Journal of BUON **15:** 213-220, 2010
© 2010 *Zerbinis Medical Publications. Printed in Greece*

REVIEW ARTICLE

Non-small cell lung cancer: The role of surgery after induction chemo and/or radiotherapy

A. Stamatelopoulos[1], S. Zaragkas[2], C. Sofoudis[3]

[1]Department of Thoracic Surgery, "KAT" General Hospital, Athens; [2]National Center of Emergency Care, EKAB, Athens; [3]Department of Surgery, "Metaxa" Cancer Hospital, Piraeus, Greece

Summary

Stages I and II non small cell lung cancer (NSCLC) are primarily treated by anatomic pulmonary resection. Selected patients with stage IIIB disease are still candidates for surgical treatment. Unfortunately, most patients with locally advanced NSCLC don't benefit from surgery alone or even by the combination of chemotherapy and radiotherapy. In order to achieve local and distant disease control, which seems to be the cause of failure of the above mentioned treatments, surgery after induction chemoradiotherapy has been proposed. This approach seems to be the state of the art of therapy for stage IIIB patients improving survival but with eventual increased risk, especially pulmonary and septic complications. This review of previously published studies indicates the important role of this combined treatment in terms of survival and its risks related either to induction treatment or to surgery.

Key words: chemotherapy, induction treatment, lung cancer, radiotherapy

Background

NSCLC remains the major cause of mortality of cancer in USA and Europe. Stages I and II are primarily treated by anatomic pulmonary resection with eventual adjuvant radiotherapy in stage II patients with N1 positive lymph nodes, in order to reduce the incidence of regional recurrence, usually without substantial benefits in the overall survival [1]. Selected patients with stage T4 N0-1 M0 disease are still considered for primary operative treatment. The majority of patients with locally advanced NSCLC (stages IIIA and IIIB) are not considered candidates for surgical treatment and have 5-year survival rates of 15% and 5%, respectively [2]. Surgery and radiotherapy are not sufficient to control stage IIIA and IIIB lung cancer [3-7]. The frequent failure of these therapeutic approaches lies in the fact that both seem inadequate to eradicate regional disease and control disseminated micrometastatic disease [8,9]. Even the combination of radiotherapy and chemotherapy, used in an attempt to achieve regional and distant control, is also related with a low 5-year survival rate of 8-17% [7,10], mostly because local failure rates are in excess of 50%. Two randomized trials published in 1994 proved that induction chemotherapy followed by surgery can improve survival in patients with stage IIIA disease [11-14]. The results of these first reports along with the known superiority of chemoradiotherapy compared to chemotherapy in the treatment of nonoperable stage III disease focused the attention on the possibility to use preoperative chemoradiotherapy followed by surgery as an approach to improve the local disease control, especially in N2 positive patients. In 1995 Sugarbaker et al. [15] achieved 22% nodal downstaging using induction chemotherapy while in the same year the Southwest Oncology Group trial yielded an improved nodal downstaging of 53% using preoperative chemoradiotherapy with a slight improvement of patients' survival [16]. Since then several trials have confirmed the superiority of chemoradiotherapy followed by surgery in the treatment of patients with locally advanced NSCLC with better results in overall survival but with significant morbidity and mortality related either to induction treatment or to surgery. Table 1 shows the different treatment modalities of stage III NSCLC and the related survival.

Correspondence to: Athanasios Stamatelopoulos, MD, MSc, PhD. 79 Alexandras Ave, 114 74 Athens, Greece. Tel: +30 6944 324503, E-mail: stamatel1970@yahoo.gr

Received 17-02-2009; Accepted 30-03-2009

Table 1. Results of different modality therapies in the treatment of locally advanced non small cell lung cancer

Year	*Authors*	*Patients, n*	*Therapy*	*Overall survival %*
1971	Paulsen, Urschel [3]	193	S	5y:7
1980	Martini et al. [4]	241	S	3y:20
1988	Naruke et al. [5]	345	S	5y:16
1982	Pearson et al. [6]	79 (N2+)	S	5y:9
1996	Dillman et al./ CALGB [7]	155	CT+RT (78 pts) RT (77 pts)	5y:17 5y:6
2000	Sause et al. [10]	458	CT+RT (142 pts) RT (152 pts) HFX RT (154 pts)	5y:8 5y:5 5y:6
1994	Rosell et al. [11]	60	CT-S-RT S-RT 	3y:20 5y:17 3y:5 5y:0
1994	Roth et al. [12]	60	CT-S-CT RT-S-RT 	3y:43 5y:36 3y:19 5y:15
1995	Sugarbaker et al. [15]	74	CT-S-RT	3y:33 nodal downstage 22
1995	Albain et al./SWOG [16]	75	CT/RT-S	3y:38 nodal downstage 53

CT: chemotherapy, RT: radiotherapy, HFX: hyperfractionated radiotherapy, S: surgery, y: year, pts: patients

Induction treatment and related toxicity

Almost all studies use platinum-based chemotherapy. Usually, initial treatment with 2-3 cycles of chemotherapy is followed by concurrent chemotherapy and radiotherapy. Concurrent chemoradiation is based on clinical data indicating that chemotherapy can sensitize the tumor cells to radiation, thus enhancing the effects of radiotherapy [17].

Almost all chemotherapeutic agents induce diffuse alveolar damage, insidious in most cases [18,19]. The concomitant use of radiotherapy and high concentrations of O2 (>50%) during surgery may exacerbate the toxic effects of the chemotherapeutic regimen used. The most reliable prognosticator of the postoperative toxic effects of induction chemotherapy seems to be the reduction in the carbon monoxide (CO) diffusing capacity [20-22].

Radiation-induced early pulmonary injury is characterized by interstitial edema and pneumonitis, and at a later stage by lung fibrosis. Radiation-related lung injury depends on the total dose and the dose per fraction delivered to the lung [23,24]. The deleterious effects of radiation on the bronchial blood flow have been well-defined by Yamamoto et al. [25] and they partially explain the major risk of bronchial stump insufficiency and the development of bronchopleural fistula (BPF). Vester et al. reported 20 cases of BPF among 33 patients after pneumonectomy who had received radiation or chemoradiation before surgery [26]. On the other hand technical difficulties of complex resections and reconstructions in a field of fibrosis and obliteration of the normal tissue plans as the one after induction treatment contributes to a higher risk of BPF and adult acute respiratory distress syndrome (ARDS), especially in the case of pneumonectomy [27,28].

Another common postoperative complication is the prolonged air leakage over 7 days with an incidence of 13-16% [29,30]. This is usually due to the fragility and the stiffness of lung parenchyma after chemotherapy that does not allow the sealing of air leaks and the complete expansion of the lung.

Induction treatment is the most important factor of pulmonary complications after surgery [31-33].

Myelosuppression, if serious, may precipitate severe pneumonia, especially in patients with obstruction of the bronchial tree as indicated by Burkes et al. [34]. It is considered wise to eliminate the obstruction preferably before the induction therapy, otherwise to cover the patient with broad spectrum antibiotics.

Cardiac toxicity is infrequent. There is a significant higher risk for patients receiving other cardiotoxic

drugs such as immunomodulating agents (interferons and IL-2), antidepressants, antiarrhythmics and others, radiation or have a history of previous cardiac disease; moreover, abnormal findings in the preoperative echocardiography increase the risk of postoperative arrhythmias [35,36]. Ginsberg proposed strict monitoring of the patients receiving cardiotoxic drugs during induction treatment [37].

Hepatic, gastrointestinal, neurological and neural toxicities are mostly related to the use of platinum-based regimens, but usually don't have any impact on the surgical resection.

Criteria for response to induction treatment

The initial evaluation of response to induction treatment is based on patient's restaging using CT scan of the thorax, brain and abdomen, bronchoscopy and complete functional evaluation (nutritional status, cardiac performance, and pulmonary function tests). Mediastinoscopy isn't part of the patient's routine restaging procedure. Tumor response is evaluated according to WHO criteria shown in Table 2 [38].

Unfortunately, the radiographic assessment after neoadjuvant therapy is often inaccurate and not related to the resectability or the survival of the patients. Structural imaging in NSCLC has several limitations. Tumors may he obscured by atelectasis or radiation pneumonitis after radiotherapy [39]. Lymph node involvement based on their size is considered positive for nodes >1 cm on CT imaging. However, lymph node enlargement may be the result of benign reactive hyperplasia. On the other hand, nodes < 1 cm may contain tumor cells at the definitive histopathologic examination. In addition, it is well known that tumors may regress gradually after induction treatment and the assessment of response in these patients requires serial CT assessments. Finally, some lesions may permanently persist radiologically even after disease control by the induction therapy [40]. In several trials there have been patients with overestimated or underestimated disease stage (Table 3) [15,16,41,42].

Therefore, pathologic response to the induction treatment is now considered more accurate for estimation of patients' response and as a predictor of future outcome. Only patients with progressive disease and those considered medically inoperable should be excluded from surgical treatment. Recent data indicate the possibility of using PET scan as a predictor of pathologic response after preoperative chemoradiation [43-45] with better results than CT in this setting (Table 4) [46-48].

Table 2. WHO criteria for response to induction treatment

Response	*Criteria*
Complete response	Disappearance of all measurable disease and absence of new lesions
Partial response	Reduction of measurable tumor >50% and absence of new lesions
Minimal response	Reduction of measurable tumor between 25 and 50% and absence of new lesions
Stable disease	Reduction of measurable tumor <25% and absence of new lesions
Progressive disease	Increase of the measurable tumor >25% or appearance of new lesions

Surgery

Surgical treatment is performed 4-8 weeks after the end of neoadjuvant therapy. Complex resections are often needed, 20-40% in stage IIIA and up to 60% in stage 1KB [16,35,36,49,50]. Studies on chemotherapy and radiotherapy as induction treatment in patients with locally advanced NSCLC report mortality rates of 0-23%, higher than those treated with surgery alone as first therapeutic intervention, indicating the increased risk of the preoperative anticancer therapy. A significantly higher mortality with pneumonectomy is also observed. Initial trials reported mortality rates of 10-17.5% [51-54]. Fowler et al. [27] and Deutch et al. [28] presented even higher mortality rates after pneumonectomy, reaching 43 and 33%, respectively. This excess in mortality rates after pneumonectomy was attributed to BPF and ARDS. Both complications are related to the induction chemo and/or radio-

Table 3. Clinical (radiologically-based) vs. histopathologic assessment of response to induction therapy

Authors	*Regimen*	*Clinical response (%)*		*Pathological response (%)*	
		CR+PR	*SD*	*CR*	*PR*
Sugarbaker et al. [15]	Chemotherapy	0	88	0	22
Martini et al. [41]	Chemotherapy	73	23	19	10
Faberet al. [42]	Chemoradiotherapy	65	23	20	26
Albain et al. SWOG 8805 [16]	Chemoradiotherapy	59	29	15	57

CR: complete response, PR: partial response, SD: stable disease

Table 4. CT and PET scans in the assessment of tumor response to induction chemotherapy

Authors	*Primary tumor Patients, n*		*Mediastinal lymph nodes*
	CT	*PET*	
Hellwig et al, 2004 [46]	CR: 0 PR: 24 NC: 2	CR: 8 PR: VT 16 SD: 1 SUV threshold 25 Sensitivity: 81% Specificity: 64% Accuracy: 76% PPV: 89% NPV: 58%	PET vs. CT (%) Sensitivity: 64 vs. 64 Specificity: 96 vs. 79 Accuracy: 91 vs. 77 PPV: 70 vs. 33 NPV: 94 vs. 93
Mc Manus et al, 2003 [47]	CR: 10 PR: 37 SD: 11 PD: 9	CR: 6, PR: 4 CR: 19, PR: 14, PD: 4 CR: 6, PR: 3, SD: 2 CR: 1, PR: 3, PD: 5	

Cerfolio et al, 2004 [48]		PET vs. CT for different SUV			
		SUV ≥60%	SUV ≥70%	SUV ≥80%	SUV ≥90%
	Sensitivity	100 vs. 63	95 vs. 47	90 vs. 47	63 vs. 42
	Specificity	95 vs. 54	97 vs. 59	100 vs. 63	100 vs. 68
	Accuracy	96 vs. 57	96 vs. 56	96 vs. 57	88 vs. 59
	PPV	90 vs. 41	94 vs. 38	100 vs. 27	100 vs. 40
	NPV	100 vs. 74	97 vs. 69	95 vs. 70	84 vs. 69

CR: complete response, PR: partial response, NC: no change, PD: progressive disease, PPV: positive predictive value, NPV: negative predictive value, SUV: standard uptake value, CT: computed tomography, PET: positron emission tomography, VT: viable tumor

therapy. Radiotherapy and the extensive lymph node dissection may devitalize the bronchial tissue contributing to BPF. The factors mentioned above alter the lymphatic drainage of the remaining lung, probably contributing to ARDS. In an attempt to resolve these problems several strategies have been taken into consideration. Covering the bronchial stump with viable tissue has reduced the incidence of bronchial stump fistula. Various tissues have been used to this purpose: flap of intercostal muscle [31], pleura, diaphragmatic flap, pericardial flap [55,56] and the serratus anterior muscle [53].

The important issue in question is the combination of the quality of the flap used, the easiness and simplicity of tissue harvesting and the effectiveness of the procedure. Intercostal muscle flap must be harvested prior to chest retraction and has the disadvantage of a tissue initially located in the radiation field. Serratus anterior is also included in the radiation field. Harvesting and transposition of the serratus anterior may lead to scapular winging. Doddoli and colleagues [57] reported 15% incidence of BPF, although the bronchial stump was covered with intercostal muscle or pleura and considered this high rate as a result of the quality of the tissue used to cover the bronchial stump. On the other hand Lardinois et al. [58] did not find any significant difference between intercostal and diaphragmatic flaps used for mediastinal reinforcement after pneumonectomy following induction therapy. Diaphragmatic and pericardial flaps seem to be less problematic. The relationship between radiation dose and bronchial stump fistula and the disappointing results reported by Fowler et al. [27] and Deutch et al. [28] have directed radiation therapy towards lower doses, around 30-45 Gy. Most trials have made clear that survival is directly associated with complete resection of the tumor and tumor response to the induction treatment [16,57,59,60]. Based on these data, few researchers have attempted to reintroduce the concept of high dose rate radiotherapy (HDRT) in order to achieve better rates of complete pathologic response and nodal downstaging. Cerfolio et al. [60], Vora et al. [61], and Sonnett et al. [62,63] using HDRT and concurrent platinum-based chemotherapy achieved 27-45% complete pathologic response rates and 64-85% nodal downstaging with improved survival (5-year overall survival 38-46.2%, disease free survival 56.4-65%). Vora et al. [61] and Sonnet et al. [62,63] proved that pneumonectomy is feasible after HDRT reporting no deaths, while Cerfolio and coworkers [60] still consider pneumonectomy as a very risky resection and report significantly high rates of morbidity (58.3%) and mortality (16.7%) (Table 5).

After neoadjuvant therapy pneumonectomy is often necessary for radical resection of the tumor. Technical difficulties in performing the operation are

Table 5. Results of surgery after high dose radiotherapy and chemotherapy

Authors	*Induction regimen*	*Patients resected, n*	*CR (%)*	*Mediastinal nodal downstaging (%)*	*Pneumon-ectomies*	*Results*
Vora et al. 1999 [61]	5940 cGy Cisplatin+Etoposide	33	27	65		Median survival 41 months 5y survival 42.8% CR 5y survival 57.1% Mediastinal CR 5y survival 46.4% Mortality: 0% Morbidity: 21% (7/21)
Sonnett et al. 1999 [62]	5940-6600 cGy Various regimens	–	42	83		Median survival 19 months No mortality Morbidity 21% (4/19)
Sonnett et al. 2004 [63]	5940-6600 cGy Various regimens	40	45	85		Median survival 53 months 5y survival 46.2% 5y DFS 56.4 No mortality Morbidity 17.5% (7/40)
Cerfolio et al. 2005 [60]	>6000 cGy Carboplatin-based chemotherapy	54	28	83		5y survival 38% 5y DFS 65% Mortality 3.7% (2/54) Morbidity 22% (12/54)
Daly et al. 2006 [55]	5940 cGy Cisplatin+Etoposide	30	33	47	30	Pneumonectomy mortality 16.7% (2/12) Median survival 33 months 5y survival 38% Mortality 13.3% (4/30)

CR: complete pathological response, y: year, DFS: disease free survival

frequent, since the resection is done in a devascularized, fibrotic and tumor-contaminated operative field. Under these conditions the attempt to proceed in a more conservative surgical resection is very challenging. If tumor infiltration can be excluded and free margins of resection can be obtained by frozen sections (confirmed by histological examination), a lobectomy with reconstruction of the bronchus or the pulmonary artery would be a valid alternative to pneumonectomy, reducing the risks for patients. Rendina et al. were the first to report the feasibility of bronchovascular reconstruction after preoperative chemotherapy [64]. In 2003 Ohta et al. reported no mortality and 7 complications in a series of 20 patients who underwent sleeve resection, with a telescopic anastomosis, after preoperative concurrent chemoradiotherapy [65].

Prevention of ARDS is based on both the surgical technique and perioperative management of the patient. Anatomic resections other than pneumonectomy are related to a minor risk of ARDS. Hyperhydration of patients in the perioperative period must be absolutely avoided, as well as blood transfusions. Daly et al. [55] used a protocol based on minimal fluid infusion of 50-70 ml/h and a tolerable urine output of 20 ml/h. Sonnet et al. combined a protocol of fluid restriction to aggressive diuresis [63]. Low inspired oxygen tension facilitated by positive end expiration pressure with maintenance of adequate tissue oxygenation reduces the risk of pulmonary fibrosis and can minimize the risk of ARDS [66].

Postoperative management

Every effort must be done to extubate the patients immediately after the operation. In case this is not possible, ventilatory support must not exceed 48 hours. Most crucial issues in the postoperative management of patients include postoperative analgesia, fluid balance and pulmonary toilet. Several approaches have been used to minimize postoperative pain. Epidural continuous analgesia seems to be the most effective, especially when it starts preoperatively [67,68] with less sedation and superior efficacy than parenteral narcotics. Additional intercostal nerve blockade provides a further benefit for post-thoracotomy pain relief [69]. More recent data indicate that continuous infusion of local anesthetics via pump to the incisional site may have better results for pain control compared to continuous epidural infusion [70]. Fluid overload is a well known factor contributing to post-pneumonectomy pulmonary edema [71]. Therefore, it is of great importance to avoid it in order to reduce the risk of ARDS in the postoperative period, especially in patients undergoing pneumonectomy. Strategies

used in this direction include fluid restriction, aggressive diuresis and use of drugs to control intraoperative hypotension than fluid administration as already mentioned [55,63]. Pulmonary toilet is essential after thoracotomy since atelectasis, pneumonia and respiratory failure are common and important complications after lung surgery [72]. Bronchodilatators and chest physical therapy along with an adequate postoperative pain relief may facilitate spontaneous pulmonary toilet, although some patients, especially those with impaired pulmonary reserves, may require repeat bronchoscopy or minitrack immediately after the first signs of sputum retention.

Conclusion

Traditionally, locally advanced NSCLC is considered an incurable disease with low survival after resection alone. Concurrent chemoradiation used as an alternative treatment leads to 5-year survival of 5-25% and a high rate of local failure of >50%. Surgery after concurrent chemoradiation has increased the overall survival of these patients, especially with HDRT. Covering the bronchial stump with viable tissue after pneumonectomy has significantly reduced the incidence of bronchial stump insufficiency. Since pneumonectomy is still considered a high risk operation by some authors, the application of more conservative resections with bronchovascular reconstruction, when possible, could be a valid alternative, although further phase II and III trials in this field are required. Simple measures in the perioperative management of the patients may maintain the incidence of ARDS in acceptable levels. The limitations of radiographic assessment of patient's response after induction treatment and the need for surgery in order to evaluate the pathologic response make the need for better preoperative evaluation of the patient's response imperative. This could lead to a better selection of patients who will benefit from the post-induction surgical treatment and will define a group of nonresponders, candidates for investigation with novel therapeutic approaches. Preliminary data on the role of PET scan in this field appear extremely promising.

References

1. Diagnosis and management of lung cancer: ACCP Evidence-Based Guidelines. Chest 2003; 123: 1S-337S.
2. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111: 1710-1717.
3. Paulson DL, Urschel HC Jr. Selectivity in the surgical treatment of bronchogenic carcinoma. J Thorac Cardiovasc Surg 1971; 62: 554-562.
4. Martini N, Flehinger BJ, Zaman MB et al. Prospective study of 445 lung cancer carcinomas with mediastinal lymph node metastases. J Thorac Cardiovasc Surg 1980; 80: 390-399.
5. Naruke T, Goya T, Tsuchiya R, Suemasu K. The importance of surgery to non-small cell carcinoma of lung with mediastinal lymph node metastasis. Ann Thorac Surg 1988; 46: 603-611.
6. Pearson FG, DeLarue NC, Lives R et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. J Thorac Cardiovasc Surg 1982; 83: 1-11.
7. Dillman RO, Hemdon JH, Seagren SL, Eaton WL, Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CAL GB) 8433 trial. J Natl Cancer Inst 1996; 88: 1210-1215.
8. Johnson DH, Turrisi AT, Pass HI. Combined modality treatment for locally advanced non small cell lung cancer. In: Pass HI, Mitchell JB, Johnson DH, Turrisi AT (Eds): Lung Cancer: Principles and Practice (1st edn). New York, Lipincott-Raven, 1996, pp 863-873.
9. Vokes EE. Interactions of chemotherapy and radiation. Semin Oncol 1993; 20: 70-79.
10. Sause W, Kolesar P, Taylor S et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Chest 2000; 117: 358-364.
11. Rosell R, Gomez-Codina J, Camps C 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: 153-158.
12. Roth JA, Fossella F, Komaki R 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: 673-680.
13. Roth JA, Atkinson EN, Fossella F et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. Lung Cancer 1998; 21: 1-6.
14. 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 randomized controlled trial. Lung Cancer 1999; 47: 7-14.
15. Sugarbaker DJ, Herndon J, Kohman LJ et al. Results of CALGB 8935: a multi-institutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. J Thorac Cardiovasc Surg 1995; 109: 473-485.
16. Albain KS, Rusch VW, Crowley JJ et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIa (N2) and TUB non-small cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995; 13: 1880-1892.
17. Bartelink H, Begg AC, Dewit C et al. Combined treatment with radiation and anticancer drugs: Experimental and clinical results. In: Lehen N (Ed): Radiobiology in Radiotherapy. Berlin, Germany, Springer, 1987, pp 177-199.
18. Martini N, Kris MG, Flehinger BJ et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. Ann Thorac Surg 1993; 55: 1365-1373.
19. Liptay MG, Fry WA. Complications from induction regimens for thoracic malignancies. Perioperative considerations. Chest Surg Clin N Am 1999; 9: 79-95.
20. Matsubara Y, Takeda S, Mashimo T. Risk stratification for lung

cancer surgery- Impact of induction therapy and extended resection. Chest 2005; 128: 3519-3525.
21. Takeda S, Funakoshi Y, Kadota Y et al. Fall in diffusing capacity associated with induction therapy for lung cancer: a predictor of postoperative complications'? Ann Thorac Surg 2006; 82: 232-236.
22. Leo F, Solli P, Spaggiari L et al. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? Ann Thorac Surg 2004; 77: 260-265.
23. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. J Clin Oncol 1990; 8: 1543-1555.
24. Roach M, Gandara DR, Yuo HS et al. Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. J Clin Oncol 1995; 13: 2606-2612.
25. Yamamoto R, Tada H, Kishi A, Tojo T. Effects of preoperative chemotherapy and radiation therapy on human bronchial blood flow. J Thorac Cardiovasc Surg 2000; 119: 939-945.
26. Vester SR, Faber LP, Kittle CF, Warren WH, Jensik RJ. Bronchopleural fistula after stapled closure of bronchus. Ann Thorac Surg 1991; 52: 1253-1257.
27. Fowler WC, Langer CJ, Curran WJ, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg 1993; 55: 986-989.
28. Deutch M, Crawford J, Leopold K et al. Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non small cell lung cancer. Cancer 1994; 74: 1243-1252.
29. Doddoli C, Thomas P, Thirion X, Seree Y, Giudicelli R, Fuentes P. Postoperative complications in relation with induction therapy for lung cancer. Eur J Cardiothorac Surg 2001; 20: 385-390.
30. Martin J, Ginsberg RJ, Abolhoda A et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. Ann Thorac Surg 2001; 72: 1149-1154.
31. Eberhardt W, Wilke H, Stamatis G et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. J Clin Oncol 1998; 16: 622-634.
32. Adelstein DJ, Rice TW, Rybicki LA et al. Mature results from a phase II trial of accelerated induction chemoradiotherapy and surgery for poor prognosis stage III non-small-cell lung cancer. Am J Clin Oncol 1999; 22: 237-242.
33. Thomas M, Rube C, Semik M et al. Impact of preoperative bimodality induction including twice-daily radiation on tumor regression and survival in stage III non-small-cell lung cancer. J Clin Oncol 1999; 17: 1185-1193.
34. Burkes RL, Ginsberg RJ, Shepherd FA et al. Induction chemotherapy with MVP (mitomycin-C+vindesine+cisplatin) for stage III (T1-3, N2, M0) unresectable non-small cell lung cancer: the Toronto experience. Lung Cancer 1993; 9: 377-382.
35. Stamatis G, Eberhard W, Pottgen C. Surgery after multimodality treatment for non-small-cell lung cancer. Lung Cancer 2004; 45: S107-S112.
36. Stamatis G, Djuric D, Eberhardt W et al. Postoperative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: an analysis of 350 operated patients. Eur J Cardiothorac Surg 2002; 22: 292-297.
37. Ginsberg RJ. Surgical considerations after preoperative treatment. Lung Cancer 1994; 10: 213-217.
38. World Health Organization. Handbook for reporting results of cancer treatment. Publication no. 48, WHO, Geneva, 1979.
39. Wemer-Wasik M, Xiao Y, Pequignot E et al. Assessment of lung cancer response after non operative therapy: Tumor diameter, bidimensional product and volume - A serial CT scan based study. Int J Radiat Oncol Biol Phys 2001; 51: 56-61.
40. Lever AM, Henderson D, Ellis DA et al. Radiation fibrosis mimicking local recurrence in non small cell carcinoma of the bronchus. Br J Radiol 1984; 57: 178-180.
41. Martini N, Kris MG, Grala R 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: 370-379.
42. Faber PL, Kittle CF, Warren WH et al. Preoperative chemotherapy and irradiation for stage III non-small cell lung cancer. Ann Thorac Surg 1989; 47: 669-677.
43. Pottgen C, Levegrun S, Theegarten D et al. Value of 18F-fluoro-2-deoxy-D-glucose-positron emission tomography/ computed tomography in non-small-cell lung cancer for prediction of pathologic response and time to relapse after neoadjuvant chemoradiotherapy. Clin Cancer Res 2006; 12: 97-106.
44. Schmucking M, Baum RP, Bonnet R, Junker K, Muller KM. Correlation of histologic results with PET findings for tumor regression and survival in locally advanced non-small cell lung cancer after neoadjuvant treatment. Pathologe 2005; 26: 178-189.
45. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small-cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol 1998; 9: 1193-1198.
46. Hellwig D, Graeter TP, Ukena D, Georg T, Kirsch CM, Schafers HJ. Value of F-18-fluorodeoxyglucose positron emission tomography after induction therapy of locally advanced bronchogenic carcinoma. J Thorac Cardiovasc Surg 2004; 128: 892-899.
47. McManus M, Hicks RJ, Matthews J et al. Positron emission tomography is superior to computed tomography scanning for response assessment after radical radiotherapy or chemoradiotherapy in patients with non small cell lung cancer. J Clin Oncol 2003; 21: 1285-1292.
48. Cerfolio RJ, Bryant AS, Winokur TS, Ohja B, Bartolucci AA. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. Ann Thorac Surg 2004; 78: 1903-1909.
49. Rusch VW, Albain KS, Crowley JJ et al. Neoadjuvant therapy: a novel and effective treatment for stage Illb non-small cell lung cancer. Southwest Oncology Group. Ann Thorac Surg 1994; 58: 290-294.
50. Stamatis G, Eberhardt W, Stuben G, Bildat S, Dahler O, Hillejan L. Preoperative chemoradiotherapy and surgery for selected non-small cell lung cancer IIIB subgroups: long-term results. Ann Thorac Surg 1999; 68: 1144-1149.
51. Rusch VW, Albain KS, Crowley JJ et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. J Thorac Cardiovasc Surg 1993; 105: 97-104.
52. Rice TW, Adelstein DJ, Koka A et al. Accelerated induction therapy and resection for poor prognosis stage III non-small cell lung cancer. Ann Thorac Surg 1995; 60: 586-591.

53. Regnard JF, Icard P, Deneuville M et al. Lung resection after high doses of mediastinal radiotherapy (sixty grays or more). Reinforcement of bronchial healing with thoracic muscle flaps in nine cases. J Thorac Cardiovasc Surg 1994; 107: 607-610.
54. Macchiarini P, Chapelier AR, Monnet I et al. Extended operations after induction therapy for stage Illb (T4) non-small cell lung cancer. Ann Thorac Surg 1994; 57: 966-973.
55. Daly BD, Fernando HC, Ketchedjian A et al. Pneumonectomy after high-dose radiation and concurrent chemotherapy for non small cell lung cancer. Ann Thorac Surg 2006; 82: 227-231.
56. Taghavi S, Maria GM, Lang G et al. Bronchial stump coverage with a pedicled pericardial flap: an effective method for prevention of postpneumonectomy bronchopleural fistula. Ann Thorac Surg 2005; 79: 284-288.
57. Doddoli C, Barlesi F, Trousse D et al. One hundred consecutive pneumonectomies after induction therapy for non-small cell lung cancer: an uncertain balance between risks and benefits. J Thorac Cardiovasc Surg 2005; 130: 416-425.
58. Lardinois D, Horsch A, Krueger T, Dusmet M, Ris HB. Mediastinal reinforcement after induction therapy and pneumonectomy: comparison of intercostal muscle versus diaphragm flaps. Eur J Cardiothorac Surg 2002; 21: 74-78.
59. Bueno R, Richards WG, Swanson SJ et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann Thorac Surg 2000; 70: 1826-1831.
60. Cerfolio RJ, Bryant AS, Spencer SA, Bartolucci AA. Pulmonary resection after high-dose and low-dose chest irradiation. Ann Thorac Surg 2005; 80: 1224-1230.
61. Vora SA, Daly BD, Blaszkowsky L et al. High dose radiation therapy and chemotherapy as induction treatment for stage III non small cell lung carcinoma. Cancer 2000; 89: 1946-1952.
62. Sonett JR, Krasna MJ, Suntharalingam M et al. Safe pulmonary resection after chemotherapy and high-dose thoracic radiation. Ann Thorac Surg 1999; 68: 316-320.
63. Sonett JR, Suntharalingam M, Edelman MJ et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004; 78: 1200-1205.
64. Rendina EA, Venuta F, De Giacomo T, Flaishman I, Fazi P, Ricci C. Safety and efficacy of bronchovascular reconstruction after induction chemotherapy for lung cancer. J Thorac Cardiovasc Surg 1997; 114: 830-835.
65. Ohta M, Sawabata N, Maeda H, Matsuda H. Efficacy and safety of tracheobronchoplasty after induction therapy for locally advanced lung cancer. J Thorac Cardiovasc Surg 2003; 125: 96-100.
66. Klein DS, Wilds PR. The use of PEEP limits the need for increased inspired oxygen tension. Can Anaesth Soc J 1983; 30: 399-405.
67. Yegin A, Erdogan A, Kayacan N, Karsli B. Early postoperative pain management after thoracic surgery; pre- and postoperative versus postoperative epidural analgesia: a randomised study. Eur J Cardiothorac Surg 2003; 24: 420-424.
68. Takamori S, Yoshida S, Hayashi A, Matsuo T, Mitsuoka M, Shirouzu K. Intraoperative intercostal nerve blockade for postthoracotomy pain. Ann Thorac Surg 2002; 74: 338-341.
69. Romana K, Chatzimichalis A, Koletsis E, Zacharia G, Bellenis I, Karamichali E. Ropivacaine and ropivacaine + clonidine for intercostal analgesia after thoracic surgery. Intern Monitor 2002; 14 (Suppl 2): 36.
70. Wheatley GH, Rosenbaum DH, Paul MC et al. Improved pain management outcomes with continuous infusion of a local anesthetic after thoracotomy. J Thorac Cardiovasc Surg 2005; 130: 464-468.
71. Slinger PD. Perioperative fluid management for thoracic surgery: the puzzle of postpneumonectomy pulmonary edema. J Cardiothorac Vasc Anesth 1995; 9: 442-445.
72. Pezzella TA, Adebonojo SA, Hooker SG, Mabogunje OA, Conlan A. Complications of general thoracic surgery. Curr Probl Surg 2000; 37: 733-858.