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Original Article / Özgün Makale

Long-term survival results of non-small cell lung cancer patients with complete pathological response after neoadjuvant therapy

Neoadjuvan tedavi sonrası patolojik tam yanıtı olan küçük hücreli dışı akciğer kanserli hastaların uzun dönem sağkalım sonuçları

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ABSTRACT

Background: This study aims to evaluate survival and recurrence rates in $pT_0/T_1N_0/M_0$ non-small cell lung cancer patients who underwent surgical resection after chemotherapy and/or radiotherapy, and investigate the role of positron emission tomography/computed tomography in preoperative evaluation.

Methods: A total of 54 patients (52 males, 2 females; mean age 59.2±9.3 years; range 42 to 77 years) with locally advanced non-small cell lung cancer without lymph node metastasis who had induction therapy and were proven to be pT_0N_0 (n=25) and pT_1N_0 (n=29) after pulmonary resection were included in the study. Patients were evaluated with thoracic computed tomography, bronchoscopy, respiratory function tests, and 18 patients with positron emission tomography/computed tomography, additionally. Those considered to be unresectable were clinically staged according to radiological findings. Invasive staging methods including transbronchial needle aspiration biopsy, mediastinoscopy, and video-assisted thoracoscopic surgery were performed for histological confirmation in those with resectable disease and N_2 findings.

Results: Mean follow-up duration was 34.8 months. Mean survival duration and five-year survival rates were 90.8 months and 86.3% in T_0 patients and 62.6 months and 53.7% in T_1 patients, respectively. Recurrence rates were significantly lower in T_0 patients (p=0.03). Sensitivity, specificity, positive predictive value, and negative predictive value of preoperative positron emission tomography/computed tomography were 78%, 56%, 64%, and 71%, respectively. Negative predictive value in T_0 and positive predictive value in T_1 patients was 100%. Accuracy values in T_0 and T_1 patients (56% and 78%, respectively) were similar (p=0.3).

Conclusion: Survival rates in pT_0 and pT_1 non-small cell lung cancer patients, who underwent lung resection after chemotherapy and/or radiotherapy, were similar with those of early stage patients who underwent surgery without induction therapy. Accuracy value of positron emission tomography/computed tomography in determining the presence of viable tumor cells was lower than expected.

Keywords: Chemotherapy, lung cancer surgery, positron emission tomography.

ÖZ

Amaç: Bu çalışmada, kemoterapi veya radyoterapi sonrası cerrahi rezeksiyon uygulanmış $pT_0/T_1N_0/M_0$ küçük hücreli dışı akciğer kanserli hastalarda sağkalım ve nüks oranları değerlendirildi ve pozitron emisyon tomografisi/bilgisayarlı tomografinin ameliyat öncesi değerlendirmedeki rolü araştırıldı.

Çalışma planı: İndüksiyon tedavisi almış ve akciğer rezeksiyonu sonrası pT_0N_0 (n=25) ve pT_1N_0 (n=29) oldukları kanıtlanmış lokal ileri evre küçük hücreli dışı akciğer kanserli 54 hasta (52 erkek, 2 kadın; ort. yaş 59.2 yıl; dağılım 42-77 yıl) çalışmaya alındı. Hastalar torasik bilgisayarlı tomografi, bronkoskopi, respiratuvar fonksiyon testleri ile 18 hasta da ek olarak pozitron emisyon tomografisi/bilgisayarlı tomografi ile değerlendirildi. Rezeke edilemez kabul edilenler radyolojik bulgulara göre klinik olarak evrelendi. Rezeke edilebilir hastalığı ve N_2 bulguları olanlarda histolojik onaylama için transbronşiyal iğne aspirasyonu biyopsisi, mediastinoskopi ve video yardımlı torakoskopik cerrahiyi içeren invaziv evreleme yöntemleri uygulandı.

Bulgular: Ortalama izlem süresi 34.8 ay idi. Ortalama sağkalım süresi ve beş yıllık sağkalım oranları sırası ile T_0 hastalarda 90.8 ay ve %86.3, T_1 hastalarda 62.6 ay ve %53.7 idi. Nüks oranları T_0 hastalarda anlamlı olarak daha düşük idi (p=0.03). Ameliyat öncesi pozitron emisyon tomografisi/bilgisayarlı tomografinin duyarlılık, özgüllük, pozitif öngörü değeri ve negatif öngörü değeri sırası ile %78, %56, %64 ve %71 idi. T_0 hastalarda negatif öngörü değeri ile T_1 hastalarda pozitif öngörü değeri %100 idi. Doğruluk değerleri T_0 ve T_1 hastalarda (sırası ile %56 ve %78) benzer idi (p=0.3).

Sonuç: Kemoterapi veya radyoterapi sonrası akciğer rezeksiyonu geçirmiş ve lenf bezi metastazı olmayan pT_0 ve pT_1 küçük hücreli dışı akciğer kanserli hastaların sağkalım oranları, indüksiyon tedavisi olmadan cerrahi geçirmiş erken evre hastalarınki ile benzer idi. Canlı tümör hücrelerinin varlığını belirlemede pozitron emisyon tomografisi/bilgisayarlı tomografinin doğruluk değeri beklenenden düşük idi.

Anahtar sözcükler: Kemoterapi, akciğer kanseri cerrahisi, pozitron emisyon tomografisi.

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It has recently been reported that surgical treatment after reevaluation at the end of chemotherapy and/or radiotherapy improves the prognosis of patients with non-small cell lung cancer (NSCLC), who were initially found to be unresectable or non-operable (especially due to N_2 disease).[1,2] In this group, there are no certain criteria regarding the selection of these patients for surgery. However, the generally accepted opinion is that patients who have no findings of N_2 disease and who undergo complete resection benefit the most.[3-9] Various studies have demonstrated that a pathologically complete or near complete response is also one of the important prognostic factors.[10-14] There is no certainty about the evaluation of complete response after treatment. When compared with other conventional methods, positron emission tomography/computed tomography (PET/CT), which is more likely to produce metabolic information than anatomical information, has been considered to be the most appropriate imaging method; however, its efficacy is limited due to the inadequacy of detecting the small amount of living tumor cells.[15-17]

In patients who were unresectable or non-operable in the initial evaluation with complete or nearly complete response after chemotherapy and/or radiotherapy, surgical treatment may be performed to particularly avoid local recurrence unless living tumor cells were present.

Therefore, in this study, we aimed to evaluate survival and recurrence rates in $pT_0/T_1N_0/M_0$ non-small cell lung cancer patients who were performed surgical resection after chemotherapy and/or radiotherapy, and investigate the role of PET/CT in preoperative evaluation.

PATIENTS AND METHODS

Between November 2001 and November 2010, lung resection (lobectomy or pneumonectomy) was performed on 195 patients with NSCLC after at least two cycles of chemotherapy and/or 4500 cGy radiotherapy. Operative mortality was observed in 10 patients. From the remaining 185 patients, 53 had nodal metastasis and 78 were pT_2, pT_3, and pT_4. The remaining 54 patients (52 males, 2 females; mean age 59.2±9.3 years; range 42 to 77 years) without lymph node metastasis, with no living tumor cells (T_0) or with tumors found in an area less than 3 cm with no invasion to the surrounding structures (T_1) postoperatively were included in this retrospective study.

Patients were initially evaluated with thoracic CT, bronchoscopy, respiratory function tests (RFT), and 18 patients with PET/CT, additionally. Those considered to be unresectable were clinically staged according to radiological findings. Invasive staging methods including transbronchial needle aspiration biopsy, mediastinoscopy, and video-assisted thoracoscopic surgery were performed for histological confirmation in those with resectable disease and N_2 findings.

At least two cycles of platin-based chemotherapy or 4500 cGy radiotherapy were used in patients with N_2 disease. Patients were reevaluated after treatment with thoracic CT, bronchoscopy, RFT, and PET/CT. Patients who were resectable without any signs of N_2 disease underwent surgery if they had sufficient cardiopulmonary reserves. Patients who were suspected to have N_2 disease were assessed with invasive staging methods and resection was performed on patients without N_2.

Patients with a history of previous distant metastasis and operative mortality were excluded even if they met the inclusion criteria. Deaths in the postoperative first 30 days or postoperative mortality before the patient was discharged were accepted as operative mortality.

Pathologically complete response (pT_0) was described as no viable cancer cells determined in the histopathological analysis of all resected materials. Patients with a tumor size less than 3 cm and irrelevant to any surrounding structure were defined as pT_1. Patients were analyzed according to recurrence and survival properties and compared as to whether they had T_0 or T_1.

Moreover, patients who were performed PET/CT in the period between surgery and chemotherapy and/or radiotherapy were analyzed and assessed by a nuclear medicine specialist visually (positive or negative). The accordance between pathology and PET/CT was analyzed.

All patients were scanned with PET/CT (Biograph LSO Duo, Siemens Medical Solutions, Inc. Malvern, PA) for staging before treatment. Patients with fasting glycaemia level of less than 200 mg/dL were accepted. Patients were scanned 60 minutes after intravenous injection of 370-555 MBq fluorodeoxyglucose (FDG). At first, scanned and tomographic section views were achieved with a two-section tomography between the vertex and upper thigh (50 mAs “Care Dose”, 110 kV). The three-dimensional mode scan was performed for three minutes to achieve a PET view between seven to nine mattresses according to the height of the patient.

In the processing unit, the fusion sections were obtained in the axial, sagittal, and coronal planes after PET views, in which the correction of attenuation was completed with CT data. The obtained data were

visually analyzed by two nuclear medicine clinicians separately, and evaluated with semi-quantitative data. Lesions with higher FDG uptake than mediastinal basal activity level were considered pathologic.

The study was approved by the Suat Seren Institutional Review Board Ethics Committee of the Chest Diseases and Thoracic Surgery Training and Research Hospital. Written informed consent was obtained from each patient, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

SPSS version 9.0 (SPSS Inc. Chicago, IL, USA) package program was used for statistical analysis. Fisher's exact test or Pearson's chi-square tests were used to compare the variables. In the survival analysis, the time interval between the day of surgery to last control or death was taken into account. Survival rates were evaluated with the Kaplan-Meier method and were compared with log-rank method. The forward stepwise method was used in the logistic regression analysis. P values greater than 0.5 were accepted as statistically significant.

Formulas used in evaluation were as follows: "Sensitivity: True Positive/(True Positive + False Negative)", "Specificity: True Negative/(True Negative + False Positive)'', "Positive predictive value: True Positive/(True Positive + False Positive)'', "Negative predictive value: True negative/(True negative + False negative)'', "Accuracy: (True positive + True negative)/ total number of patients''.

RESULTS

Overall survival rates according to clinical and tumor characteristics of the patients are listed in Table 1. The mean follow-up time was 37.3±26.5 months (range 2.5 to 103.7 months) and the five-year general survival rate was 68.7% (Figure 1).

The five-year survival rate was 53% in the pT_1 group and 86.3% in the pT_0 group, and the difference was not statistically significant (p=0.1) (Figure 2). There was also no significant difference between two groups in terms of the variables affecting survival, except for preoperative chemotherapy.

Recurrence rates in the pT_0 group were significantly lower than those in the pT_1 group (4.0% and 27.6%, respectively; p=0.03) (Table 2). Complete response to treatment was the only variable affecting recurrence, according to the logistic regression analysis, including sex, operation type, clinical T stage, clinical

Table 1. Five-year survival rates according to clinical and tumor characteristics and a comparison of survival rates of two patient groups

Parameters	Overall	T_0			T_1			(T_0 vs. T_1)
	5-year SR			5-year SR			5-year SR	
	%	n	%	%	n	%	%	*p*
All patients (n=54)	68.7	25	46.3	86.3	29	53.7	53.7	0.1
cT								
cT_2 (n=5)	100	2	8	100	3	10.3	66.7	0.56
cT_3 (n=3)	75	1	4	100	2	6.9	100	1
cT_4 (n=46)	67.5	22	88	85.2	24	82.8	52.2	0.15
cN								
cN_0 (n=35)	73.4	15	60	92.9	20	69	59	0.11
cN_1/N_2 (n=19)	53.6	10	40	75	9	31	32.8	0.41
Neoadjuvant therapy								
Chemotherapy (n=38)	69.9	16	64	100	22	93.1	52.7	0.017
Radiotherapy (n=9)	50	2	8	50	7	6.9	50	0.81
Chemoradiotherapy (n=7)	66.7	7	28	66.7	0	0	–	–
Operation								
Lobectomy (n=36)	80.9	17	68	93.8	19	65.5	66.9	0.17
Pneumonectomy (n=18)	56.1	8	32	71.4	10	35.5	45.7	0.54
Adjuvant therapy								
No (n=47)	71.8	22	88	84.9	25	86.2	61.2	0.31
Yes (n=7)	42.9	3	12	100	4	13.8	0	0.19

SR: Survival rates; cT: Clinical T stage; cN: Clinical N stage.

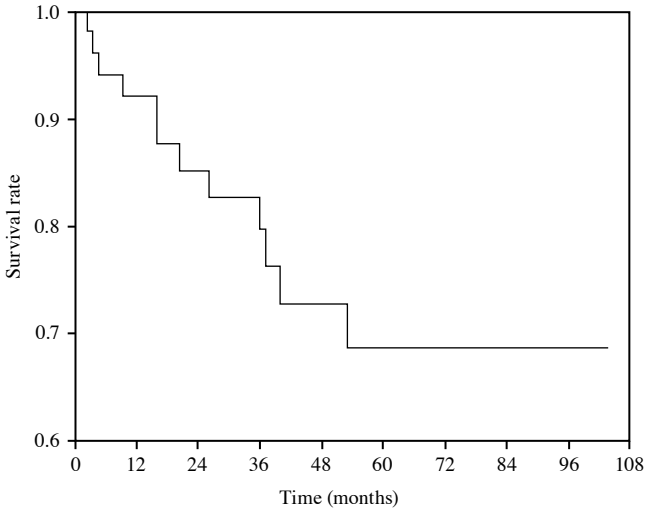

Figure 1. Five-year overall survival estimates.

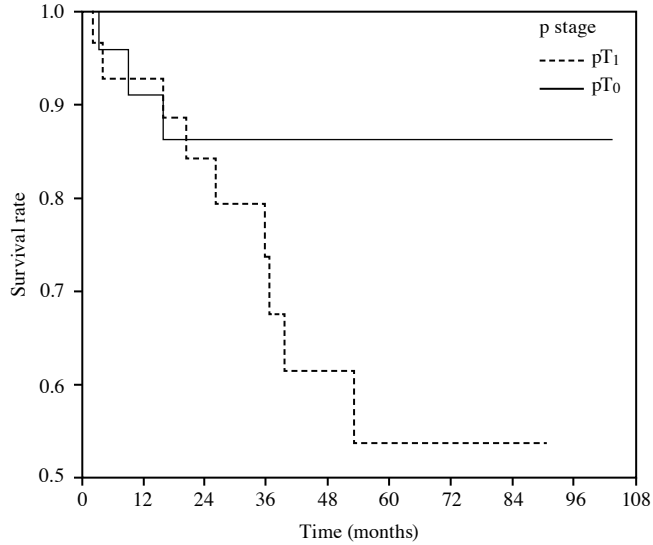

Figure 2. Five-year survival curves in patients with pT_1 (dashed line) and pT_0 (straight line). pT: Pathological T stage.

N stage, clinical stage, pathological stage, preoperative treatment, and type of adjuvant therapy (Table 3). Sensitivity, specificity, positive and negative predictive value of preoperative PET/CT were 78%, 56%, 64%, and 71%, respectively (Table 4).

DISCUSSION

Treatment for locally advanced (stage 3A and IIIB) NSCLC continues to be controversial. With these patients, surgical treatment alone is far from providing the expected results, and multimodality treatments (surgical treatment with chemotherapy and/or radiotherapy) are shown to increase resectability and survival rates. In particular, patients who had regression in N_2 disease and underwent complete resection are reported to have better prognosis.[3-9]

The issue is to be able to clearly detect the nodal status preoperatively and the degree of the response to the neoadjuvant treatment regimen. It is mandatory to perform PET/CT and evaluate the results and obtain samples from the nodal involvement areas using invasive methods. Surgical exploration aiming R_0 resection should be performed in cases where the response to treatment is evaluated as sterilization/medical clearance beyond regression.

Patients that received chemotherapy and/or radiotherapy were reported to have complete response at rates of 4% to 23%, respectively. Near complete response was detected in approximately 10% of cases. Patients that received high dose radiotherapy in addition to chemotherapy are reported to have complete pathological response rates up to 55%.[5-9,18-26]

Pathologically complete or near complete response is reported to be a prognostic factor by some authors.[10-14] Although prognosis is preferably good in this group of patients, distant recurrences in particular may reduce success rates.[3,8,25]

However, in cases when local control cannot be achieved completely, the survival expectancy of R_0 resections or R_1-R_2 resections to diminish the tumor burden relying on the adjuvant treatment

Table 2. The rates of recurrence and a comparison of two patient groups

	Total		pT_0		pT_1		
Recurrence	n	%	n	%	n	%	*p*
N/A	45	83.3	24	96.0	21	72.4	0.03
Yes	9	16.7	1	4.0	8	27.6	
Local	3	33.3	0	–	3	37.5	
Distant	5	55.6	1	100	4	50.0	0.6
Local + distant	1	11.1	0	–	1	12.5	

pT: Pathological T stage; N/A: Not applicable.

Table 3. Logistic regression analysis for variables affecting occurrence of recurrence

	Univariate analysis			Logistic regression analysis	
	Recurrence				
	n	%	*p*	OR	*p*
cT					
cT_2	1	20	0.72	–	0.8
cT_3	0	0			
cT_4	8	17.4			
cN					
cN_0	6	17.1	1	–	0.92
cN_1/N_2	3	15.8			
Clinical stage					
IIIA	1	12.5	1	–	0.6
IIIB	8	17.4			
Neoadjuvant therapy					
Chemotherapy	7	16.3	0.89	–	0.09
Radiotherapy	1	25.0			
Chemoradiotherapy	1	14.3			
Operation					
Lobectomy	4	11.1	0.14	–	0.12
Pneumonectomy	5	27.8			
pT					
T_0	1	4.0	0.003	–	0.04
T_1	8	27.6			
Adjuvant therapy					
No	8	17.0	1	–	0.8
Yes	1	14.3			

OR: Odds ratio; cT: Clinical T stage; cN: Clinical N stage; pT: Pathological T stage.

regimens may not be met. Data obtained by PET/CT may be depreciated because of the high negative prognostic value of the method, especially in small tumoral masses. Because of the challenges and relatively low applicability of re-mediastinoscopy, one should be careful when comparing the values before and after the neoadjuvant therapy and one may select to perform the mediastinoscopic examination after the treatment, when necessary. Video-assisted thoracoscopic surgery should always be included in the staging and the number of exploratory thoracotomies should be decreased. Another important issue is the dimensions of the resection. The planned dimensions in the pre-treatment period may be diminished after the treatment. Extensive resections do not always mean complete resections. However, mortality and morbidity issues may directly affect survival. Therefore, if it is possible to obtain R_0 resections after treatment with more limited resections, the decisions of extensive resections made before the treatment may be revised.

Table 4. Diagnostic performance of study population for positron emission tomography/computed tomography

	Total	pT_0	pT_1
	%	%	%
Sensitivity	78	–	78
Specificity	56	56	–
Positive predictive value	64	–	100
Negative predictive value	71	100	–
Accuracy	67	56	78

pT: Pathological T stage.

Kim et al.[21] reported five-year survival rates in pneumonectomy patients after chemoradiotherapy; 48% of those had a pathologically complete response and 43% were at stage 1. Decaluwé et al.[11] demonstrated that patients with $pT_{0\text{-}1}$ tumors who underwent lung resection after chemotherapy because of resectable N_2 diseases had significantly better survival rates than $pT_{2\text{-}4}$ patients (survival rates 64.9% and 24.3%, respectively; $p<0.01$). Five-year survival rates in pT_0 and pT_1 patients were 83.6% and 53.7%, respectively, which were similar to the survival rates reported

for pT_1 and pT_2 tumors operated on without any preoperative treatment.[27-31]

In particular, distant recurrences are a serious problem in the postoperative period in patients with complete or near complete response after oncological treatments.[10-26] In the current study, recurrence developed in one patient in the pT_0 tumor group, which was a distant recurrence. Four of the eight recurrences in the pT_1 tumor group were distant and one was both local and distant. In the multivariate analysis, the only variable that had an effect on recurrence was the pathological existence of the tumor.

Currently, while assessing the response after chemotherapy and/or radiotherapy, serial measurements of tumor diameter are achieved with CT. However, due to the changes in living tumor fractions, tumor tissue shifting with necrotic and fibrotic tissue or accompanying atelectasia might not result in major changes in tumor size. As a result, these conventional imaging methods may not always display the difference between those various kinds of tissue types.

Positron emission tomography is more useful than conventional methods to obtain information about metabolic response after neoadjuvant chemotherapy by comparing the FDG uptakes before and after the treatment.[32,33] However, due to its limited resolution in detecting a limited number of living tumor cells and relatively low metabolic signal of small tumors, the efficacy of PET decreases.[15-17] In addition, its success in defining complete or near complete response is more limited in patients who received oncological treatment before surgery compared to those who did not.[34]

Cerfolio et al.[35] reported the positive predictive value of PET as 100% and negative predictive value as 67% (one out of three patients was a false negative) after chemotherapy. In the current study, the accuracy rates of PET/CT in patients with pT_0 and pT_1 tumors were 56% and 78%, respectively.

In conclusion, surgical treatment was applied to prevent local recurrence and due to the lack of proving the presence of living tumor cells in patients who were accepted as unresectable or nonoperable in the beginning and who had complete or near complete response after chemotherapy and/or radiotherapy. For those patients, different applications may be administered in the postoperative period. Usually, close follow-up may be conducted without any additional therapy; while at other times, adjuvant therapy may be performed. In addition, distant metastasis is another problem appearing in these patients and it is not clear if postoperative prophylactic therapy, as in small cell lung cancer, is necessary or not. Survival rates of pT_0 and pT_1 non-small cell lung cancer patients who underwent lung resection surgery after chemotherapy and/or radiotherapy with any lymph node metastasis are similar with those who had surgery without induction therapy. The accuracy of positron emission tomography/computed tomography in determining the existence of viable tumor cells was lower than expected.

Declaration of conflicting interests

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REFERENCES

1. Ratto GB, Costa R, Maineri P, Alloisio A, Bruzzi P, Dozin B. Is there a subset of patients with preoperatively diagnosed N2 non-small cell lung cancer who might benefit from surgical resection? J Thorac Cardiovasc Surg 2009;138:849-58.
2. Song WA, Zhou NK, Wang W, Chu XY, Liang CY, Tian XD, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. J Thorac Oncol 2010;5:510-6.
3. Vansteenkiste J, De Leyn P, Deneffe G, Menten J, Lerut T, Demedts M. Present status of induction treatment in stage IIIA-N2 non-small cell lung cancer: a review. The Leuven Lung Cancer Group. Eur J Cardiothorac Surg 1998;13:1-12.
4. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. Induction therapy for non-small cell lung cancer with involved mediastinal nodes in multiple stations. Chest 2000;118:123-8.
5. Ciriaco P, Rendina EA, Venuta F, De Giacomo T, Della Rocca G, Flaishman I, et al. Preoperative chemotherapy and immunochemotherapy for locally advanced stage IIIA and IIIB non small cell lung cancer. Preliminary results. Eur J Cardiothorac Surg 1995;9:305-9.
6. Kandioler-Eckersberger D, Kappel S, Mittlböck M, Dekan G, Ludwig C, Janschek E, et al. The TP53 genotype but not immunohistochemical result is predictive of response to cisplatin-based neoadjuvant therapy in stage III non-small cell lung cancer. J Thorac Cardiovasc Surg 1999;117:744-50.
7. Granetzny A, Striehn E, Bosse U, Wagner W, Koch O, Vogt U, et al. A phase II single-institution study of neoadjuvant stage IIIA/B chemotherapy and radiochemotherapy in non-small cell lung cancer. Ann Thorac Surg 2003;75:1107-12.
8. Voltolini L, Luzzi L, Ghiribelli C, Paladini P, Di Bisceglie M, Gotti G. Results of induction chemotherapy followed by surgical resection in patients with stage IIIA (N2) non-small cell lung cancer: the importance of the nodal down-staging after chemotherapy. Eur J Cardiothorac Surg 2001;20:1106-12.
9. Segawa Y, Ueoka H, Kiura K, Kamei H, Tabata M, Sakae K, et al. A phase II study of cisplatin and 5-fluorouracil with

concurrent hyperfractionated thoracic radiation for locally advanced non-small-cell lung cancer: a preliminary report from the Okayama Lung Cancer Study Group. Br J Cancer 2000;82:104-11.

10. Pisters KM, Kris MG, Gralla RJ, Zaman MB, Heelan RT, Martini N. Pathologic complete response in advanced non-small-cell lung cancer following preoperative chemotherapy: implications for the design of future non-small-cell lung cancer combined modality trials. J Clin Oncol 1993;11:1757-62.
11. Decaluwé H, De Leyn P, Vansteenkiste J, Dooms C, Van Raemdonck D, Nafteux P, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433-9.
12. Yokomise H, Gotoh M, Okamoto T, Yamamoto Y, Ishikawa S, Nakashima T, et al. Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer. J Thorac Cardiovasc Surg 2007;133:1179-85.
13. Cyjon A, Nili M, Fink G, Kramer MR, Fenig E, Sandbank J, et al. Advanced non-small cell lung cancer: induction chemotherapy and chemoradiation before operation. Ann Thorac Surg 2002;74:342-7.
14. Junker K, Langner K, Klinke F, Bosse U, Thomas M. Grading of tumor regression in non-small cell lung cancer : morphology and prognosis. Chest 2001;120:1584-91.
15. Chen TM, Gould M. Evaluation of patients with small, subcentimeter nodules. Semin Respir Crit Care Med 2008;29:241-7.
16. Port JL, Andrade RS, Levin MA, Korst RJ, Lee PC, Becker DE, et al. Positron emission tomographic scanning in the diagnosis and staging of non-small cell lung cancer 2 cm in size or less. J Thorac Cardiovasc Surg 2005;130:1611-5.
17. Port JL, Kent MS, Korst RJ, Keresztes R, Levin MA, Altorki NK. Positron emission tomography scanning poorly predicts response to preoperative chemotherapy in non-small cell lung cancer. Ann Thorac Surg 2004;77:254-9.
18. Betticher DC, Hsu Schmitz SF, Tötsch M, Hansen E, Joss C, von Briel C, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752-9.
19. Milleron B, Westeel V, Quoix E, Moro-Sibilot D, Braun D, Lebeau B, et al. Complete response following preoperative chemotherapy for resectable non-small cell lung cancer: accuracy of clinical assessment using the French trial database. Chest 2005;128:1442-7.
20. Cappuzzo F, Selvaggi G, Gregorc V, Mazzoni F, Betti M, Rita Migliorino M, et al. Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable Stage IIIA-bulky N2 and Stage IIIB nonsmall cell lung carcinoma: an Italian Lung Cancer Project Observational Study. Cancer 2003;98:128-34.
21. Kim AW, Faber LP, Warren WH, Basu S, Wightman SC, Weber JA, et al. Pneumonectomy after chemoradiation therapy for non-small cell lung cancer: does "side" really matter? Ann Thorac Surg 2009;88:937-43.
22. Phernambucq EC, Spoelstra FO, Paul MA, Senan S, Melissant CF, Postmus PE, et al. Evaluation of a treatment strategy for optimising preoperative chemoradiotherapy in stage III non-small-cell lung cancer. Eur J Cardiothorac Surg 2009;36:1052-7.
23. Weder W, Collaud S, Eberhardt WE, Hillinger S, Welter S, Stahel R, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg 2010;139:1424-30.
24. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. J Thorac Cardiovasc Surg 2006;131:1229-35.
25. Sonett JR, Suntharalingam M, Edelman MJ, Patel AB, Gamliel Z, Doyle A, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004;78:1200-5.
26. Krasna MJ, Gamliel Z, Burrows WM, Sonett JR, Kwong KF, Edelman MJ, et al. Pneumonectomy for lung cancer after preoperative concurrent chemotherapy and high-dose radiation. Ann Thorac Surg 2010;89:200-6.
27. Christian C, Erica S, Morandi U. The prognostic impact of tumor size in resected stage I non-small cell lung cancer: evidence for a two thresholds tumor diameters classification. Lung Cancer 2006;54:185-91.
28. Goya T, Asamura H, Yoshimura H, Kato H, Shimokata K, Tsuchiya R, et al. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. Lung Cancer 2005;50:227-34.
29. Pfannschmidt J, Muley T, Bülzebruck H, Hoffmann H, Dienemann H. Prognostic assessment after surgical resection for non-small cell lung cancer: experiences in 2083 patients. Lung Cancer 2007;55:371-7.
30. Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. Lung Cancer 2006;52:207-12.
31. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.
32. Mac Manus M, Hicks RJ. The use of positron emission tomography (PET) in the staging/evaluation, treatment, and follow-up of patients with lung cancer: a critical review. Int J Radiat Oncol Biol Phys 2008;72:1298-306.
33. Ukena D, Hellwig D. Value of FDG PET in the management of NSCLC. Lung Cancer 2004;45:75-8.
34. Eschmann SM, Friedel G, Paulsen F, Reimold M, Hehr T, Budach W, et al. Repeat 18F-FDG PET for monitoring neoadjuvant chemotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 2007;55:165-71.
35. Cerfolio RJ, Ojha B, Mukherjee S, Pask AH, Bass CS, Katholi CR. Positron emission tomography scanning with 2-fluoro-2-deoxy-d-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma. J Thorac Cardiovasc Surg 2003;125:938-44.