Thoracic Cancer ISSN 1759-7706

INVITED REVIEW

Role of particle beam therapy in a trimodality approach to locally advanced non-small cell lung cancer

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Keywords
NSCLC; particle beam radiotherapy; trimodality therapy.

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Received: 24 July 2012;
accepted 14 September 2012.

doi: 10.1111/j.1759-7714.2012.00174.x

Abstract

Lung cancer accounts for nearly one-fifth of all cancer deaths worldwide and is the most common cause of cancer-related death in the United States. Outcomes for locally advanced non-small cell lung cancer remain extremely poor with regards to both local control and overall survival. Modest gains in local control were obtained with the incorporation of multimodality treatment, including preoperative chemotherapy followed by surgical resection; combination chemoradiotherapy also improved survival, secondary to improved local control. While the natural progression to trimodality therapy resulted in superior local control, it did not translate to improved overall survival, secondary to increased toxicity. The additional morbidity is likely from radiation toxicity, the minimization of which will be crucial to the future success of trimodality therapy. One strategy to decrease toxicity is to utilize charged particles, such as protons, which deposit a high dose at the Bragg peak with a minimal dose beyond the peak, thereby reducing the dose to distal normal tissues. Trimodality therapy incorporating preoperative proton radiation therapy and chemotherapy, followed by surgery, is currently being evaluated as a potential strategy to achieve improved local control and overall survival in locally advanced non-small cell lung cancer.

Introduction

Worldwide, there are about 1.6 million cases of lung cancer every year, comprising 13% of all cancer diagnoses, and 1.4 million lung cancer-related deaths, accounting for 18% of all cancer-related deaths.[1] In the United States, the American Cancer Society estimates 156 940 individuals (85 600 men and 71 340 women) died from lung cancer in 2011.[2] Lung cancer is the second most commonly diagnosed cancer and the most common cause of cancer-related death in both men and women. After five years, only 16% of patients with lung cancer are still alive, as most patients present with either locally advanced or metastatic disease.[3] About 80–90% of lung cancer is associated with smoking or exposure to second hand smoke, and radon exposure is the second most common cause of lung cancer.[4] Rates of cigarette use have declined in the US, as a result of aggressive smoking cessation campaigns, but a significant difference in smoking patterns among men and women have led to differences in the rates of lung cancer. In men, rates of lung cancer increased from 1930–1990 and peaked in 1990s, after which they started to decrease. In women, however, rates of lung cancer started to decrease in 2007, about two decades later than in men.[5] This difference in lung cancer incidence and mortality reflects that cigarette smoking peaked 20 years later in women compared to men.

Pathologically, lung cancer is classified primarily as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). About 80% of all lung cancer cases are diagnosed as NSCLC and 17% as SCLC. NSCLC is further classified per histology as adenocarcinoma, squamous cell carcinoma or large cell carcinoma. Recently, distinct oncologic driver mutations have been identified in adenocarcinoma – such as mutations in the epidermal growth factor receptor (EGFR) and the EML4/ALK fusion oncogene – which allow for targeted therapies for patients with these specific mutations.[6–8] For the scope of this review, we will be focusing only on NSCLC.

Significance of local control in locally advanced NSCLC and evolution of the role of surgery

At diagnosis, 15% of patients present with localized disease, 22% with lymph node involvement, 56% with metastatic disease, and 7% with unknown stage disease.[9] Generally, stage I and II patients are managed with surgical resection. Lobectomy offers superior local control compared to wedge resection, with only a 6% risk of local recurrence;[10] certain cases with higher risk features are also recommended for adjuvant chemotherapy. Overall survival of stage I and II node-negative disease is about 80% and 70%, respectively.[11] Management of stage III disease, which has worse local control and worse survival compared to stage I and II patients, is more controversial. Patients with resectable stage IIIA (T3N1) have approximately a 25% survival rate at five years. Outcomes for N2 disease with resection are worse, with an overall survival rate of 5% at three years.[12] Moreover, outcomes for these N2 patients with concurrent chemoradiotherapy are also abysmal, with 29% locoregional progression at five years and 15% overall survival at five years.[13] Hence, various combined modality therapies including neoadjuvant chemotherapy or chemoradiotherapy, followed by surgery, have been attempted to improve local control and drive an improvement in overall survival.

The role of surgery in the management of stage III NSCLC with N2 disease has been widely debated and dates back to the 1980s.[14] In 1981, Martini and co-investigators published outcomes for N2 disease patients treated with complete surgical resection and mediastinal lymph node dissection (MLND), with most patients receiving postoperative mediastinal irradiation. Overall, survival was 47% at three years and 38% at four years; increased survival was associated with adenocarcinoma histology, small primary tumors, and non-bulky mediastinal nodes. This study suggested a potential role for surgical resection in select patients with N2 disease.[15] Martini and colleagues then published a second report of patients who underwent surgical resection, about half of whom had clinical mediastinal nodal involvement. They reported an overall survival rate of 74% at one year, 43% at three years, and 29% at five years. Survival in patients with clinical stage I or II was favorable at 50% at three years, but survival in patients with obvious clinical N2 disease was very poor: 8% at three years.[12] The authors concluded that patients with gross mediastinal (N2) disease at diagnosis did not benefit from surgical resection.

Given the promising results of these trials, other trials were initiated with the goal of optimizing the neoadjuvant approach for N2 disease, either with preoperative chemotherapy or chemoradiotherapy. In 1988, Martini and colleagues reported on patients with bulky clinical N2 disease who received two to three cycles of high-dose cisplatin with vindesine or vinblastine, with or without mitomycin C. Thirty-one of the 41 patients had a major radiographic response, 28 patients underwent thoracotomy, and 21 had complete resection of the disease. Eight patients had a pathologic complete response and an additional four patients had limited microscopic disease. Overall survival at three years was 34% for all patients and 54% for those who had complete resection with a median follow-up of 44 months.[16] Based upon these promising results, Rosell and co-investigators prospectively randomized 60 patients with pathologically confirmed IIIA NSCLC to immediate surgical resection or three cycles of mitomycin C, ifosfamide, and cisplatin (MIP) chemotherapy, followed by surgical resection. All patients in this trial also received post-operative mediastinal irradiation. The median survival was 26 months for the patients who received chemotherapy and surgery *versus* eight months for the patients who received surgery alone ($P < 0.001$). Overall survival at three and five years for the chemotherapy arm was 20% and 17%, respectively, *versus* 5% and 0% for the surgery arm.[17]

Roth and colleagues prospectively randomized 60 patients with resectable, pathologically confirmed IIIA NSCLC to receive either six cycles of perioperative cyclophosphamide, etoposide, and cisplatin and surgery or surgery alone. Patients randomized to perioperative chemotherapy and surgery had an estimated median survival of 64 months compared to 11 months ($P < 0.008$) for patients who had surgical resection alone. The estimated two and three year survival rates were 60% and 56% for the chemotherapy patients and 25% and 15% for those who had surgery alone.[18] Similarly, in 2002, Depierre and colleagues published results from the largest randomized trial examining the role of preoperative chemotherapy. A total of 355 patients with stage I-IIIA (excluding T1N0) were randomized to immediate surgical resection *versus* two cycles of preoperative mitomycin, ifosfamide, and cisplatin and two additional postoperative cycles for responding patients. In both arms, patients with pT3 or pN2 disease received post-operative thoracic radiotherapy. The median survival was 26 months in the immediate surgery arm *versus* 37 months with preoperative chemotherapy ($P = 0.15$). On subgroup analysis, however, a survival benefit was seen in patients with N0 or N1 disease (RR of 0.68; $P = 0.027$), whereas there was no benefit to preoperative chemotherapy in the 122 patients with N2 disease ($RR = 1.04$; $P = 0.85$).[19]

This progression of studies incorporating multimodality treatment for locally advanced NSCLC succeeded in making some modest improvements in outcomes.

Role of radiation in improving local control and overall survival

The importance of local control in locally advanced NSCLC remains an area of active controversy. Surgical resection and

high dose thoracic radiation therapy come at the cost of significant morbidity to the patient. Given that the majority of these patients succumb to distant metastatic disease, it is controversial as to whether such aggressive measures are warranted. Data suggests, however, that improvements in local control in locally advanced NSCLC can drive improvements in overall survival. In a randomized controlled trial of 563 patients treated from 1990–1995, over 60% of whom had Stage III disease, continuous, hyperfractionated, accelerated radiotherapy (CHART) was compared to conventional radiation therapy.[20] Of note, there was no chemotherapy utilized in this study. CHART improved both two (23% vs. 16%) and three year (17% vs. 12%) local control, compared to conventional radiation therapy, which translated to improved two (29% vs. 20%) and three year (20% vs. 13%) overall survival. Although patients in the CHART arm did experience earlier dysphagia, with 19% experiencing severe dysphagia, compared to 3% in the conventional radiation therapy arm, this was resolved with no apparent difference in late effects.[21] This durable survival with dose intensification without apparent increased toxicity could be attributed to improved local control. Notably, 61% of the deaths on this trial were as a result of the primary tumor, while only 21% were secondary to metastatic disease.

Improved survival due to improved local disease control was also seen in an EORTC trial – initially a three-arm randomized Phase II trial which compared radiation therapy alone versus radiation therapy with low-dose concurrent cisplatin administered either daily or weekly. The study was converted to a Phase III trial after the first 100 patients supported the addition of chemotherapy, and a total of over 300 patients were eventually treated between 1984 and 1989.[22] The greatest benefit was seen in the daily-cisplatin group, compared to radiation therapy alone, with improved one (59% vs. 41%) and two year (31% vs. 19%) local control translating to improved one (54% vs. 46%), two (26% vs. 13%), and three year (16% vs. 2%) overall survival.[23] Although improved local control was again associated with increased toxicity – 78% of patients who received concurrent daily cisplatin had nausea and vomiting, 28% classified as severe – the risk of late toxic reactions was not increased by the administration of concurrent cisplatin.

These studies illustrate that improved local control can lead to improved overall survival, albeit at the expense of increased late toxicity. Subsequent strategies to improve local control have struggled to maintain the therapeutic ratio while improving local control. The RTOG sponsored a Phase III trial (06–17) which enrolled over 400 Stage III NSCLC patients randomized to one of four treatment arms: radiation therapy to 60 Gy or 74 Gy, with carboplatin and paclitaxel ± concurrent cetuximab. In 2011, it was reported that the 74 Gy arm had crossed a futility boundary and did not result in improved overall survival, leading to closure of the high-dose arm.[24] No significant differences in treatment-related toxicity were identified between the standard dose and high dose treatment arms. Final analysis of this trial is ongoing and the results, including local control data, are eagerly anticipated.

Trimodality therapy for locally advanced NSCLC

Both surgery and radiation, in combination with chemotherapy, have shown improved local control and overall survival in locally advanced lung cancer. In light of such data, multiple trials have combined induction chemoradiation with surgical resection in an attempt to further improve local control rates, including a Phase II prospective study sponsored by the Southwest Oncology Group (8805). One hundred and twenty-six Stage IIIA and IIIB NSCLC patients, unsuitable for initial resection, received induction cisplatin and etoposide and radiation therapy to 45 Gy, followed by pulmonary resection.[25] Eighty-five percent of the Stage IIIA patients and 80% of the Stage IIIB patients were subsequently resected. Those patients who remained unresectable or had positive margins, incomplete resections or positive mediastinal nodes, received boost cisplatin and etoposide and radiation therapy to an additional 14.4 Gy. After a median follow-up of 2.4 years, no survival difference was seen in the Stage IIIA versus Stage IIIB patients, including similar median (13 vs. 17 months), two (37% vs. 39%), and three year (27% vs. 24%) survival rates. The strongest predictor of survival was the response of mediastinal lymph nodes to induction: three year survival was 44% (median survival 30 months) in patients with a pathologic nodal complete response, compared to 18% (median survival nine months) in those that did not. In an exploratory analysis performed on the 27 patients who had N3 disease, at two years, none had survived with contralateral mediastinal disease. Interestingly, 35% survived with supraclavicular nodal disease at two years. Based upon these results, N3 patients were excluded in subsequent SWOG trials examining trimodality therapy.[25]

Although induction chemoradiation was well tolerated, 15% of all deaths were secondary to toxicity from treatment compared to 64% from disease progression. This included 11 deaths in the postoperative or chemoradiation boost period, and is consistent with a number of previous reports that pulmonary events occurred at a higher rate when combined with other modalities, compared to lung resection alone.[16,26–29]

The results of SWOG 8805 and other prior studies prompted a Phase III Intergroup trial (0139) designed specifically to examine the role of trimodality therapy in locally advanced NSCLC.[30] A total of 396 patients with T1-3N2 NSCLC received concurrent chemoradiation with cisplatin and etoposide to 45 Gy as per SWOG 8805, and were then randomized to surgical resection and mediastinal node sampling versus continued chemoradiation to 61 Gy without a

treatment break. All patients received two cycles of cisplatin and etoposide as consolidation. Progression-free survival was significantly improved in the surgical arm (12.8 vs. 10.5 months). There was no significant difference in overall survival (23.6 months vs. 22.2 months, P = 0.24).

Significantly more grade 3–4 esophagitis was seen in the chemoradiation arm (23% vs. 10%), but there was no difference in nausea/vomiting or grade 3–4 neutropenia (41% vs. 38%). Treatment-related mortality was higher in the surgical arm (16 deaths/8% vs. 4 deaths/2%), but most deaths were due to the adult respiratory distress syndrome in the setting of right-sided pneumonectomy, rather than lobectomy (38% post-operative mortality with right-sided pneumonectomy vs. 1% with lobectomy).

This data showed that trimodality therapy provides superior local control compared to chemoradiation alone in Stage IIIA patients. This improvement in local control did not translate into improved overall survival, however, secondary to increased toxicity associated with trimodality therapy. The increased toxicity with pneumonectomy following induction chemoradiation was seen in a single-institution retrospective series from Toronto, in which 40 patients were treated per the surgical arm of Intergroup 0139.[31] While the overall operative mortality rate was 7.5%, no patients died following lobectomy, while 27% of patients died following pneumonectomy. Of note, all the pneumonectomy deaths occurred in the center's first two years of experience with post-chemoradiation resections, again demonstrating that minimizing toxicity is critical to the success of trimodality therapy. Furthermore, comparison of the toxicity of surgery, especially pneumonectomy with chemoradiation versus chemotherapy alone, suggests that the additional morbidity is from radiation toxicity. In a German Lung Cancer Cooperative Group trial of Stage IIIA-B patients, the treatment-related death following preoperative chemoradiation (14%) was more than double that of preoperative chemotherapy alone (6%).[32]

The Intergroup trial has been criticized for relatively poor surgical outcomes, as evidenced by the high number of deaths among its pneumonectomy patients. The lack of modern radiation therapy also suggests that it may not be directly relevant to patients now being diagnosed with locally advanced NSCLC. More recently, an RTOG Phase II trimodality trial achieved a 63% rate of mediastinal nodal clearance (MNC) following induction paclitaxel and full-dose radiation therapy (50.4 Gy to the mediastinum and primary tumor and a 10.8 Gy boost to gross disease) in Stage III NSCLC patients.[33] Surgeons participating in the trial were required to demonstrate expertise in operating post-chemoradiation. Perhaps as a result of this criterion, there was only a 14% incidence of grade 3 post-operative pulmonary complications and only a single grade 5 toxicity (3%). With a median follow-up of 24 months, the two year overall survival rate was 54% for all patients and 75% for patients who achieved MNC; similarly, the median overall survival was 26.6 months for all patients, but had not yet been reached for those with MNC.

Further evidence to support the efficacy of trimodality treatment can be found in studies of patients with superior sulcus/Pancoast tumors, whose location results in decreased surgical mortality, compared to most primary lung tumors. The Southwest Oncology Group sponsored the largest trial to date, enrolling 111 patients with superior sulcus tumors to receive neoadjuvant chemoradiation followed by surgery.[34] Although only T3-4 N0-1 patients were eligible, the pathologic complete response rate was 65% and there were only three treatment-related deaths (2.7%). The two year overall survival was 55% for all patients, and 70% for those who had a complete resection. Similar excellent survival and toxicity rates were seen in a smaller Japanese study of 18 patients with Pancoast tumors who received preoperative radiation therapy.[35] With one operative death (5.6%), five year overall survival was 38.5% for all patients, and 56.4% in those patients who had a complete resection.

In spite of the promise of trimodality therapy to increase both local control and overall survival, the additional toxicity involved has proven limiting.

Proton beam radiotherapy and its role in the treatment of NSCLC

Principles of radiation therapy dictate maximization of the dose to the tumor and minimization of the dose to the normal tissues and organs at risk (OARs) in order to achieve the highest therapeutic ratio possible. Although many techniques have been previously utilized to reduce the dose to the normal tissue, such as intensity modulation, there is still an entrance and exit dose associated with photon treatment. Charged particles, such as protons, differ from photon radiotherapy in that most of their energy is deposited at a specific depth, known as the Bragg peak. The dose immediately beyond the Bragg peak is essentially zero, which allows tissues beyond the tumor to be spared. By combining Bragg peaks from protons of various intensity and/or energy, a spread-out Bragg peak is created, the width and energy of which can be designed to conform to the target volume, while depositing minimal dose beyond it (Fig 1). Therefore, the integral dose to the normal tissues can be minimized, even while a high dose is delivered to the tumor volume. This is critical in the treatment of patients with NSCLC because of the exquisite sensitivity of the normal lung to radiation.

Based upon radiobiological studies, protons are expected to have a similar biological potency to photons.[36] Therefore, the clinical advantage of proton beam radiotherapy over standard photon beam radiation results from a reduction of the dose to the surrounding normal tissues. There are currently a number of phase I/II trials examining the role of protons in definitive treatment of lung cancer.

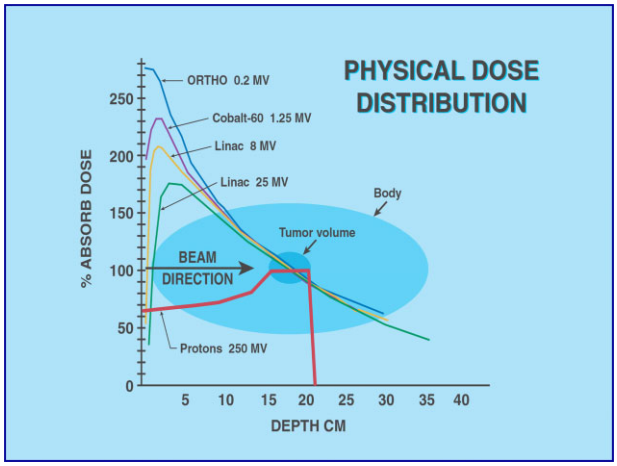

Figure 1 Comparisons of photon and proton depth–dose distributions for a single-entry port. The blue (0.2 MV), purple (1.25 MV), yellow (8 MV), and green (25 MV) lines show the depth–dose distribution of photon beams of various energies. The red line shows the dose distribution of a spread-out Bragg peak of a 250 MV proton beam, which is the sum of individual Bragg peaks.

The rationale for trimodality proton beam radiotherapy in NSCLC and ongoing clinical trials

As discussed above, there is compelling evidence that trimodality therapy can significantly improve local control and, potentially, overall survival in locally advanced NSCLC, but toxicity remains a major obstacle. Proton radiation therapy can be used to overcome this issue as it has the potential to deliver a similar dose as photon radiation therapy while reducing the dose to the OARs and maintaining a favorable therapeutic ratio. Limited data suggests that this is indeed feasible.

Dosimetric evaluation of proton plans compared to 3DCRT and IMRT for stage III unresectable NSCLC demonstrated that proton plans offered a 29% and 26% respective reduction in normal lung V20 and a 33% and 27% respective reduction in mean lung dose.[37] More clinically relevant data includes a phase II study from MD Anderson of 44 patients with unresectable stage III NSCLC treated with high dose proton radiation therapy (74 Gy RBE) with concurrent carboplatin and paclitaxel. Overall survival and progression free survival was 86% and 63% at one year, and only four patients had isolated local failure. In terms of toxicity, there was no grade 4 or 5 toxicity and grade 3 toxicity was limited. Although follow-up was limited, results were, nonetheless, encouraging.[38]

At present, there is no data available examining the role of protons in a trimodality (pre-operative chemotherapy and radiation therapy followed by surgery) approach for treatment of locally advanced NSCLC.

The University of Pennsylvania is currently examining this question in a phase I/II trial of preoperative proton beam radiotherapy with concurrent chemotherapy in patients with resectable IIIA NSCLC. Patients are evaluated by all members of the thoracic team prior to enrolment and those who are deemed by the operating surgeon to require a right sided pneumonectomy are excluded. Patients initially receive 50.4 Gy (cGE) with proton radiation therapy over 5.5 weeks with concurrent cisplatin and etoposide. Four to six weeks after completion of chemoradiotherapy, the patient undergoes complete surgical resection. The primary endpoint of this study is feasibility. Secondary endpoints include pathologic complete response rate in patients who undergo surgery, dosimetric comparison of proton and photon plans, and acute and late toxicity from proton therapy.

As part of the phase I study, after feasibility is met with the first 12 patients treated to 50.4 Gy (cGE), 10 additional patients will be enrolled and treated to 59.4 Gy (cGE), followed by another 10 patients treated to 66.6 Gy (cGE). Once the maximum tolerated dose is established, patients will be enrolled onto the phase II study to evaluate rates of pathologic complete response, progression-free survival, and late toxicity.

Conclusion

Lung cancer is responsible for the highest number of cancer-related deaths in the US. Outcomes for locally advanced lung cancer remain abysmal, with poor local control and overall survival. Improvement in local control is crucial to improving overall survival rates in patients diagnosed with locally advanced lung cancer. Although data with trimodality treatment appears to be promising, the associated excessive toxicity has been a major limitation of this approach. Trimodality therapy outcomes have been determined following photon radiation therapy, where there is an entrance and exit dose. Protons offer a dosimetric advantage over photons, as they deposit a high dose at the Bragg peak and a minimal dose beyond the peak, thereby decreasing the dose to the nearby lung and other surrounding normal structures. Trimodality therapy utilizing proton radiation therapy, with the potential for reduced normal tissue toxicity, may be a promising option to achieve the local control benefits of trimodality therapy without excessive toxicity. Current trials re-evaluating trimodality therapy using preoperative proton radiation therapy with chemotherapy, followed by surgery, are under way to evaluate such a strategy.

Disclosure

No authors report any conflict of interest.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69–90.

2 Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**: 212–36.

3 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A American Joint Committee on Cancer. *AJCC Cancer Staging Manual 7th Edition*. Springer, New York 2010.

4 Ezzati M, Henley SJ, Lopez AD, Thun MJ. Role of smoking in global and regional cancer epidemiology: current patterns and data needs. *Int J Cancer* 2005; **116**: 963–71.

5 Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA *et al*. Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system. *J Natl Cancer Inst* 2011; **103**: 714–36.

6 Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**: 2129–39.

7 Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB *et al*. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009; **27**: 4247–53.

8 Crino L, Kim. D, Riely GJ, *et al*. Initial phase II results with Crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005. 2011 ASCO Annual Meeting Proceedings *Proc Am Soc Clin Oncol* 2011; **29**: (Suppl. May Part 1): Abstract 7514.

9 Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R *et al. SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations)*. National Cancer Institute, Bethesda, MD 2012.

10 Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995; **60**: 615–22; discussion 622–13.

11 Martini N, Rusch VW, Bains MS, Kris MG, Downey RJ *et al*. Factors influencing ten-year survival in resected stages I to IIIa non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999; **117**: 32–6; discussion 37–8.

12 Martini N, Flehinger BJ, Nagasaki F, Hart B. Prognostic significance of N1 disease in carcinoma of the lung. *J Thorac Cardiovasc Surg* 1983; **86**: 646–53.

13 Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K *et al*. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2181–90.

14 Rengan R, Chetty I, Decker R, Langer CJ, O'Meara WP *et al*. *Thoracic Tumors. Perez and Brady's Principles and Practice of Radiation Oncology*, 6th edn. Lippincott Williams and Wilkins, Philadelphia. In press.

15 Martini N, Flehinger BJ, Zaman MB, Bettie EJ, Jr. Results of surgical treatment in N2 lung cancer. *World J Surg* 1981; **5**: 663–6.

16 Martini N, Kris MG, Gralla RJ, Bains MS, McCormack PM *et al*. The effects of preoperative chemotherapy on the resectability of non-small cell lung carcinoma with mediastinal lymph node metastases (N2 M0). *Ann Thorac Surg* 1988; **45**: 370–9.

17 Rosell R, Gómez-Codina J, Camps C, Maestre J, Padille J *et al*. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994; **330**: 153–8.

18 Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB, Jr *et al*. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994; **86**: 673–80.

19 Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E *et al*. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002; **20**: 247–53.

20 Saunders M, Dische S, Barrett A, Harvey A, Griffiths G *et al*. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999; **52**: 137–48.

21 Saunders M, Dische S, Barrett A, Harvey A, Gibson D *et al*. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. *Lancet* 1997; **350**: 161–5.

22 Schaake-Koning C, Maat B, van Houtte P, van den Bogaert W, Dalesio O *et al*. Radiotherapy combined with low-dose cis-diammine dichloroplatinum (II) (CDDP) in inoperable nonmetastatic non-small cell lung cancer (NSCLC): a randomized three arm phase II study of the EORTC Lung Cancer and Radiotherapy Cooperative Groups. *Int J Radiat Oncol Biol Phys* 1990; **19**: 967–72.

23 Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J *et al*. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992; **326**: 524–30.

24 Bradley JD. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/− cetuximab for stage IIIA/IIIB non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617. Fifty-Third Annual Meeting of the American Society for Radiation Oncology. Miami Beach, Florida. 2011; Abstract BLA2.

25 Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT, 3rd *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**: 1880–92.
26 Fowler WC, Langer CJ, Curran WJ, Jr, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. *Ann Thorac Surg* 1993; **55**: 986–9.
27 Choi NC, Kanarek DJ. Toxicity of thoracic radiotherapy on pulmonary function in lung cancer. *Lung Cancer* 1994; **10** (Suppl. 1): S219–230.
28 Mathru M, Blakeman B, Dries DJ, Kleinman B, Kumar P. Permeability pulmonary edema following lung resection. *Chest* 1990; **98**: 1216–8.
29 Rusch VW, Albain KS, Crowley JJ, Rice TW, Lonchyna V *et al.* Neoadjuvant therapy: a novel and effective treatment for stage IIIb non-small cell lung cancer. Southwest Oncology Group. *Ann Thorac Surg* 1994; **58**: 290–4; discussion 294–95.
30 Albain KS, Swann RS, Rusch VW, Turrisi AT, 3rd, Shepherd FA *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009; **374**: 379–86.
31 Uy KL, Darling G, Xu W, Yi QL, De Perrot M *et al.* Improved results of induction chemoradiation before surgical intervention for selected patients with stage IIIA-N2 non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2007; **134**: 188–93.
32 Thomas M, Rübe C, Hoffknecht P, Macha HN, Freitag L *et al.* Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008; **9**: 636–48.
33 Suntharalingam M, Paulus R, Edelman MJ, Krasna M, Burrows W *et al.* Radiation Therapy Oncology Group Protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 2012; **84**: 456–63.
34 Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M *et al.* Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg* 2001; **121**: 472–83.
35 Okubo K, Wada H, Fukuse T, Yokomise H, Inui K *et al.* Treatment of Pancoast tumors. Combined irradiation and radical resection. *Thorac Cardiovasc Surg* 1995; **43**: 284–6.
36 Gerweck LE, Kozin SV. Relative biological effectiveness of proton beams in clinical therapy. *Radiother Oncol* 1999; **50**: 135–42.
37 Nichols RC, Huh SN, Henderson RH, Mendenhall NP, Flampouri S *et al.* Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage III non-small-cell lung cancer: a dosimetric study. *Clin Lung Cancer* 2011; **12**: 252–7.
38 Chang JY, Komaki R, Lu C, Wen HY, Allen PK *et al.* Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer* 2011; **117**: 4707-13.

