22 (5 year)
Thomas *et al.* (GLCCG) [28]	558	PE – concurrent CbVdHFRT – S – HFRT	15	24 (3 year)
		PE – S – PORT	17	23 (3 year)
Fleck *et al.* [29]	96	P, 5FU concurrent RT – S – (PORT)	NR	Better resection rate and
		MVP – S – (MVP)	NR	freedom from progression

[a] NR, not reported; PE, cisplatin etoposide; S, surgery; 5-FU, 5-fluorouracil; MIP, mitomycin, ifosfamide, cisplatin; MVP, mitomycin, vinblastine, cisplatin; PEC, cisplatin, etoposide, cyclophosphamide; RT, radiotherapy; PVd, cisplatin vindesine; CbVd, carboplatin vindesine; HFRT, hyperfractionated RT; (PORT) (PEC, PORT) (MIP, PORT) (PVd-PORT) (MVP) indicates particular patient groups received post-operative radiotherapy, chemotherapy.

physician, but the influence of radiotherapy was not examined [21,22]. The French study randomised 373 stage I–IIIA patients to neo-adjuvant MIP therapy or no CT. Two further CT courses were planned postoperatively for patients who had responded to initial CT [26]. In both arms patients with pT3 and/or pN2 disease and incomplete resection were given PORT. There was a trend for increased survival in the CT arm and subgroup analysis did suggest a survival benefit for N0 N1 disease. There was a non-significant increase in treatment-related mortality in the induction CT arm (10% versus 5%). These studies suggest that neo-adjuvant CT may be of value in resectable NSCLC. In the German trial addition of concurrent CT with twice daily RT fractions following neo-adjuvant PE before surgery (and PORT if incomplete resection) was of no benefit compared with neo-adjuvant PE alone, surgery and standard PORT fractionation [28]. Currently, several phase III trials are comparing induction CT followed by surgery to surgery alone in resectable disease with no requirement for RT. SWOG 9900 is comparing induction paclitaxel, carboplatin then surgery, the Italian CHEST trial is evaluating neoadjuvant gemcitabine plus cisplatin; and the MRC EORTC Dutch trial is assessing cisplatin-based CT with either gemcitabine, vinorelbine, docetaxel, or the MIP regimen.

The magnitude of the positive benefit from the above trials is undefined given the small patient numbers, heterogeneity of the population, the use of

older CT regimens and the variable use of RT. Indeed we still do not know whether RT as a part of the induction regimen improves survival. The Fleck trial attempted to address the question but was underpowered and did not report on overall survival [29]. Despite these considerations the European Society for Medical Oncology (ESMO) (September 2001) stated that ' pre-operative chemotherapy was standard' for resectable stage IIIA NSCLC.

Induction CT and RT for potentially resectable stage III NSCLC

Several randomised trials have investigated multimodality therapy in patients with potentially resectable NSCLC to determine whether surgery improves survival compared with RT after either induction CT alone, or induction CT and RT, with or without further ' adjuvant' CT (Table 3) [30–34]. Three trials closed early because of recruitment issues. A further trial had a somewhat unusual design, which randomised patients to neo-adjuvant docetaxel or no CT before surgery or curative intention RT depending on stage and patient' s condition, with a trend to longer survival with CT [33]. The role of surgery still remains undefined given these results and particularly now, following the large North American intergroup trial of stage IIIA (p N2) patients [34]. In this trial the PE regimen was given concurrently with RT in the induction regimen. Interim analysis was of 392 patients out of 429 recruited. A complete resection was performed in 88% of patients. Significantly more patients who underwent surgery (42%) did not receive consolidation adjuvant CT compared with 21% of patients who did not undergo surgery. Treatment-related death occurred in 1.6% in the CTRT arm and 7% in the CT/RT-surgery arm. There were no significant differences in median or 3-year survivals [34].

Table 3
Stage III (N2) induction chemotherapy then surgery versus radiotherapy[a]

Trial [ref.]	Patients (*n*)	Median survival (months)	
Shepherd *et al.* [30]	31	PV – S	18.7
		RT alone	16.2
Stephens *et al.* [31]	42	MIP or MVP – S	14
		RT alone	11
Johnstone *et al.* [32]	75	MVP or PV – S – CT	19.4
		CT – RT – CT	17.4
Mattson *et al.* [33]	274	D – S – CT	14.8
		S or RT	12.6
Albain *et al.* [34]	392	PE/RT – S – CT	22.1
		PE/RT – RT – CT	21.7

[a] S, surgery; RT, radiotherapy; PV, cisplatin, vinblastine; MIP, mitomycin, ifosfamide, cisplatin; MVP, mitomycin, vinblastine, cisplatin; D, docetaxel; PE/RT, concurrent cisplatin, etoposide with radiotherapy.

A number of phase II studies have reported the effectiveness of induction regimens with newer drugs such as gemcitabine, docetaxel and paclitaxel (Table 4) [35–40]. In these studies PORT was given to patients with positive resection margins, involvement of mediastinal nodes, incomplete resection or to patients in whom resection was not possible after induction therapy. Although no randomised trials are available improved survival with pre-operative PE and concurrent RT followed by surgery for superior sulcus tumours has also been reported [41].

The place of resection following induction therapy is the subject of several current trials that also include RT. Important questions include CT or CTRT as induction, identifying the best induction regimen, surgery or RT after induction, optimal staging, defining the optimal patients, the role of predictive markers and integration of new drugs, and RT techniques. The EORTC 08941 trial randomised inoperable N2 patients to surgery or RT after a response to initial platinum-based CT and the results are expected in 1–2 years. The CT allows a variety of platinum-based regimens and PORT was given for positive resection margins or persistent N2 disease at surgery [42]. A West German trial follows encouraging trimodality phase 2 work in bulky stage IIIA and B disease [43]. Induction chemotherapy with cisplatin and paclitaxel is followed (if there is no disease progression) with hyperfractionated radiotherapy (HFRT) concurrent with PVi. After restaging, patients are randomised to surgery or concurrent PVi with standard RT. A Nordic trial randomises patients to carboplatin and paclitaxel, then RT or to the same CT then surgery and PORT. The North American intergroup trial will also use induction with cisplatin and docetaxel (PD) then randomisation to concurrent CT/RT or not. Both arms then go to resection followed by additional adjuvant CT [16].

The additional toxicity and possible treatment mortality of RT with CT is a reason for caution [16,17] and given the unsubstantiated role of RT pre and postoperatively, focusing on neo-adjuvant CT alone, rather than CTRT followed by resection with or without adjuvant CT or RT would be interesting. The Swiss trial is evaluating PD induction, then if there is no disease progression patients are randomised to resection or RT then resection. If RT does not add a survival benefit to CT and surgery, the next question of

Table 4
Phase II trials using third generation chemotherapy drugs within the induction regimen and radiotherapy[a]

Trial [ref.]	Stage subset	Study design	Response rate		Complete resection (%)	pCR (%)	Median survival (months)
			n	Rate (%)			
Betticher *et al.* [35]	IIIA (pN2), mixed bulk	PD × 3 → surgery → variable RT	90	66	48	16	27.6
De Marinis *et al.* [36]	IIIA (pN2), bulky	GTP × 3 → surgery → variable RT	49	74	55	16	23
Cappuzzo *et al.* [37]]	IIIA, IIIB (clin), bulky	GP × 4 → surgery → variable RT	129	62	29	2	19.4
van Zandwijk *et al.* [38]	IIIA (pN2) bulky	GC × 3 → surgery or RT	47	70	71	NR	18.9
O' Brien*et al.* [39]	IIIA (pN2) bulky	TC × 3 → surgery or RT	52	64	80	NR	20.5
Date *et al.* [40]	IIIA(pN2) bulky	PI × 2 → surgery → to variable RT/CT	15	73	73	7	20

[a] RT, radiotherapy; T, paclitaxel; C, carboplatin; P, cisplatin; D, docetaxel; G, gemcitabine; I, irinotecan; NR, not reported; pCR (%), pathological complete response.

interest is whether adjuvant CT is required in addition to neo-adjuvant CT.

Unresectable stage III disease

A meta-analysis of 1780 patients from 11 trials showed a small survival advantage of 4% at 2 years, and 2% at 5 years with the addition of cisplatin-based CT to RT against RT alone [2]. Subsequent trials have been undertaken to define optimal treatment regimens (Table 5) [44–49]. Superior survival for patients receiving cisplatin and vinblastine (PVb) then standard sequential RT versus standard RT alone was reported but hyperfractionated RT alone was not statistically superior to standard RT [44]. In a British study using up to 4 courses of MIP then RT versus RT alone, there was a non-significant survival difference, however quality of life was significantly better with CT [45]. The ECOG 2597 design compared induction paclitaxel and carboplatin CT then sequential standard RT against CT then hyperfractionated accelerated RT (HART). Again poor recruitment led to early closure but the median survival was 13.7 months with standard CT–RT compared with 22.2 months with CT-HART [50]. The logic of using hyperfractionated RT is to reduce tumour cell re-population and to protect late reacting normal tissues. Four other trials published after the 1995 meta-analysis examined concurrent CT/RT versus RT alone (Table 5) [46–49]. Three concurrent trials used low-dose, radiosensitising platinum doses and only one evaluated full dose cisplatin [47]. In the trial of Jeremic and colleagues [49] a survival benefit was demonstrated for patients who received HFRT concurrent with daily carboplatin and etoposide (43% 2-year survival) versus 26% 2-year survival for patients who received HFRT alone. Two other trials evaluated induction CT followed by low-dose carboplatin or hydroxyurea concurrently with RT with no survival benefit from the concurrent approach [51,52]. The EORTC 08972 trial compared sequential CT with cisplatin and gemcitabine then RT against concurrent CTRT with daily (radiosensitising low doses) of cisplatin but closed early in March 2003 because of poor accrual.

In a review of larger trials, some of which were included in the 1995 meta-analysis, three of five trials reported between 1988 and 2000 of sequential platinum-based CT–RT versus RT alone reported a significant survival benefit for CT–RT. Three of eight trials reported between 1990 and 1999 of concurrent platinum based CT/RT versus RT alone that included one trial of induction CT [51] described significantly better survival for CT/RT, but with greater toxicity [53]. Higher doses of platinum have not improved survival [54]. Taken together, these data demonstrate a role for CT in improving the outcome compared with RT alone for unresectable stage III disease.

The converse situation, i.e. the value of adding RT to CT, was examined in a three-arm randomised trial which compared single agent vindesine, standard RT alone and CT plus RT. The 5-year survival rates of 1%, 3% and 3% for each treatment arm respectively, were not significantly different, suggesting no survival benefit with immediate RT [55]. Two other small

Table 5
Phase III studies of chemotherapy and radiotherapy versus radiotherapy alone in non-small cell lung cancer, published after NSCLC meta-analysis[a] [3]

Trial [ref.]	Patients (*n*)	Therapy	Median survival (months)	2-year survival (%)	Difference
		Sequential CT–RT			
Sause *et al.* [44]	490	RT	11.4	21	
		HF RT	12	24	NS
		PVd –RT	13.2	31	0.04
Cullen *et al.* [45]	461	RT	11.7	20	
		MIP –RT	9.7	16	NS
		Concurrent CT/RT			
Ball *et al.* [46]	204	RT	14	26	
		HFRT	14	28	
		RT/Cb	17	29	
		HFRT/Cb	15	20	NS
Blanke *et al.* [47]	240	RT	11.5	13	
		RT/P (q. 3 weeks)	10.7	18	NS
Jeremic *et al.* [48]	169	HFRT	8	25	
		HFRT/CbE (low)	18	35	0.003
		HFRT/CbE (high)	13	27	NS
Jeremic *et al.* [49]	131	HFRT	14	26	
		HFRT/CbE (daily)	22	43	0.021

[a] RT, standard radiotherapy; HFRT, hyperfractionated radiotherapy; PVd, cisplatin, vindesine; MIP, mitomycin, ifosfamide, cisplatin; P, cisplatin, Cb, carboplatin; CbE, carboplatin, etoposide low- or high-dose or daily.

randomised trials compared cisplatin CT followed by RT with the same CT alone. A superior 3-year survival rate with sequential CT-RT was reported in patients whose disease did not progress with initial MVdP, PVd or an alternating PE/VdM regimen [56]. In the other study patients whose disease responded to MIP were randomised to further MIP or RT with no survival difference [57]. There is perhaps then a provocative question as to whether immediate RT can be omitted in patients with inoperable stage III NSCLC whose disease has responded to CT.

A meta-analysis showed a similar treatment effect when trials of concurrent and sequential chemoradiotherapy were considered [58]. Nevertheless, there have been two fully published trials [59,60] and a number of randomised phase II and III trial abstracts that have suggested superior survival (not all statistically significant) with the use of concurrent CT/RT versus sequential CT–RT albeit with increased toxicity (Table 6) [59–64]. The recent Cochrane meta-analysis, which included three of the trials found a significant reduction in the risk of death at 2 years (relative risk (RR) 0.86, $P=0.003$) with concurrent therapy, although caution was advised in adopting concurrent CT/RT given uncertainties about the true magnitude of benefit, short follow up and uncertainty about toxicity [65]. The CALGB database of combined modality trials examined the prognostic factors and toxicity in 694 patients. Baseline haemoglobin <12 g/dl, Performance Status 1 and RT alone predicted for poorer survival, whilst grade 3 or greater oesophagitis (21% of patients) was the main RT toxicity with concurrent CT/RT [66].

Other attempts to improve therapy have addressed whether induction or consolidation therapy is better retaining the base of concurrent CT/RT. The BROCAT German trial was a complicated design in which 2 cycles of induction CT were administered then patients were randomised (if no progression) to RT alone or RT with concurrent single agent paclitaxel (Table 6) [64]. The CALGB 9431 randomised phase II trial evaluated two cycles of cisplatin with either gemcitabine, paclitaxel or vinorelbine as induction therapy followed by another 2 cycles of the same CT given concurrently with RT (66 Gy) and there was no clear superiority between the regimens [67]. Gemcitabine being a potent radiosensitiser, was associated with an increase in oesophagitis but numerically lower rates of grade 3 and 4 dyspnoea and acquired respiratory distress syndrome (ARDS) with concurrent CT/RT [67]. In the subsequent CALGB 9801 trial that compared concurrent CT/RT with low dose paclitaxel and carboplatin (TCb) versus systemic TCb doses then the same CT/RT concurrent regimen, there was

Table 6
Completed trials comparing chemoradiotherapy sequencing[a]

Trial reference	Patients (*n*)	CT cycles and RT dose	Schedule	Median survival (years)	Survival (%)	*P*-value
Furuse *et al.* [59]	320	MVP × 2 – 56 Gy – MVP	Sequential	13.3	9	0.04
		MVP × 2 – 56 Gy / MVP	Concurrent	16.5	16 (5 year)	
Curran *et al.* [61]	610	PVi × 2 – 60 Gy	Sequential	14.6	12 (4 year)	
		PVi × 2 / 60 Gy	Concurrent	17.10	21	0.04
		PE × 2 / 69.6 Gy	Concurr. bd	15.2	17	0.3
Fournel *et al.* [62]	212	PVi × 3 – 66 Gy	Sequential	13.8	23	
		PE × 2 – 66 Gy / PVi × 2	Concurrent	15.0	35 (2 year)	0.3
Bonomi *et al.* [63]	184	TCb × 2 – 63 Gy	Sequential	13.1	31 (2 year)	NS
		TCb / 63 Gy – TCb × 2	Concurrent	16.1		
Zatloukal *et al.* [60]	102	P ± Vi × 4 – 60 Gy	Sequential	12.9	9	0.02
		P ± Vi × 4 / 60 Gy	Concurrent	16.6	19 (3 year)	
Huber *et al.* [64]	303	TCb × 2 – 60 Gy	Sequential	14.1		
		TCb × 2 – T / 60 Gy	Concurrent	18.7	NR	NS

[a] MVP, mitomycin, vindesine, cisplatin; PVi, cisplatin, vinorelbine; PE, cisplatin, etoposide; TCb, paclitaxel, carboplatin.

no significant survival difference [68]. The SWOG 9504 trial used a standard concurrent PE/RT approach followed by three cycles of docetaxel. The impressive median survival of 26 months and 2-year survival of 54% has led to the general adoption of this regimen despite the trial being non-randomised [69]. Several trials are now being conducted to confirm the value of consolidation treatment following CTRT (Fig. 1). To evaluate consolidation with docetaxel, a Hoosier trial is randomising between the SWOG 9504 treatment or the same induction CT/RT regimen then observation. SWOG S0023 again uses the SWOG 9504 core then randomises to observation or gefitinib. Given the above results [64,68] the strategy of induction CT before concurrent CT/RT is as yet unproven. The question also remains as to whether the survival in the sequential CT–RT arms could have been improved by additional CT courses, e.g. a total of 4, rather than the 2 commonly used before thoracic RT was given.

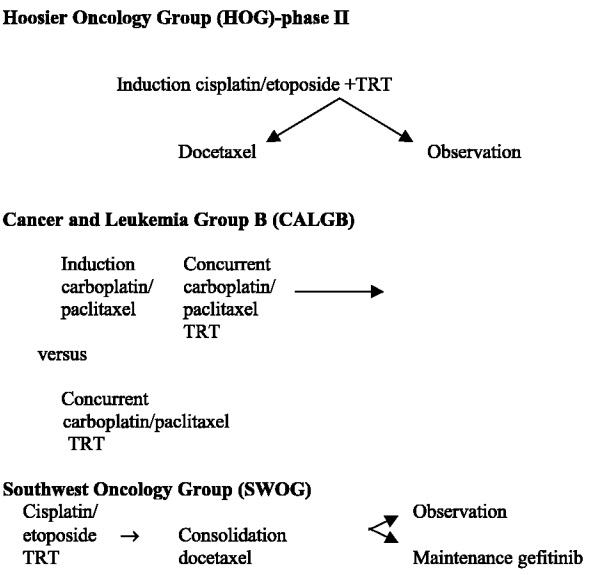

Fig. 1. Trials of consolidation therapy following chemoradiotherapy.

Conclusion

Given the recent adjuvant CT results, surgery alone can be considered substandard for stages I and II. Adjuvant radiotherapy is of unproven benefit. The value of neo-adjuvant CTRT in patients with a high probability of resection is still not definite and there is no clear benefit from resection in bulky stage III tumours after concurrent CT/RT. For the T4, N0 or N1 subset a randomised trial is required to confirm the phase II trial results that suggest the value of resection after CTRT. For patients with locally advanced, unresectable stage III cancers a combined CTRT approach is standard, with the evidence leaning towards concurrent CTRT. The possible added benefit of resection, induction CT, consolidation CT or hyperfractionated RT over standard CTRT is unproven.

The major need is still to improve the systemic control of metastatic disease, which continues to be the prime cause of death in patients with NSCLC. Only a selected proportion of patients, for example those with best performance status, and best lung function, have been included in the recent studies particularly of concurrent CTRT. There remains a need to develop the sequencing of combined modality treatment using

newer drugs and RT techniques for the broader patient population.

References

1 Turrisi AT, Bogart J, Sherman C, *et al.* The role of radiotherapy and chemotherapy for curative management of medically inoperable and stage III non-small cell lung cancer, and radiotherapy for palliation of symptomatic disease. *Respir Care Clin* 2003, **9**, 163–190.

2 Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995, **311**, 899–909.

3 PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998, **352**, 257–263.

4 Burdett S, Stewart L. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005, **47**, 81–83.

5 Trodella L, Granone P, Valente S, *et al.* Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomised trial. *Radiother Oncol* 2002, **62**, 11–19.

6 Feng QF, Wang M, Wang LJ, *et al.* A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. *Int J Radiat Oncol Biol Phys* 2000, **47**, 925–929.

7 Machtay M, Lee JH, Shrager JB, *et al.* Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma. *J Clin Oncol* 2001, **19**, 3912–3917.

8 Keller SM, Sudeshna A, Wagner H, *et al.* A randomised trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. *N Engl J Med* 2000, **343**, 1217–1222.

9 Scagliotti GV, Fossati R, Torri V, *et al.* Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003, **95**, 1453–1461.

10 A.The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004, **350**, 351–360.

11 Waller D, Peake MD, Stephens RJ, *et al.* Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardio-thoracic Surg* 2004, **26**, 173–182.

12 Perry MC, Kohman LJ, Bonner JA, *et al.* A phase III study of surgical resection and chemotherapy (paclitaxel/carboplatin) (CT) with or without adjuvant radiation therapy (RT) for resected stage III non-small cell lung cancer (NSCLC): CALG B9734. *Lung Cancer* 2003, **41**(Suppl 2), pS55; abstr 0-183.

13 Strauss GM, Herndon MA, Maddaus, *et al.* Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of Cancer and Leukemia Group B (CALGB) Protocol 9633[LBA]. *Proc Am Soc Clin Oncol* 2004, **23**, abstr 7019.

14 Winton TL, Livingston R, Johnson D, *et al.* A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR.10.[LBA]. *Proc Am Soc Clin Oncol* 2004, **23**, abstr 7018.

15 Hotta K, Matsuo K, Ueoka H, *et al.* Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomised controlled trials. *J Clin Oncol* 2004, **22**, 1–8.

16 Pisters KMW, Mirkovic N, Pass H , Albain KS. Preoperative chemotherapy/radiation therapy for early stage and locally advanced non-small cell lung carcinoma. In Pass HI, Carbone DP, Johnson DH, Minna JD, Turrisi ATI III, eds. *Lung Cancer Principles and Practice 2005*, 3rd edn. Philadelphia, Lipincott Williams and Wilkins, 626–649.

17 Robinson LA, Wagner Jr H, Ruckdeschel JC. Treatment of stage IIIA non-small cell lung cancer. *Chest* 2003, **123**, 202S–220S.

18 Pass HI, Pogrebniak HW, Steingerg SM, *et al.* Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg* 1992, **53**, 992–998.

19 Rosell R, Gomez-Codina J, Camps C, *et al.* A randomised trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994, **330**, 153–158.

20 Rosell R, Gomez-Codina J, Camps C, *et al.* Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomised controlled trial. *Lung Cancer* 1999, **47**, 7–14.

21 Roth JA, Fossella F, Komaki R, *et al.* A randomised trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994, **86**, 673–680.

22 Roth JA, Atkinson EN, Fossella F, *et al.* Long-term follow-up of patients enrolled in a randomised trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998, **21**, 1–6.

23 Wagner H J, Lad T, Piantadosi, *et al.* Randomized phase II evaluation of preoperative radiation therapy and preoperative chemotherapy with mitomycin, vinblastine and cisplatin in patients with technically unresectable stage IIIA and IIIB non small cell cancer of thelung LCSG 881. *Chest* 1994, **106**, 348s–354s.

24 Yoneda S, Hibino S, Gotoh I, *et al.* A comparative trial on induction chemoradiotherapy followed by surgery (CRS) or immediate surgery (IS) for stage III non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1995, **14**, 367; abstr 1128.

25 Elias AD, Kumar P, Herndon J 3rd, *et al.* Radiotherapy versus chemotherapy plus radiotherapy in surgically treated IIIA N2 non-small-cell lung cancer. *Clin Lung Cancer* 2002, **4**, 95–103.

26 Depierre A, Milleron B, Moro-Sibilot D, *et al.* Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1NO), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002, **20**, 247–253.

27 Nagai K, Tsuchiya R, Mori T, *et al.* A randomised trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). *J Thorac Cardiovasc Surg* 2003, **125**, 254–260.

28 Thomas M, Macha H, Ukena D, *et al.* Cisplatin/etoposide (PE) followed by twice–daily chemoradiation (hfRT/CT) versus PE alone before surgery in stage III non-small cell lung cancer (NSCLC): a randomised phase III trial of the German Lung Cancer Cooperative Group (GLCCG). *Proc Am Soc Clin Oncol* 2004, **23**, 616; abstr 7004.

29 Fleck J, Camargo J, Godoy D, *et al.* Chemoradiation therapy (CRT) versus chemotherapy (CT) alone as a neo-adjuvant treatment for stage III non-small cell lung cancer (NSCLC). Preliminary Report of a Phase III Prospective Randomized Trial. *Proc Am Soc Clin Oncol* 1993, **12**, 333; abstr 1108.

30 Shepherd FA, Johnston MR, Payne D, *et al.* Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study. *Br J Cancer* 1998, **78**, 683–685.

31 Stephens RJ, Girling DJ, Hopwood P, *et al.* Randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1–3, N2, M0 non-small cell lung cancer. *Lung Cancer* 2005 (in press).

32 Johnstone DW, Byhardt RW, Ettinger D, *et al.* Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. *Int J Radiat Oncol Biol Phys* 2002, **54**, 365–369.

33 Mattson KV, Abratt RP, ten Velde G and Krofta K. Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study. *Ann Oncol* 2003, **14**, 116–122.

34 Albain KS, Scott CB, Rusch VR, *et al.* Phase III comparison of concurrent chemotherapy plus radiotherapy (CT/RT) and CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): initial results from intergroup trial 0139 (RTOG 93-09). *Proc Am Soc Clin Oncol* 2003, **22**, 621; abstr 2497.

35 Betticher DC, Schmitz S-FH, Totsch M, *et al.* Mediastinal lymph node clearance after docetaxel-cisplatin Neoadjuvant chemotherapy is prognostic survival in patients with stage IIIA pN2 non-small cell lung cancer. A Multicenter Phase II Trial. *J Clin Oncol* 2003, **21**, 1752–1759.

36 De Marinis F, Nelli F, Migliorino MR, *et al.* Gemcitabine, paxlitaxel and cisplatin as induction chemotherapy for patients with biopsy-proven stage IIIA(N2) non-small cell lung carcinoma. *Cancer* 2003, **98**, 1707–1715.

37 Cappuzzo F, Selvaggi G, Gregorc V, *et al.* Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable stage IIIA-Bulky N2 and stage IIIB nonsmall cell lung carcinoma. *Cancer* 2003, **98**, 128–134.

38 Van Zandwijk N, Smith EF, Kramer GWP, *et al.* Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC 08955). *J Clin Oncol* 2000, **18**, 2658–2664.

39 O' Brien MER, Splinter T, Smit EF, *et al.* Carboplatin and paclitaxol (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: an EORTC phase II study (EORTC 08958). *Eur J Cancer* 2003, **39**, 1416–1422.

40 Date H, Kiura K, Ueoka H, *et al.* Preoperative induction chemotherapy with cisplatin and irinotecan for pathological N2 non-small cell lung cancer. *Br J Cancer* 2002, **86**, 530–533.

41 Archie VC, Thomas Jr CR. Superior sulcus tumors: a mini-review. *Oncologist* 2004, **9**, 550–555.

42 Splinter TA van Schil PE, Kramer GW, *et al.* Randomized trial of surgery versus radiotherapy in patients with stage IIIA (N2) non small-cell lung cancer after a response to induction chemotherapy. EORTC 08941. *Clin Lung Cancer* 2000, **2**, 69–72.

43 Eberhardt W, Gauler T, Hepp R, *et al.* The role of chemoradiotherapy in the treatment of stage III non-small-cell lung cancer. *Ann Oncol* 2004, **15**(Suppl 4), iv71–iv80.

44 Sause W, Kolesar P, Taylor S, *et al.* – Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. *Chest* 2000, **117**, 358–364.

45 Cullen MH, Billingham LJ, Woodroffe CM, *et al.* Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. *J Clin Oncol* 1999, **17**, 3188–3194.

46 Ball D, Bishop J, Smith J, *et al.* A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial. *Radiother Oncol* 1999, **52**, 129–136.

47 Blanke C, Ansari R, Mantravadi R, *et al.* Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol. *J Clin Oncol* 1995, **13**, 1425–1429.

48 Jeremic B, Shibamoto Y, Acimovic L, *et al.* Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. *J Clin Oncol* 1995, **13**, 452–458.

49 Jeremic B, Shibamoto Y, Acimovic L, *et al.* Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomised study. *J Clin Oncol* 1996, **14**, 1065–1070.

50 Belani CP, Wang W, Johnson DH, *et al.* Induction chemotherapy followed by standard thoracic radiotherapy (Std.TRT) vs. hyperfractionated accelerated radiotherapy (HART) for patients with unresectable stage III A & B non-small cell lung cancer (NSCLC): Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597). *Proc Am Soc Clin Oncol* 2003, **22**, 622; abstr 2500.

51 Clamon G, Herndon J Cooper R, *et al.* Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999, **17**, 4–11.

52 Mantravadi A, Sandler J, Montebello R, *et al.* Randomized phase III study of cisplatin (P) and vinblastine (V) followed by thoracic radiotherapy with or without hydroxyurea (HX) in previously untreated limited unresectable non-small cell lung cancer (NSCLC): A Hoosier Oncology Group (HOG) study. *Proc Am Soc Clin Oncol* 1998, **17**, p454a; abstr 1746.

53 Jassem J. Combined chemotherapy and radiotherapy in inoperable non-small cell lung cancer. *Lung Cancer* 2002, **38**, S43–S46.

54 Sculier J-P, Lafitte J-J, Berghmans T, *et al.* A phase III randomised study comparing two different dose-intensity regimens as induction chemotherapy followed by thoracic irradiation in patients with advanced locoregional non-small-cell lung cancer. *Ann Oncol* 2004, **15**, 399–409.

55 Johnson DH, Einhorn LH, Bartolucci A, *et al.* Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small-cell lung cancer. *Ann Intern Med* 1990, **113**, 33–38.

56 Kubota K, Furuse K, Kawahara M, *et al.* Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. *J Clin Oncol* 1994, **12**, 1547–1552.

57 Sculier JP, Paesmans M Lafitte JJ, *et al.* A randomised phase III trial comparing consolidation treatment with further chemotherapy to chest irradiation in patients with initially unresectable locoregional non-small-cell lung cancer responding to induction chemotherapy. *Ann Oncol* 1999, **10**, 295–303.

58 Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A Meta-Analysis. *Ann Intern Med* 1996, **125**, 723–729.

59 Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999, **17**, 2692–2699.

60 Zatloukal PV, Petruzelka L, Zemanova M, *et al.* Concurrent versus sequential radiochemotherapy and vinorelbine in locally advanced non-small cell lung cancer. A randomised phase study. *Lung Cancer* 2004, **46**, 87–98.

61 Curran WJ, Scott C B, Langer C J, *et al.* Long-term benefit is observed in a Phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III nsclc (NSCLC): Initial Report of Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2003, **22**, 621; abstr 2499.

62 Fournel P, Perol M, Robinet G, *et al.* A randomised phase III trial of sequential chemo-radiotherapy versus concurrent chemo-radiotherapy in locally advanced non small cell lung cancer (NSCLC) (GLOT-GFPC NPC 95-01 study). *Proc Am Soc Clin Oncol* 2001, **20**, p312a; abstr 1246.

63 Bonomi P, Curran W, Choy H, *et al.* Randomised 3-arm phase II study of paclitaxel (T), carboplatin (C) and thoracic radiation (TRT) for patients with stage III non-small cell lung cancer (NSCLC). Report of locally advanced multimodality protocol (LAMP)-ACR 427. *Lung Cancer* 2003, **41**(Suppl 2), s77; abstr O-263.

64 Huber RM, Flentje M, Gosse H, *et al.* Induction chemotherapy and following simultaneous radiochemotherapy versus induction chemotherapy and radiotherapy alone in inoperable NSCLC (Stage IIIA/IIIB): update of CT/RT 99/97. *Proc Am Soc Clin Oncol* 2004, **23**, 632; abstr 7075.

65 Rowell NP, O' Rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer (Review). *The Cochrane Library* 2004, Issue 4.

66 Socinski MA, Zhang C, Herndon JE, *et al.* Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity. *Ann Oncol* 2004, **15**, 1033–1041.

67 Vokes EE, Herndon JE II, Crawford J, *et al.* Randomized phase II study of cisplatin with gemcitabine or paxlitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. *J Clin Oncol* 2002, **20**, 4191–4198.

68 Vokes EE, Herndon ME, Kelley MJ, *et al.* Induction chemotherapy followed by concomitant chemoradiotherapy (CT/XRT) versus CT/XRT alone for regionally advanced unresectable non-small cell lung cancer (NSCLC): initial analysis of a randomised phase III trial. *Proc Am Soc Clin Oncol* 2004, **23**, p616; abstr 7005.

69 Gandara DR, Chansky K, Albain KS, *et al.* Consolidation Taxotere after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003, **21**(10), 2004–2010.