

Treatment of Non-small Cell Lung Cancer, Stage IIIB*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

James R. Jett, MD, FCCP; Steven E. Schild, MD; Robert L. Keith, MD, FCCP; and Kenneth A. Kesler, MD, FCCP

Objective: To develop evidence-based guidelines on best available treatment options for patients with stage IIIB non-small cell lung cancer (NSCLC).

Methods: A review was conducted of published English-language (abstract or full text) phase II or phase III trials and guidelines from other organizations that address management of the various categories of stage IIIB disease. The literature search was provided by the Duke University Center for Clinical Health Policy Research and supplemented by any additional studies known by the authors.

Results: Surgery may be indicated for carefully selected patients with T4N0-1M0. Patients with N3 nodal involvement are not considered to be surgical candidates. For individuals with unresectable disease, good performance score, and minimal weight loss, treatment with combined chemoradiotherapy results in better survival than radiotherapy (RT) alone. Concurrent chemoradiotherapy seems to be associated with improved survival compared with sequential chemoradiotherapy. Multiple daily fractions of RT when combined with chemotherapy have not been shown to result in improved survival compared with standard once-daily RT combined with chemotherapy. The optimal chemotherapy agents and the number of cycles of treatment to combine with RT are uncertain.

Conclusion: Prospective trials are needed to answer important questions, such as the role of induction therapy in patients with potentially resectable stage IIIB disease. Future trials are needed to answer the questions of optimal chemotherapy agents and radiation fractionation schedule. The role of targeted novel agents in combination with chemoradiotherapy is just starting to be investigated.

(CHEST 2007; 132:266S–276S)

Key words: chemoradiotherapy; hyperfractionated radiotherapy; radiotherapy; treatment stage IIIB

Abbreviations: CHART = continuous hyperfractionated radiotherapy; ECOG = Eastern Cooperative Oncology Group; F2 = 17 Gy in two fractions; F13 = 39 Gy in 13 fractions; MST = median survival time; NSCLC = non-small cell lung cancer; PS = performance score; RM = radiation myelopathy; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SVC = superior vena cava

Stage IIIB non-small cell lung cancer (NSCLC) includes patients with T4 tumors; any N; M0; and any T, N3, M0.¹ It is estimated that 10 to 15% of all patients are at stage IIIB at the time of diagnosis of their disease.¹ On the basis of the

Surveillance, Epidemiology, and End Results registry 2004, Wisnivesky et al² evaluated >80,000 cases of NSCLC with adequate documentation of

*From the Division of Pulmonary Medicine and Medical Oncology (Dr. Jett), Mayo Clinic, Rochester, MN; the Department of Radiation Oncology (Dr. Schild), Mayo Clinic, Scottsdale, AZ; the Division of Pulmonary Sciences and Critical Care Medicine (Dr. Keith), Denver VA Medical Center, University of Colorado Health Sciences Center, Denver, CO; and the Division of Thoracic Surgery (Dr. Kesler), Indiana University, School of Medicine, Indianapolis, IN.

The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Manuscript received May 30, 2007; revision accepted June 5, 2007. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: James R. Jett, MD, FCCP, Division of Pulmonary Medicine and Medical Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: JETT.JAMES@mayo.edu
DOI: 10.1378/chest.07-1380

tumor size (53% of total Surveillance, Epidemiology, and End Results registry) and reported that 17.6% were stage IIIB. The anticipated 5-year survival for the vast majority of patients who present with clinical stage IIIB NSCLC is 3 to 7%.¹ Data on pathologically staged IIIB disease was not available from the Mountain International Classification but will be included in the revised international staging system that is planned for 2009.

The optimal treatment for stage IIIB NSCLC depends on several variables, including the extent of disease, age, comorbid risk factors, patient performance status (PS), and weight loss. Radiotherapy (RT) alone has been used in the past but should be limited to patients with poor PS. Chemotherapy alone is similarly not a good treatment option, except for patients with malignant pleural effusions (discussed in the "Treatment of Non-small Cell Lung Cancer, Stage IV" chapter). Palliative chemotherapy is not addressed in this article. Surgery can be offered to highly selected patients, either as a single modality or after induction (neoadjuvant) chemotherapy with or without RT. Concurrent chemoradiotherapy is recommended for most cases.

MATERIALS AND METHODS

This section of the evidence-based guidelines is based on an extensive review of the medical literature from 2002 through mid-2006. A literature search was provided by the Duke University Center for Clinical Health Policy Research and supplemented by additional studies known by the authors. These reports included selected case series and pooled data analysis for rare clinical situations, such as superior vena cava (SVC) resection for T4 tumors. Data from four additional guidelines published since 2002 was reviewed along with 10 phase III trials and numerous phase II treatment trials addressing the more common treatment questions related to stage IIIB disease. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

RESULTS

Limited Role of Surgery

Surgery may be indicated for meticulously culled patients with stage IIIB disease³ (see "Special Treatment Issues in Lung Cancer" chapter). Patients who have T4N0-1 solely on the basis of a satellite tumor nodule(s) within the primary lobe have been reported to have 5-year survival rate of approximately 20%. These reports⁴⁻⁶ are retrospective

case series and pooled data analysis. Carinal resections with lobectomy or pneumonectomy have been performed for T4N0-1 disease.⁷⁻¹⁰ Carinal resections carry an appreciable operative mortality of 10 to 15% in experienced centers.^{7,8} Sleeve pneumonectomy has been estimated to have an operative mortality two to four times that of standard pneumonectomy.⁹ The 5-year survival in these carefully selected retrospective series is approximately 20%. Similarly, surgical resection of the SVC for direct tumor invasion has been performed selectively.^{11,12} A review¹¹ of 109 SVC resections from four international centers included 78 cases of resection for tumor involvement of the SVC and 31 cases for mediastinal lymph nodal involvement of the SVC. Fifty percent of the cases required a pneumonectomy. The operative mortality rate was 12%, and the 5-year survival rate was 21%. Both pneumonectomy and complete resection of the SVC with a prosthetic replacement were associated with a significant increased risk for death.

Trials of neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection have generally excluded patients with stage IIIB disease. Reports¹³⁻¹⁵ of carefully chosen patients with stage IIIB disease have shown a similar survival to patients with stage IIIA disease when treated with induction therapy followed by resection. The overall 5-year survival rate is $\leq 20\%$. However, the subset of patients who have stage IIIB disease and demonstrate a complete pathologic response after induction therapy with no residual viable neoplasm identified in the surgical specimen may experience better survival rates. In patients who have stage IIIB NSCLC and are believed to be surgical candidates but are anticipated to require pneumonectomy, surgery with consideration of adjuvant chemotherapy without RT may be a preferable treatment option, because induction chemoradiation therapy followed by pneumonectomy has been shown to be associated with significant mortality risk.¹⁶ For patients with stage IIIB disease and T4 tumors, the presence of N2 disease is considered to be a strong contraindication to surgery, which is consistent with the British Thoracic Society and National Comprehensive Cancer Network guidelines.^{3,17} To date, no phase III data demonstrate that neoadjuvant treatment followed by surgery in patients with IIIB disease results in prolonged survival compared with treatment with chemoradiation therapy without surgery. Given the apparent low benefit/risk ratio, any patient who has clinical stage IIIB and is believed potentially to be a surgical candidate would best be evaluated by several disciplines, including a pulmonologist, medical and radiation oncologists, and thoracic surgeon, before treatment.

RECOMMENDATIONS

1. In selected patients with clinical T4N0-1 NSCLC as a result of satellite tumor nodule(s) in the same lobe, carinal involvement, or SVC invasion, it is recommended that evaluation be performed by a multidisciplinary team that includes a thoracic surgeon with lung cancer expertise to determine whether the tumor is operable. Surgery is not recommended when there is N2 involvement. Grade of recommendation, 1C

2. For patients with stage IIIB NSCLC as a result of N3 disease, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended. Grade of recommendation, 1C

RT Alone vs Combination Chemoradiotherapy

The vast majority of patients with IIIB disease do not benefit from surgery and are best treated with chemoradiotherapy or RT alone, depending on sites of tumor involvement, extent of disease, and PS. Since the American College of Chest Physicians guidelines in 2003, four additional guidelines have been published by the American Society of Clinical Oncology, Cochrane group, National Comprehensive Cancer Network, and Cancer Care Ontario.^{17–20} The data for these guidelines were derived from randomized, prospective trials that evaluated patients with both unresectable IIIA and IIIB disease. Results of patients with IIIB disease alone are not independently available. Data in the Cancer Care Ontario guidelines included six metaanalyses and 17 randomized trials of chemotherapy vs RT.²⁰ The largest metaanalysis was performed by the NonSmall Cell Lung Cancer Collaborative Group as referenced in the last American College of Chest Physicians guidelines²¹; of 22 randomized trials evaluated, only 11 of these trials were with cisplatin-based chemotherapy. The trials with non-cisplatin-based chemotherapy did not demonstrate any survival benefit. The results showed a significant benefit with cisplatin-based chemoradiotherapy. There was a 13% reduction in the risk for death (hazard ratio, 0.87) and an absolute benefit of 4% at 2 years and 2% at 5 years ($p = 0.005$). Results of all four practice guidelines favored cisplatin-based chemoradiotherapy vs RT alone for patients with good PS (0 or 1) and minimal weight loss ($\leq 5\%$).

RECOMMENDATIONS

3. For patients with stage IIIB disease without malignant pleural effusions, PS of 0 or 1, and minimal weight loss ($\leq 5\%$), platinum-based

combination chemoradiotherapy is recommended. Grade of recommendation, 1A

4. In patients with stage IIIB NSCLC and PS of 2 or those with substantial weight loss ($>10\%$), chemoradiotherapy is recommended only after careful consideration. Grade of recommendation, 1C

Concurrent vs Sequential Therapy

Phase III trials have been performed to compare sequential and concurrent radiation and chemotherapy. The West Japan Lung Cancer Group conducted a randomized phase III trial of concurrent vs sequential thoracic RT and cisplatin-based chemotherapy with >150 patients in each arm.²² Seventy-two percent had stage IIIB disease. Radiation was begun on day 2 (2 Gy per fraction for 14 days) followed by a 10-day rest and then repeated for a total dose of 56 Gy. In the sequential study arm, the same chemotherapy was administered but RT was initiated after chemotherapy was completed and consisted of 56 Gy (2 Gy per fraction for 14 days) without a break. The median survival time (MST) was superior for patients who were in the concurrent therapy study arm (16.5 months vs 13.3 months), and the 5-year survival difference was 15.8% vs 8.9% ($p = 0.039$; Table 1).

The Radiation Therapy Oncology Group (RTOG) conducted a phase III trial (RTOG-9410) that compared concurrent with sequential chemoradiotherapy.²³ The chemotherapy was vinblastine and cisplatin. Radiation was begun on day 1 with chemotherapy or day 50 after chemotherapy. The total dose was 63 Gy. A third arm in the trial evaluated concurrent bid RT (69.6 Gy in 1.2-Gy bid fractions) with cisplatin and oral etoposide.²³ The median and 4-year survival rates were 17 months and 21%, respectively, on the concurrent therapy arm with once-daily radiation and 14.6 months and 12%, respectively, on the sequential treatment study arm ($p = 0.046$). The twice-daily radiation arm had an intermediate survival rates of 15.2 months and 17%, respectively.

A French phase III trial of concurrent vs sequential chemoradiotherapy randomly assigned 205 patients. RT administered was 66 Gy in 33 fractions.²⁶ Chemotherapy consisted of vinorelbine and cisplatin for three cycles followed by RT, or concurrent cisplatin and etoposide for two cycles with RT followed by cisplatin and vinorelbine for two additional cycles of consolidative therapy. MSTs were 16.3 months vs 14.5 months in favor of concurrent therapy ($p = 0.24$). The 2-, 3-, and 4-year survival rates were better in the concurrent study arm (39%, 25%, and 21%, respectively) than in the sequential study arm (26%, 19%, and 14%, respectively).

Table 1—Phase III Trials Comparing Concurrent With Sequential Chemoradiotherapy for Stage III NSCLC: 1995 to Present

Study/Year	Patients, No.	RT Dose per Fraction/Frequency (Total Dose), Gy	Chemotherapy	MST, mo	Overall Survival at 2 yr, %	Toxicity, %			
						Treatment-Related Deaths	Pneumonitis Grades 3–4	Acute Esophagitis Grades 3–4	Neutropenia Grades 3–4
Curran et al ²³ /2003	610	1.8 and 2.0 (63)	Concurrent Sequential	17 14.6*	37 31	3 2	4 7	25 4	58 56
Zatloukal et al ²⁴ /2003	102	2.0 qd (60)	Concurrent Sequential	16.6 12.9*	35 14			17 4	65 40
Fournel et al ²⁵ /2001	178	2.0 qd (66)	Concurrent Sequential	15 13.8	35 23	11 7		26 0	75 88
Furuse et al ²² /1999	314	2.0 qd (56)	Concurrent Sequential	16.5 13.3*	35 27		1 1	3 2	99 77

*p < 0.05 for comparison of sequential with concurrent chemotherapy.

A trial²⁷ from the Czech Republic randomly assigned 102 patients (85% with stage IIIB disease) to concurrent (started day 4 of cycle 2) or sequential RT after four cycles of vinorelbine and cisplatin. The concurrent study arm had the superior survival with MST and 3-year survival rates of 16.6 months and 18.6% vs 12.9 months and 9.5%, respectively. The hazard ratio was 0.61 in favor of concurrent therapy.²⁷

All of these trials have shown that concurrent chemoradiotherapy is associated with increased toxicity, primarily esophagitis, and some trials showed increased neutropenia and nausea/vomiting (Table 2). Concurrent therapy did not increase the number of treatment-related deaths. The most common chemotherapeutic agents used concurrently with RT have been vinorelbine, vinblastine, and etoposide in conjunction with cisplatin or weekly paclitaxel and carboplatin.^{28–30} No randomized phase III trials of concurrent chemoradiotherapy have shown the superiority of one chemotherapy regimen over another. The consensus opinion reported in the Cancer Care Ontario Guidelines 2005²⁰ was that there are insufficient data to determine the most effective chemotherapy.

One phase II trial and one phase III trial^{28,29} have evaluated induction chemotherapy followed by concurrent chemoradiotherapy vs initial treatment with concurrent therapy followed by consolidative treatment. In the randomized phase II trial,^{27,29} concurrent weekly paclitaxel, carboplatin, and thoracic RT followed by consolidative therapy seemed to have the best outcome vs sequential chemoradiotherapy or induction chemotherapy followed by identical concurrent chemoradiotherapy (MST, 16.3 months vs 13 months or 12.7 months). However, this was a phase II trial, and it was not designed to compare the three study arms directly. A phase III trial was conducted by the Cancer and Acute Leukemia Group B,²⁸ who compared immediate treatment with weekly paclitaxel/carboplatin and thoracic RT (study arm 1) with two cycles of induction paclitaxel and carboplatin followed by identical concurrent chemoradiotherapy (study arm 2). No consolidative treatment was administered in either study arm.²⁸ MSTs (11.4 months and 13.7 months [study arm 2]) and 3-year survival rates (18% and 24% [study arm 2]) were similar and not statistically different (p = 0.14). The authors²⁸ concluded that induction chemotherapy followed by concurrent chemoradiotherapy was not superior to initial treatment with concurrent therapy. Because of the poor overall results, they questioned whether the low-dose weekly chemoradiotherapy approach might be inferior to the approach with full-dose chemotherapy and thoracic RT.

Table 2—Summary of Survival and Toxicity From Trials Comparing Concurrent With Sequential Chemoradiotherapy*

Parameters	Comparisons, No.	Rate, % (Total No.)		Ratio (95% CI)†	p Value	
		Concurrent	Sequential		Treatment Effect	Heterogeneity p Value/I ² , %
2-yr survival, summary	3	n = 356	n = 355	0.86 (0.78–0.95)	0.003	0.39/0
Curran et al ²³ /2003		37 (201)	31 (201)	0.91 (0.79–1.05)		
Fournel et al ²⁵ /2001		35 (103)	23 (104)	0.85 (0.71–1.01)		
Zatloukal et al ²⁴ /2003		35 (52)	14 (50)	0.76 (0.61–0.95)		
Furuse et al ²² /1999‡		35 (156)	27 (158)	0.90 (0.77–1.00)		
Summary including Furuse et al ²² ‡	4	n = 512	n = 513	0.87 (0.80–0.95)	0.001	0.55/0
Toxicity						
Treatment-related deaths	2	n = 290	n = 290	1.60 (0.75–3.40)	0.02	0.90/0
Curran et al ²³ /2003		3 (201)	2 (201)	1.50 (0.43–5.20)		
Fournel et al ²⁵ /2001		11 (89)	7 (89)	1.70 (0.63–4.40)		
Acute pneumonitis, grades 3–4	2	n = 253	n = 251	0.66 (0.33–1.45)	0.3	0.34/0
Curran et al ²³ /2003		4 (201)	7 (201)	0.57 (0.25–1.30)		
Zatloukal et al ²⁴ /2003		1 (52)	0.5 (50)	1.92 (0.18–20.00)		
Furuse et al ²² /1999‡		1 (156)	1 (158)	1.01 (0.14–7.10)		
Summary including Furuse et al ²² ‡	3	n = 409	n = 409	0.70 (0.33–1.50)	0.34	0.59/0
Acute esophagitis, grades 3–4	3	n = 342	n = 340	6.77 (2.90–15.00)	<0.0001	0.28/22
Curran et al ²³ /2003		25 (201)	4 (201)	6.20 (3.00–2.80)		
Fournel et al ²⁵ /2001		26 (89)	0 (89)	47.00 (2.90–762.00)		
Zatloukal et al ²⁴ /2003		17 (52)	4 (50)	4.30 (0.98–19.00)		
Furuse et al ²² /1999‡		3 (156)	2 (158)	1.40 (0.31–5.90)		
Summary including Furuse et al ²² ‡	4	n = 498	n = 498	5.10 (2.90–9.10)	<0.0001	0.12/49
Neutropenia, grades 3–4	3	n = 342	n = 340	1.07 (0.81–1.43)	0.6	0.003/83
Curran et al ²³ /2003		58 (201)	56 (201)	1.04 (0.87–1.20)		
Fournel et al ²⁵ /2001		75 (89)	88 (89)	0.86 (0.75–0.99)		
Zatloukal et al ²⁴ /2003		65 (52)	40 (50)	1.60 (1.10–2.40)		
Furuse et al ²² /1999‡		99 (156)	77 (158)	1.30 (1.20–1.40)		
Summary including Furuse et al ²² ‡	4	n = 498	n = 498	1.14 (1.07–1.22)	<0.0001	0.01/89

*Adapted from Rowell and O'Rourke.¹⁹ CI = confidence interval.

†Ratio <1 favors concurrent chemoradiotherapy.

‡No quality-of-life data were reported.

Southwestern Oncology Group investigators³⁰ have reported some of the best results from a single-arm phase II trial for patients with stage IIIB disease. This trial included concurrent full-dose etoposide and cisplatin and thoracic RT followed by consolidative docetaxel chemotherapy.³⁰ MST was 26 months, and the 3-year survival rate was 37%. These results are awaiting confirmation in a phase III trial. All patients will receive identical initial treatment with concurrent chemoradiotherapy and are randomly assigned to consolidative docetaxel or no consolidative treatment. It is uncertain how many cycles of chemotherapy are optimal in treatment of patients with stage III disease. The American Society of Clinical Oncology guidelines recommend two to four cycles of platinum-based chemotherapy. Two cycles should be administered concurrently with thoracic RT.¹⁸

RECOMMENDATIONS

5. For patients with stage IIIB NSCLC and PS 0 or 1 and minimal weight loss (≤5%), concurrent

chemoradiotherapy is recommended. Grade of recommendation, 1A

6. The most efficacious chemotherapy drugs to be combined with thoracic RT and the number of cycles of chemotherapy needed to yield the best results are uncertain. No one combination chemotherapy regimen can be recommended. Grade of recommendation, 2C

Radiation Dose Fractionation Studies

Multiple trials have explored the use of altered-dose fractionation schedules as a means of improving the therapeutic index. Two general approaches have been evaluated. Pure hyperfractionated RT uses two or three small doses of RT per day administered over the standard treatment duration. Because smaller radiation fractions result in less damage to normal tissues as compared with rapidly replicating tumor cells, this permits an increase in the total radiation dose administered to the tumor without worsening normal tissue toxicity. Pure accelerated fractionation RT administers the same total dose using standard fraction sizes that are administered multiple times

per day. This results in a decrease in the overall treatment time and provides greater tumor kill because there is less time between treatments for repopulation by rapidly growing cells. Most clinical trials have combined accelerated fractionation and hyperfractionated RT in a hybrid approach, termed *accelerated hyperfractionated RT* (Table 3).

Randomized prospective studies have failed to demonstrate an advantage for twice-daily RT compared with once-daily RT for stage III NSCLC. The RTOG performed a randomized, prospective study^{23,34} (RTOG 9410) to compare chemotherapy plus either twice-daily RT or once-daily RT for locally advanced NSCLC. Patients were randomly assigned to three study arms and received sequential therapy with cisplatin plus vinblastine followed by 63 Gy in 34 daily fractions; concurrent therapy with cisplatin, vinblastine, and 63 Gy in 34 daily fractions; or concurrent twice-daily RT (69.6 Gy in 1.2-Gy fractions bid) with cisplatin and oral etoposide. The median and 4-year survival rates were 17 months and 21% in the concurrent once-daily RT study arm, 14.6 months and 12% in the sequential once-daily RT study arm, and 15.2 months and 17% in the concurrent twice-daily RT study arm. The difference in survival between the concurrent once-daily RT study arm and the sequential once-daily RT study arm was significant ($p = 0.046$). In addition to the RTOG 9410 trial, a phase III study³⁵ was performed by the North Central Cancer Treatment Group (94-24-52) to compare concurrent etoposide plus cisplatin with either standard once-daily RT (60 Gy in 30 daily frac-

tions) or etoposide and cisplatin plus split-course twice-daily RT (60 Gy in 40 fractions bid with a 2-week break in the middle). MST and 5-year survival rates for the once-daily RT study arm were 14 months and 13%, respectively, vs 15 months and 20%, respectively, for the twice-daily RT study arm ($p = 0.4$). There was no advantage to twice daily RT with regard to survival, disease control, or toxicity in either trial.

RT three times daily has shown promise for NSCLC. Saunders et al³³ performed a randomized study that compared once-daily RT (60 Gy in 30 fractions over 6 weeks) with continuous hyperfractionated accelerated RT (CHART) 54 Gy in 36 fractions tid (6 h apart over 12 total days). Sixty-one percent of patients had stage IIIA or IIIB disease. No chemotherapy was administered. Patients who received CHART had a 2-year survival rates of 29%, vs 20% in those who received once-daily ($p = 0.008$). These findings demonstrate the critical importance of the overall treatment time on RT outcome. CHART was delivered in only 12 days, whereas the twice -daily RT programs used in North Central Cancer Treatment Group 94-24-52 and RTOG 9410 were approximately 6 weeks long. Accelerated repopulation of tumor cells during RT occurred to a lesser degree during CHART, yielding more favorable results. However, the CHART trial lacked chemotherapy, which seems to be a critically important addition to RT (Table 3).

The Eastern Cooperative Oncology Group (ECOG) initiated a phase III trial (E-2597) of chemotherapy (two cycles of paclitaxel and carboplatin) followed by either once-daily RT (64 Gy in 32 fractions for 6.5

Table 3—Phase III Trials Evaluating Multiple Daily Fractions of RT Compared to Once-Daily Fractions of RT for Stage III NSCLC (1995-present)*

Study/Year	Patients, No.	RT	RT Dose per Fraction/Frequency (Total Dose), Gy	CT	MST, mo	Overall Survival, %			
						2 yr	3 yr	4 yr	5 yr
Belani et al ²⁹ /2005 ECOG 2597	141	HART	1.5 tid (57.6)	Sequential	20.3	44	24		
		Conv	2 qd (64)	Sequential	14.9	24	18		
Curran et al ²³ /2003 RTOG 9410	610	HF	1.2 bid (69.6)	Concurrent	15.2			17	
		Conv	1.8 and 2.0 (63)	Concurrent		17†		21†	
		Conv	1.8 and 2.0 (63)	Sequential	14.6†			12†	
Schild et al ³¹ /2005	234	HF	1.5 bid (60)	Concurrent	15	40			20
		Conv	split course 2 qd (60)	Concurrent	14	37			13
Komaki et al ³² /1997 RTOG 8808/ECOG 4588	490	HF	1.2 bid (69.6)	None	12.3	24		9	
		Conv	2 qd (60)	None	13.6‡	31‡		4	
		Conv	2 qd (60)	Sequential	11.4‡	20‡		11	
Saunders et al ³³ /1999 CHART	563	CHART	1.5 tid (54)	None	16.5	30§	20		
		Conv	2 qd (60)	None	13	21§	13		

*HART = hyperfractionated accelerated RT; Conv = conventionally fractionated RT; HF = hyperfractionated RT.

† $p < 0.05$ for comparison of sequential to concurrent chemotherapy.

‡ $p < 0.05$ for comparison of none to sequential chemotherapy.

§ $p < 0.05$ for comparison of conventionally fractionated RT to CHART.

weeks) or three-times-daily RT (57.6 Gy in 36 fractions for 12 weekdays) for stage III NSCLC.³⁶ Unfortunately, accrual was slow and the study was closed before completion. MSTs were 14.9 months with once-daily RT vs 20.3 months with three-times-daily RT ($p =$ not significant).

Very few patients have been treated with concurrent chemotherapy and three-times-daily RT. Oral et al³⁷ reported a 20-patient trial that included concurrent CHART and paclitaxel. Unfortunately, this resulted in excessive toxicity, with 50% of patients having grade 3 or greater pneumonitis. Mayo Clinic investigators³¹ performed a trial with 20 patients who were treated with escalating doses of daily cisplatin administered concurrently with the same regimen of three-times-daily RT used in the ECOG trial. The maximum tolerated dose of daily cisplatin was 7.5 mg/d. The median survival was 22 months, and 5-year survival was 25%.³¹

For patients with stage IIIB NSCLC, there are convincing data that RT three times daily (CHART) alone is better than standard once-daily RT alone. However, there are problems that preclude this type of RT from being recommended for use. First, CHART is logistically difficult and has not been embraced by most radiation oncology facilities worldwide. Second, there is definitive proof that systemic chemotherapy improves survival when added to RT, especially when the two therapies are administered concurrently. Integrating chemotherapy with RT three times daily has posed difficult challenges. There has been some use of sequential therapy and a very small experience with concurrent therapy. No phase III trials have proved that chemotherapy plus multiple daily fraction RT yields significantly better survival than chemotherapy plus once-daily RT (Table 3). Although ECOG 2597 was provocative, it was never completed, leaving unanswered the question as to whether RT three times daily would be better than once-daily RT when used as part of a combined modality program.

RECOMMENDATION

7. For patients with stage IIIB NSCLC, once-daily thoracic RT plus chemotherapy is recommended. Grade of recommendation, 1B

Palliation of Lung Cancer With RT

A patient can be treated with curative intent when the disease can be contained within a reasonable RT field. In addition, the patient should be physically fit enough to withstand the effects of therapy. Usually, patients are considered able to withstand potentially

curative therapy when they have Zubrod PS of 0 to 2 and adequate pulmonary function (spirometry with $FEV_1 \geq 1$ L/s).

The most common symptoms that are considered for palliative thoracic RT include dyspnea, cough, hemoptysis, and pain. These symptoms occur as a result of tumor-related obstruction and irritation of the normal intrathoracic structures. In addition, RT is frequently used for the palliation of metastases to other normal structures, such as the brain, spine, or bones (palliation of sites outside the chest are covered elsewhere).

Many studies^{38–52} have been performed to identify the optimal thoracic RT regimen for the palliation of NSCLC. The perfect regimen would rid the patients of all symptoms permanently, cause no adverse effects, extend survival, and require little time. Clearly, these goals are not 100% attainable, but one should strive to maximize palliation and minimize adverse effects. Several phase III trials have compared various RT dose-fractionation regimens. Most of these trials detected no significant benefit for the study of RT regimens. Of the phase III trials performed, the trials that had positive findings are reviewed here. There is heterogeneity among the trials in intent and design, which makes them difficult to compare directly with one another.

Nestle et al⁴⁷ and Macbeth et al⁵⁰ performed a trial that included 509 patients with nonmetastatic inoperable NSCLC that was too extensive for radical RT. Patients received either 17 Gy in two fractions (F2) 1 week apart or 39 Gy in 13 fractions (F13) 5 d/wk. Survival was better in the F13 group; MST was 7 months in the F2 group, compared with 9 months in the F13 group ($p = 0.03$). The most common symptoms were cough, shortness of breath, fatigue, worrying, and chest pain. These were more rapidly palliated by the F2 regimen. Three patients (two F13, one F2) exhibited evidence of myelopathy. Nestle et al⁴⁷ and Macbeth et al⁵⁰ concluded that the F2 regimen had a more rapid palliative effect, but survival was longer in the F13 group.

Teo et al³⁹ performed a trial that included 291 patients who had inoperable advanced NSCLC and were randomly assigned to 45 Gy in 18 fractions for 4.5 weeks administered in study arm 1 or 31.2 Gy in four fractions for 4 weeks administered in study arm 2. MST was 20 weeks and was similar in both study arms. Study arm 1 was superior to study arm 2 in achieving symptom palliation (71% vs 54%; $p < 0.02$). Both study arms were equally well tolerated. Toxicity was mild and included radiation esophagitis, pneumonitis, and pulmonary fibrosis.

Reinfuss et al⁴⁴ included 240 patients with stage III, unresectable, asymptomatic NSCLC and were randomly assigned to one of the three treatment

arms: conventional RT, hypofractionated RT, and a control group treated with delayed RT when symptoms required treatment. In the conventional irradiation treatment arm (79 patients), a dose of 50 Gy in 25 fractions in 5 weeks was delivered to the primary tumor and the mediastinum. In the hypofractionated irradiation treatment arm (81 patients), two courses of irradiation were separated by an interval of 4 weeks. Each of the two courses included 20 Gy in five fractions in 5 days to the same treatment volume as the conventional irradiation group. The delayed RT arm included 80 patients who received a single course of palliative hypofractionated irradiation (20 to 25 Gy in four to five fractions in 4 to 5 days) administered to the primary tumor. The 2-year actuarial survival rates for patients in the conventional irradiation, hypofractionated irradiation, and control group arms were 18%, 6%, and 0%, with MSTs of 12 months, 9 months, and 6 months, respectively. The differences between survival rates were statistically significant. The comparison of conventional and hypofractionated irradiation shows a survival advantage for the conventional schedule.

Bezjak et al⁴⁸ randomly assigned 230 patients to either 10 Gy in one fraction or 20 Gy in five fractions. The changes in the scores on the Lung Cancer Symptom Scale indicated that the fractionated RT (five fractions) group had greater improvement in symptoms related to lung cancer ($p = 0.009$), pain ($p = 0.0008$), ability to carry out normal activities ($p = 0.037$), and better global quality of life ($p = 0.039$). The European Organization for Research and Treatment of Cancer QLQ-C30 scores showed that patients who received five fractions had a greater improvement in scores with respect to pain ($p = 0.04$). No significant difference was found in treatment-related toxicity. Patients who received five fractions survived on average 2 months longer ($p = 0.0305$) than patients who received one fraction. They concluded that the fractionated regimen was preferable.

Erridge et al⁴⁶ performed a phase III trial to determine whether palliation of chest symptoms from a 10-Gy single fraction was equivalent to that from 30 Gy in 10 fractions. They randomly assigned 149 patients and analyzed 74 patients in each treatment arm. The total symptom score improved in 49 patients (77%) with 10 Gy and in 57 patients (92%) with 30 Gy, a difference of 15%, which was not significantly different. However, complete resolution of all symptoms was achieved in 3 patients (5%) with 10 Gy and in 14 patients (23%) with 30 Gy ($p < 0.001$). Although this trial met the predetermined criteria for equivalence between the two palliative regimens, significantly

more patients achieved complete resolution of symptoms and palliation of chest pain and dyspnea with the fractionated regimen.

Kramer et al⁴⁹ compared the efficacy of 2×8 Gy vs 10×3 Gy in 297 patients with inoperable stage IIIA/B (with an ECOG PS of 3 to 4 and/or substantial weight loss) and stage IV NSCLC. The primary end point was a patient-assessed score of treatment effect on seven thoracic symptoms. Palliation in the 10×3 -Gy treatment arm was more prolonged (until week 22) with fewer worsening symptoms than in the 2×8 -Gy treatment arm. Survival in the 10×3 -Gy treatment arm was significantly ($p = 0.03$) better than in the 2×8 -Gy treatment arm, with 1-year survival rates of 19.6% vs 10.9%. They concluded that the 10×3 -Gy RT schedule was preferred over the 2×8 -Gy schedule for palliative treatment because it improved survival and resulted in a longer duration of the palliation.

Senkus-Konefka et al⁵¹ compared two palliative RT schedules for inoperable symptomatic NSCLC. One hundred patients were randomly assigned to 20 Gy in five fractions for 5 days (treatment arm A) or 16 Gy in two fractions for 1 and 8 days (treatment arm B). Treatment tolerance was good and did not differ between study arms. No significant differences between study arms were observed in the degree of relief of symptoms. Overall survival time differed significantly in favor of treatment arm B (median, 8.0 months vs 5.3 months; $p = 0.016$). Both irradiation schedules provided comparable, effective palliation of tumor-related symptoms. The improved overall survival and treatment convenience of a two-fraction schedule suggest its usefulness in the routine management of symptomatic inoperable NSCLC.

Radiation myelopathy (RM) is one of the most serious and feared complications of RT. Macbeth et al⁵² described the Medical Research Council Lung Cancer Working Party experience. Five cases of RM occurred among 1,048 patients who had inoperable NSCLC and were treated with palliative RT in three randomized trials. Seven RT regimens were used in these trials: 10 Gy in a single fraction on 1 day (114 patients); 17 Gy in two fractions over 8 days (524 patients); 27 Gy in six fractions over 11 days (47 patients); 30 Gy in six fractions over 11 days (36 patients); 30 Gy in 10 fractions over 12 days (88 patients); 36 Gy in 13 fractions over 16 days (86 patients); and 39 Gy in 13 fractions over 17 days (153 patients). Of the five instances of RM, three occurred in the 524 patients who were treated with 17 Gy in 2 fractions and two in the 153 patients who were treated with 39 Gy in 13 fractions. The estimated cumulative

risks of RM by 2 years were 2.2% for the 17-Gy group, 2.5% for the 39-Gy group, and 0% for the remainder. This suggests that one might consider avoiding the regimens of 17 Gy in 2 fractions over 8 days and 39 Gy in 13 fractions over 12 days to avoid this potential devastating complication.

The general trend in studies with positive findings were that higher dose, more fractionated regimens resulted in better palliation and longer survival. This is not a particular surprise because palliation of tumor-related symptoms requires the death of enough tumor cells to relieve pressure and irritation of normal structures. As is true of all treatment, there seems to be dose dependence in achieving the desired outcome, symptomatic relief. The most commonly used palliative RT regimen is 30 Gy in 10 fractions, which would be a reasonable choice for a patient who requires palliative RT for thoracic symptoms. However, the use of common sense in customizing therapy to the needs of the patient is still the best approach. A patient with good PS could be treated with a longer fractionated regimen as opposed to a very ill-appearing patient who has poor PS and may be better served with a short regimen, such as 10 Gy in one fraction or 16 Gy in two fractions (days 1 and 8). Because of the Medical Research Council findings of RM in some patients, one might consider avoiding the regimens of F2 for 8 days and F13 for 12 days.

For patients who have stage IIIB disease and poor PS or disease that is too extensive to treat with curative intent and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Patients who seem to be more vigorous should be treated with a longer RT program because this will likely palliate symptoms for a greater period and may increase survival. Representative RT regimens were already presented. Patients with very tenuous health and very short estimated survival should be treated with a short course of RT because it is likely that this will help the symptoms without using up a great amount of their limited lifespan.

RECOMMENDATION

8. For patients with stage IIIB disease, either poor PS or disease that is too extensive to treat with curative intent, and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Grade of recommendation, 1A

SUMMARY OF RECOMMENDATIONS

1. In selected patients with clinical T4N0-1 NSCLC as a result of satellite tumor nodule(s) in the same lobe, carinal involvement, or SVC invasion, it is recommended that evaluation be performed by a multidisciplinary team that includes a thoracic surgeon with lung cancer expertise to determine whether the tumor is operable. Surgery is not recommended when there is N2 involvement. Grade of recommendation, 1C

2. For patients with stage IIIB NSCLC as a result of N3 disease, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended. Grade of recommendation, 1C

3. For patients with stage IIIB disease without malignant pleural effusions, PS of 0 or 1, and minimal weight loss ($\leq 5\%$), platinum-based combination chemoradiotherapy is recommended. Grade of recommendation, 1A

4. In patients with stage IIIB NSCLC and PS of 2 or those with substantial weight loss ($>10\%$), chemoradiotherapy is recommended only after careful consideration. Grade of recommendation, 1C

5. For patients with stage IIIB NSCLC and PS of 0 or 1 and minimal weight loss ($\leq 5\%$), concurrent chemoradiotherapy is recommended. Grade of recommendation, 1A

6. The most efficacious chemotherapy drugs to be combined with thoracic RT and the number of cycles of chemotherapy needed to yield the best results are uncertain. No one combination chemotherapy regimen can be recommended. Grade of recommendation, 2C

7. For patients with stage IIIB NSCLC, once-daily thoracic RT plus chemotherapy is recommended. Grade of recommendation, 1B

8. For patients with stage IIIB disease, either poor PS or disease that is too extensive to treat with curative intent, and symptoms as a result of chest disease, palliative RT is recommended. The fractionation pattern should be chosen on the basis of the physician's judgment and the patient's needs. Grade of recommendation, 1A

REFERENCES

- 1 Mountain C. Revisions in the International System for Staging Lung Cancer. *Chest* 1977; 111:1710-1717

- 2 Wisnivesky JP, Yankelevitz D, Henschke CI. Stage of lung cancer in relation to its size: part 2; evidence. *Chest* 2005; 127:1136–1139
- 3 British Thoracic Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. Guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001; 56:89–108
- 4 Deslauriers J, Brisson J, Cartier R, et al. Carcinoma of the lung: evaluation of satellite nodules as a factor influence prognosis after resection. *J Thorac Cardiovasc Surg* 1989; 97:504–512
- 5 Osaki TS, Hanagiri T, Takenoyama M, et al. Survival and prognostic factors of surgically resected T4 non-small cell lung cancer. *Ann Thorac Surg* 2003; 75:1745–1751
- 6 Urschel JD, Urschel DM, Anderson TM, et al. Prognostic implications of pulmonary satellite nodules: are the 1997 staging revisions appropriate? *Lung Cancer* 1998; 21:83–87
- 7 Dartevelle PG, Khalife J, Chapelier A, et al. Tracheal sleeve pneumonectomy for bronchogenic carcinoma: a report of 55 cases. *Ann Thorac Surg* 1988; 46:68–72
- 8 Mathison DJ, Grillo HC. Carinal resection for bronchogenic carcinoma. *Thorac Cardiovasc Surg* 1991; 102:16–22; discussion 22–23
- 9 Deslauriers JG, Jacques LF, Piraux M. Sleeve pneumonectomy. *Thoac Surg Clin* 2004; 14:183–190
- 10 Rice TW, Blackstone EH. Radical resections for T4 lung cancer. *Surg Clin North Am* 2002; 82:573–587
- 11 Spaggiari LM, Kondo H, Thomas P, et al. Results of superior vena cava resection for lung cancer: analysis of prognostic factors. *Lung Cancer* 2004; 44:339–346
- 12 Shargall Y, de Perrot M, Keshavjee S, et al. 15 years single center experience with surgical resection of the superior vena cava for non-small cell lung cancer. *Lung Cancer* 2004; 45:357–363
- 13 Pant AB, Kesler K, Brooks J, et al. The role of surgery in selected patients with stage IIIB non-small cell lung cancer: the Indiana University Experience [abstract]. *Proc Am Soc Clin Oncol* 2003; 22:694
- 14 Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small cell lung cancer: mature results of Southwest Oncology Group Phase II Study 8805. *J Clin Oncol* 1995; 13:1880–1892
- 15 Barlesi FD, Torre JP, Giudicelli R, et al. Comparative prognostic features of stage IIIB and IIIB non-small cell lung cancer patients treated with surgery after induction therapy. *Eur J Cardiothorac Surg* 2005; 28:629–634
- 16 Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer: outcome update of North America Intergroup 0139 (RTOG 9309). *Am Soc Clin Oncol* 2005; 23:624S
- 17 Ettinger DJ. Update: NCCN small cell and non-small cell lung cancer clinical practice guidelines. *J Natl Compr Canc Netw* 2005; 3(suppl):S18–S21
- 18 Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small cell lung cancer guideline: update 2003. *J Clin Oncol* 2004; 22:330–353
- 19 Rowell NP, O'Rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2004; (4):CD002140
- 20 Okawara G, Mackay JA, Evans WK, et al. Management of unresected stage III non-small cell lung cancer: a systematic review. *J Thorac Oncol* 2006; 1:377–393
- 21 Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995; 311:899–909
- 22 Furuse KF, Kawahara M, Nishikawa H, 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
- 23 Curran WJ, Scott CB, Anger CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiotherapy for patients with unresected stage III NSCLC: RTOG 9410 [abstract]. *Proc Am Soc Clin Oncol* 2003; 22:621
- 24 Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent vs sequential radiochemotherapy with vinorelbine plus cisplatin (V-P) in locally advanced non-small cell lung cancer: a randomized phase II study; long-term follow-up data. *Lung Cancer* 2003; 41(suppl):76
- 25 Fournel P, Perol M, Robinet G, et al. A randomized phase III trial of sequential chemo-radiotherapy vs concurrent chemoradiotherapy in locally advanced non small cell lung cancer (NSCLC) (GLOT-GFPC NPC 9501 study) [abstract]. *Proc Am Soc Clin Oncol* 2001; 20:312
- 26 Fournel PP, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small cell lung cancer (GLOT-GFPC NPC 9501 study). *J Clin Oncol* 2005; 23:5910–5917
- 27 Zatloukal PP, Zemanova M, Havel L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004; 46:87–98
- 28 Vokes EE, Herndon JE, 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 randomized phase III trial [abstract]. *Proc Am Soc Clin Oncol* 2004; 23:616
- 29 Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005; 23:5883–5891
- 30 Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21:2004–2010
- 31 Schild SE, Wong WW, Vora SA, et al. The long-term results of a pilot study of three times a day radiotherapy and escalating doses of daily cisplatin for locally advanced non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2005; 62:1432–1437
- 32 Komaki R, Scott CB, Sause WT, et al. Induction cisplatin/vinblastine and irradiation vs. irradiation in unresectable squamous cell lung cancer: failure patterns by cell type in RTOG 8808/ECOG 4588; Radiation Therapy Oncology Group. Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1997; 39:537–544
- 33 Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomized multicentre trial; CHART Steering Committee. *Radiother Oncol* 1999; 52:137–148
- 34 Komaki R, Seiferheld W, Curran W, et al. Sequential vs concurrent chemotherapy and radiation therapy for inoperable non-small cell lung cancer (NSCLC): analysis of failures

- in a phase III study (RTOG 9410) [abstract]. *Int J Radiat Oncol Biol Phys* 2000; 48:113
- 35 Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once daily or twice daily radiotherapy in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002; 54:370–378
 - 36 Belani CP, Wang W, Johnson DH, et al. Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. *J Clin Oncol* 2005; 23:3760–3767
 - 37 Oral EN, Bavbek S, Kizir A, et al. Preliminary analysis of a phase II study of paclitaxel and CHART in locally advanced non-small cell lung cancer. *Lung Cancer* 1999; 25:191–198
 - 38 Simpson JR, Francis ME, Perez-Tamayo R, et al. Palliative radiotherapy for inoperable carcinoma of the lung: final report of a RTOG multi-institutional trial. *Int J Radiat Oncol Biol Phys* 1985; 11:751–758
 - 39 Teo P, Tai TH, Choy D, et al. A randomized study on palliative radiation therapy for inoperable non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 1988; 14:867–871
 - 40 Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions; Report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer* 1991; 63:265–270
 - 41 Abratt RP, Shepherd LJ, Salton DG. Palliative radiation for stage III non-small cell lung cancer: a prospective study of two moderately high dose regimens. *Lung Cancer* 1995; 13:137–143
 - 42 A Medical Research Council (MRC) randomized trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. *Br J Cancer* 1992; 65:934–941
 - 43 Rees GJ, Devrell CE, Barley VL, et al. Palliative radiotherapy for lung cancer: two versus five fractions. *Clin Oncol (R Coll Radiol)* 1997; 9:90–95
 - 44 Reinfuss M, Glinski B, Kowalska T, et al. Palliative radiotherapy for lung cancer: two versus five fractions. *Cancer Radiother* 1999; 3:475–479
 - 45 Sundstrom S, Bremnes R, Aasebo U, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. *J Clin Oncol* 2004; 22:801–810
 - 46 Erridge SC, Gaze MN, Price A, et al. Symptom control and quality of life in people with lung cancer: a randomized trial of two palliative radiotherapy fractionation schedules. *Clin Oncol (R Coll Radiol)* 2005; 17:61–67
 - 47 Nestle U, Nieder C, Walter K, et al. A palliative accelerated irradiation regimen for advanced non-small cell lung cancer vs. conventionally fractionated 60 GY: results of a randomized equivalence study. *Int J Radiat Oncol Biol Phys* 2000; 48:95–103
 - 48 Bezjak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC. 15). *Int J Radiat Oncol Biol Phys* 2002; 54:719–728
 - 49 Kramer GW, Wanders SL, Noordijk EM, et al. Results of the Dutch National study of the palliative effect of irradiation using two different treatment schemes for non-small cell lung cancer. *J Clin Oncol* 2005; 23:2962–2970
 - 50 Macbeth FR, Bolger JJ, Hopwood P, et al. Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status: Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)* 1996; 8:167–175
 - 51 Senkus-Konefka E, Dziadziuszko R, Bednarski M, et al. A prospective, randomized study to compare two palliative radiotherapy schedules for non-small cell lung cancer (NSCLC). *Br J Cancer* 2005; 92:1038–1045
 - 52 Macbeth FR, Wheldon TE, Girling DJ, et al. Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of palliative radiotherapy for non-small cell lung cancer; the Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)* 1996; 8:176–181