ORIGINAL ARTICLE

UDC: 616.24-006-08-036:[616-033.1::616.831
DOI: 10.2298/VSP1108643P

Risk factors for brain metastases in surgically staged IIIA non-small cell lung cancer patients treated with surgery, radiotherapy and chemotherapy

Faktori rizika od pojave metastaza u mozgu kod bolesnika sa stadijumom IIIA nemikrocelularnog karcinoma pluća lečenih hirurški, zračenjem i hemioterapijom

Marina Petrović*†, Nevenka Ilić‡, Olivera Lončarević§, Ivan Čekerevac*†, Zorica Lazić*†, Ljiljana Novković*†, Vojislav Ćupurdija†, Gordana Kostić*

***University of Kragujevac, Faculty of Medicine, Kragujevac, Serbia**; †Clinical Center Kragujevac, Center for Pulmonary Diseases, **Kragujevac, Serbia; ‡Institute of Public Health, Kragujevac, Serbia; §Military Medical Academy,** Department of Pulmonary Diseases, **Belgrade, Serbia**

Abstract

Introduction/Aim. Lung cancer is a leading cause of mortality among patients with carcinomas. The aim of this study was to point out risk factors for brain metastases (BM) appearance in patients with IIIA (N2) stage of non-small cell lung cancer (NSCLC) treated with three-modal therapy. **Methods.** We analyzed data obtained from 107 patients with IIIA (N2) stage of NSCLC treated surgically with neoadjuvant therapy. The frequency of brain metastases was examined regarding age, sex, histological type and the size of tumor, nodal status, the sequence of radiotherapy and chemotherapy application and the type of chemotherapy. **Results.** Two and 3-year incidence rates of BM were 35% and 46%, respectively. Forty-six percent of the patients recurred in the brain as their first failure in the period of three years. Histologically, the patients with nonsquamous cell lung carcinoma had significantly higher frequency of metastases in the brain compared with the group of squamous cell lung carcinoma (46% : 30%; $p = 0.021$). Examining treatment-related parameters, treatment with taxane-platinum containing regimens was associated with a lower risk of brain metastases, than platinum-etoposide chemotherapy regimens (31% : 52%; $p = 0.011$). Preoperative radiotherapy, with or without postoperative treatment, showed lower rate of metastases in the brain compared with postoperative radiotherapy treatment only (33% : 48%; $p = 0.035$). **Conclusion.** Brain metastases are often site of recurrence in patients with NSCLC (IIIA-N2). Autonomous risk factors for brain metastases in this group of patients are non-squamous NSCLC, N1-N2 nodal status, postoperative radiotherapy without preoperative radiotherapy.

Key words:
carcinoma, non-small-cell lung; neoplasm metastasis; brain; antineoplastic combined chemotherapy protocols; radiotherapy; risk factors.

Apstrakt

Uvod/Cilj. Karcinom pluća vodeći je uzrok mortaliteta među obolelima od malignih bolesti. Cilj ove studije bio je da se ukaže na faktore rizika od pojave metastaza u mozgu kod bolesnika sa stadijumom IIIA (N2) nemikrocelularnog karcinoma (*non-small cell lung cancer* – NSCLC) lečenih trimodalitetnom terapijom. **Metode.** Analizirani su podaci 107 bolesnika sa stadijumom IIIA (N2) NSCLC lečenih hirurški uz dodatnu neoadjuvantnu terapiju. Učestalost metastaza u mozgu ispitivana je u zavisnosti od starosti, pola, histološkog tipa i veličine tumora, nodalnog statusa, redosleda primene zračne i hemioterapije i vrste hemioterapije. **Rezultati.** Dvogodišnja i 3-godišnja incidencija moždanih metastaza iznosila je 35% i 46%, respektivno. Četrdeset i šest procenata bolesnika imalo je metastaze u mozgu kao prvo mesto relapsa u trogodišnjem periodu. Histološki, bolesnici sa neskvamocelularnim karcinomom pluća imali su značajno veću učestalost metastaza u mozgu u odnosu na grupu skvamocelularnih karcinoma (46% : 31%; $p = 0,021$). Ispitivanjem terapijskih parametara, lečenje bolesnika primenom režima koji uključuju taksane i platinu bilo je povezano sa nižim rizikom od pojave metastaza u mozgu u

Correspondence to: Marina Petrović, University of Kragujevac, Faculty of Medicine, Beogradska bb, 34 000 Kragujevac, Serbia. Phone: +381 34 370 286. E-mail: drmarinapetrovic@yahoo.com

odnosu na etoposid-cisplatin režim (31% : 52%; $p = 0{,}011$). Bolesnici koji su preoperativno zračeni, sa ili bez postoperativne zračne terapije, imali su nižu stopu metastaza u mozgu u odnosu na one koji su lečeni samo postoperativnom zračnom terapijom (33% : 48%; $p = 0{,}035$). **Zaključak.** Metastaze u mozgu često su mesto relapsa kod bolesnika sa NSCLC (IIIA-N2). Nezavisni faktori rizika od pojave metastaza u mozgu u ovoj grupi bolesnika su neskvamocelularni karcinom, nodalni status N1-N2 i postoperativna zračna terapija bez preoperativne zračne terapije.

Ključne reči:
pluća, nesitnoćelijski karcinom; neoplazme, metastaze; mozak; lečenje kombinovanjem antineoplastika, protokoli; radioterapija; faktori rizika.

Introduction

In patients with lung cancer metastases frequently occur in the brain. Around 20%–40% of patients with non-small cell lung cancer (NSCLC) develop brain metastases. The frequency of brain metastases in NSCLC is smaller than in small-cell lung cancer (SCLC), but their occurrence after treatment possess a big problem. Brain metastases in NSCLC attract attention because combined modalities of treatment bring progress in local control and overall survival rate among patients with NSCLC. With the increase of survival rate after combined modalities of treatment it can be noticed that the frequency of brain metastases is still increasing [1–3].

Big studies on NSCLC show increased risk from distant metastases, especially brain ones, after treatment has been completed. Andre et al. [2] in a retrospective study including clinical N2 patients, surgically treated with or without neoadjuvant therapy, have shown that overall frequency of brain metastases is 32% and 18%, respectively ($p < 0.05$). Ceresoli et al. [3] have shown that among patients with stage III NSCLC, treated with combined modalities of therapy, the brain has been the primary spot of relapse in 23% of the patients, and total of 50% of the patients have developed brain metastases in the further course of the disease.

Approximately 40,000 patients a year in the world are diagnosed with locally advanced, non-metastatic NSCLC (stage III). Patients with diagnosed IIIA stage of NSCLC belong to pretty wide varieties of different subgroups: some of them have favorable outcomes, such as patients with locally invasive tumor (T3) and hilar and/or peribronchial nodes (N1) or microscopically with N2 disease, and others groups have less than favorable outcomes, such as patients with bulky mediastinal adenopathy [4].

Nowadays priority treatment for the patients with stage IIIA is controversial. Some centers apply chemotherapy with full dose of radiation therapy without surgery, while others recommend surgery as an independent treatment or after neoadjuvant chemotherapy together with competitive radiation therapy or without it. Independent surgery is possible in 10%–40% patients with stage IIIA, depending on patient selection and the degree of lymph node involvement. Surgical treatment includes resection (lobectomy and pneumonectomy) and analysis of mediastinal lymph glands (mediastinal mapping). Complete dissection of lymph glands should be performed if the carcinoma is resectable and if mediastinal lymph glands are involved. However, even though carcinoma may be resectable in stage IIIA with N2 there is usually no use of surgical treatment. There is a clear biological difference when carcinoma is coinciding with N2 disease in comparison to N1 subcategory [5]. With patients in N2 substage of stage III only surgical treatment is considered (selected patients) and its expediency. In the last 30 years, many studies have been exploring the role of multi-modality approach in treatment of locally advanced NSCLC, that consist of combination of loco-regional surgical therapy and/or radiation therapy and systemic chemotherapy. Most of trials [6–10], but not all of them [11, 12], suggest preoperative induction chemotherapy due to better control of the disease and increase of survival rate. Combined chemotherapy, together with surgical and radiation therapy, can reduce the occurrence of brain metastases in patients with stage IIIA of NSCLC, and it can also improve the quality of life and survival expectancy.

The aim of this study was to present the risk factors for brain metastases occurrence in patients with stage IIIA of NSCLC, after completed surgical, radiation and chemotherapy.

Methods

The research involved 107 patients with NSCLC, IIIA stage of the disease, who underwent lung resection in the period from 1999 to 2008, in the Centre for Toracal Surgery of the Clinical Center Kragujevac, Institute for Pulmonary Disease of the Clinical Center of Serbia in Belgrade and the Clinic for Toracal Surgery of the Military Medical Academy, Belgrade. Histopathological confirmation of the disease was performed on tissue samples using standard hematoxylin and eosine (H&E) staining method. Histologically confirmed NSCLC was classified as stadium IIIA according to the TNM classification. The analysis included only the patients that had pulmonary resection and received preoperational therapy after mediastinoscopy. Most patients received neoadjuvant chemotherapy, radiation therapy or both modalities. The decision on the type of therapy depended on the size of the tumor, nodal status and patient's performance status. Preoperative chemotherapy was indicated in patients with IIIA (N2) stage of NSCLC, good performance status and minimal lymph nodes (< 1.5 cm), as well as in patients with bordering performance status (PS-2, ECOG scale) with lymph nodes size 1.5–3 cm. Patients in good physical state with N2 status (1.5–3 cm, bulky) received combined chemo and radiation therapy as induction therapy. Decision on the type of chemotherapy depended on the attitude of oncological consortium for lungs of the institution where the treatment was performed. Characteristics of tested patients (gen-

der, age, performance status, histological type of cancer) did not vary for different types of chemotherapy.

All patients that received preoperational therapy prior to surgical treatment of the lungs had to repeat CT of the chest and upper abdomen for the purpose of testing the progress of the disease. Computed tomography of central nervous system (CNS) was performed on each of the patients before the lung treatment.

Post-treatment screening was performed in all of the patients who had signs or symptoms of CNS ailment such as: defects of visual field, nausea, vomiting, motoric and sense dysfunctions, dysfunction of cranial nerves, new headaches, confusion or convulsions. Identification of brain metastases in most of the patients was performed by using computed tomography of CNS, only a few underwent magnetic resonance imaging. Other metastases were confirmed with CT of the chest or abdomen, *via* ultrasound of abdomen or scintigraphy of skeletal system. All patients with good performance status (0–2, ECOG scale) with confirmed metastases in CNS underwent radiation therapy of CNS. Patients with confirmed metastases of other localizations and good physical condition continued the treatment with secondary chemotherapy according to docetaxel-cisplatin protocol.

After the treatment of primary lung cancer had been completed, the risk of brain metastases was estimated, treating brain as the first place of relapse or relapse in further course of the disease.

Following factors were estimated using univariate analysis to determine the possible risk of appearance of brain metastases: age, gender, histological type, tumor size, nodal status, chronology of application of radiation therapy, chemotherapy and the type of chemotherapy. Log-rank test was used for univariate analysis. Proportional hazard regression model was used for multivariate analysis and identification of independent prognostic factors.

Pearson's chi-square test was used for statistical analysis, as well as univariate and multivariate analysis. Statistically significant value was $p < 0.05$.

Results

Demographic characteristics and variables analyzed in examined group of patients are shown in Table 1. There were 107 patients in examined group (64 men and 43 women); their average age was 61 (range from 37 to 73 year). Most of examined patients had squamous cell lung carcinoma (50.5%).

Table 1

Characteristics of the examined patients with NSCLC

Characteristics	n	%
Total number of patients	107	100
Gender		
male	64	60
female	43	40
Average age (range), years	61 (37–73)	
Histological type		
squamous cell	54	50,5
adenocarcinoma	48	45
bronchialveolar	1	1
large cell	4	3,5
Tumor status, postoperative		
T0	10	9,5
T1	34	32
T2	45	42
T3	11	10
T4	7	6,5
Nodal status, postoperative		
N0	33	31
N1	24	22
N2	50	47

Most of primary lung tumor resections consisted of lobectomy (61.5%), and pneumonectomy (27%) (Table 2). Postoperative death rate was 2.8 % and determined number of deaths within 30 days since the operation. Chemotherapy according to the paclitaxel and cisplatin protocol, received 38% of the patients. Twenty nine (27%) patients received preoperative radiotherapy, 38% postoperative, while 12% of the patients received preoperative and postoperative radiotherapy (Table 2). Out of total number of patients, 72 (67%) received combined chemo and radiotherapy as a beginning of the disease initial treatment.

Out of 107 NSCLC treated patients, 44% had metastasis in the brain in the third year after the treatment was finished. Risk factors for appearance of metastases in the brain, examined with univariate analysis, are shown in Table 3. Patients with non-squamous cell lung carcinoma had significantly higher incidence of metastases in the brain within 3-year period compared to those with squamous cell carcinoma (46% : 31%; $p = 0.021$). The treatment with chemotherapy according to paclitaxel and cisplatin protocol was connected with lower brain metastases incidence within 3-year period, compared with that including chemotherapy according to the etoposide-cisplatin protocol (31% : 52%; $p = 0.011$) (Table 3).

Table 2

Treatment of the examined patients with non-small cell lung cancer (NSCLC)

Treatment	n	%
Total number of patients	107	100
Surgical approach		
lobectomia	66	61,5
pneumonectomia	29	27
bilobectomia	6	5,5
segmentectomia	3	3
other	3	3
Chemotherapy		
etoposide and cisplatin	52	49
paclitaxel and cisplatin	41	38
other, postoperative	1	1
without therapy	13	12
Neoadjuvant and adjuvant therapy		
tri-modality	72	67
chemotherapy and surgery	15	14
radiation therapy and surgery	17	16
no therapy	3	3

Table 3

Risk factors for brain metastases

Variables	Risk factors (%)			*p*
	One year	Two-year	Three-year	
Patients (total number of patients 107; died 68)	20	33	49	
Gender				
male	19	35	48	0,652
female	22	39	52	
Age (years)				
≤ 60	18	37	39	0,535
> 60	16	48	49	
Tumor status, postoperative				
T0-T1	19	36	37	0,652
T2-T4	21	44	47	
Nodal status, postoperative				
N0	18	29	31	< 0,001
N1-N2	31	45	49	
Histological type				
squamous cell	15	28	35	0,021
non-squamous cell	32	43	46	
Chronology of radiotherapy				
pre ± postoperative	17	27	33	0,035
only postoperative	29	42	48	
Chemotherapy				
etoposide and cisplatin	19	26	31	0,011
paclitaxel and cisplatin	32	44	52	

Preoperative radiotherapy with postoperative therapy or without it, showed lower rate of metastases in the brain, compared with just postoperative therapy within period of three years (33% : 48%; $p = 0.035$) (Table 3).

Within 3-year period, incidence of metastases in the brain of patients with N0 status was significantly lower than that in the N1-N2 group (31% : 49%; $p < 0.001$) (Table 3).

Risk factors for occurrence of metastases in the brain, as a first site of relapse after the treatment was finished, examined by univariate analysis, were: histological type, nodal status, type of chemotherapy and radiotherapy order (table 4). Patients with squamous cell lung carcinoma compared to those with nonsquamous cell carcinoma (32% : 44%; $p = 0.033$), as well as patients treated with preoperative radiotherapy compared to those just postoperative treated with radiotherapy (33% : 48%; $p = 0.065$), have lower rate of brain metastases in the 3-years period (Table 4).

Multivariate analysis showed that autonomous risk factors for brain metastases after finished treatment were: nonsquamous cell lung carcinoma ($p < 0.01$), nodal status ($p < 0.001$) and the order of radiotherapy use ($p < 0.01$).

Analysis of metastases incidence in the brain of patients with NSCLC in relation to histological type and nodal status showed that non-squamous cell carcinoma with N1-N2 nodal status had significantly higher one-year (32%), two-year (51%) and three-year incidence compared to that in patients with squamous cell carcinoma and N1-N2 status ($p = 0.002$) (Table 5).

With univariate analysis we examined which of the risk factors for brain metastases affected the survival length of examined patients (Table 6). Age, tumor size, nodal status

Table 4

Incidence rate of meatastases in the brain as first relapse

Variables	Incidence of brain metastases (%)			*p*
	One year	Two-year	Three-year	
Patients (total number of patients 107; died 68)	17	35	46	
Gender				
male	17	32	45	0.405
female	21	35	49	
Age (years)				
≤ 60	17	34	33	0.462
> 60	16	41	42	
Tumor status, postoperative				
T0-T1	16	32	34	0.538
T2-T4	19	41	45	
Nodal status, postoperative				
N0	16	25	28	0.015
N1-N2	27	41	45	
Histological type				
squamous cell	12	24	32	0.033
non-squamous cell	28	39	44	
Chronology of radiotherapy				
pre ± postoperative	15	25	31	0.069
only postoperative	26	40	45	
Chemotherapy				
etoposide and cisplatin	17	24	29	0.023
paclitaxel and cisplatin	30	41	48	

Table 5

Incidence rate of metastases in the brain in relation to histological type and nodal (N) status

Histology and N status	Incidence of brain metastases (%)			*p*
	One year	Two-year	Three-year	
Squamous cell, N0	14	24	29	0.002
Non-squamous cell, N0	19	29	32	
Squamous cell, N1-N2	20	29	35	
Non-squamous cell, N1-N2	32	51	59	

Table 6

Prognostic factors for patients with stage IIIA of non-small cell lung cancer (NSCLC)

Variables	Average period of survival (months)	Survival (%)			*p*
		One year	Two-year	Three-year	
Patients (total number of patients 107; died 68)	25	74	52	41	
Gender					
male	30	76	58	46	0.231
female	27	72	54	43	
Age (years)					
≤ 60	23.6	73	58	36	< 0.001
> 60	15.3	47	33	24	
Tumor status, postoperative					
T0-T1	27.9	79	58	46	< 0.001
T2-T4	17.6	64	45	28	
Nodal status, postoperative					
N0	37.1	85	68	57	< 0.001
N1-N2	19.5	69	48	31	
Histological type					
squamous cell	28.2	80	54	43	0.351
non-squamous cell	23.7	70	49	36	
Chronology of radiotherapy					
pre ± postoperative	29.4	77	55	48	0.674
only postoperative	25.3	76	54	37	
Chemotherapy					
etoposide and cisplatin	36.6	88	70	49	< 0.001
paclitaxel and cisplatin	19.2	69	34	27	

and the type of chemotherapy were all significant factors in the group of patients with IIIA stage of NSCLC (Table 6).

Three-year survival rate was significantly higher in the group of patients aged ≤ 60 (36%) ($p < 0.001$), with tumor size T0-T1 (46%) ($p < 0.001$) and nodal status N0 (57%) ($p < 0.001$), compared to that in the group of patients older than 60 years, with tumor size T2-T4 (28%) and nodal status N1-N2 (31%) (Table 6).

In the group of patients who received chemotherapy according to the protocol paclitaxel-cisplatin, 2-year (70%) and 3-year survival rate (49%) was significantly higher compared with the patients received combination cisplatin- etoposid ($p < 0.001$) (Table 6).

Discussion

We analyzed the patients with IIIA (N2) stage of NSCLC treated with multimodal therapy, including surgery, radiotherapy and chemotherapy. All the patients in this study were surgically treated, and the biggest number of them were, before thoracotomy, subjected to mediastinoscopy and biopsy of lymph nodes. ESMO recommendations from 2009 suggest that preoperative chemotherapy based on cisplatin can be considered in patients with IIIA-N2 stage [13]. In the last 10–15 years most of phase II trials suggest that neoadjuvant chemotherapy with radiotherapy or without it, can improve surgical respectability, controlling the disease and survival rate at the stage IIIA N2 NSCLC [14–17]. Recent studies point out that aggressive chemo and radiotherapy can significantly reduce even the incidence of metastases in CNS in patients with IIIA stage, especially in three-modality therapy [18, 19]. Randomized studies and meta-analyses support the conclusion that combined treatment, which includes chemotherapy on the basis of platinum preparations, improves survival compared with radiotherapy only [19, 20].

Most common chemotherapy protocols at the end of 20th century implied the inclusion of the protocols based on platinum. Results of our analysis showed higher rate of 3-year survival in the group of patients who received protocols with taxane (46%) in comparison with that in the group of patients who received protocols without taxane (25%) ($p < 0.001$).

Aggressive approach to the primary tumor with three-modality therapy results also in a low rate of loco-regional recurrence with 14%. Although this result was better than the results that are achieved with only chemo or radiotherapy, most trials with definite chemo and radiotherapy are limited only to patients with non-resectable tumor and commonly to combined patients with IIIA i IIIB diseases [21–23]. Despite this, three-year survival in our analysis was just 40%, due to high percent of distant metastases, primarily in the brain. Forty-nine percent of our patients developed metastases in the brain in the three-year period (46% as the first site of relapse). The obtained results are compatible with the data from the literature [1, 2, 18, 23–25].

Moreover, results are consistent with the earlier reports, which have shown increased incidence of brain metastases in patients with non-squamous cell carcinoma [11, 19, 20, 25–27]. In univariate analysis, nodal status, after the induction therapy, and also a type of chemotherapy showed significant connection to decrease of brain metastases.

Robnett et al. [28] have shown that the delay of radio or chemotherapy, with surgery as the initial treatment, increases the incidence of brain metastases. Our results are similar to these data in which preoperative radiotherapy, compared with postoperative one is associated with a tendency to reduce the risk for metastases occurrence in the brain.

In SCLC incidence of metastases in the brain is higher than in NSCLC, and meta-analysis of seven randomized trials suggests prophylactic radiotherapy of endocranium as a progress in reducing brain metastases incidence and overall survival inprovement [29–32]. Some trials have shown that prophylactic brain radiotherapy in NSCLC affects decreasing the incidence of brain metastases, but not the overall survival [33]. Notwithstanding the fact that brain metastases are still a major problem of morbidity and death rate in patients with NSCLC, Radiation Therapy Oncology Group has now given a priority to randomized phase III with prophylactic radiotherapy in patients with IIIA stage of NSCLC. In our analysis, we identified a subgroup of patients with NSCLC (patients with residual nodal glands after neoadjuvant therapy and non-squamous cell histologic type) which have shown high risk for the occurrence of brain metastases. Results confirm other data that metastatic disease is, primarily of CNS, bigger and more significant problem than local disease in patients with IIIA stage of NSCLC. For that reason, improving the survival will require also the improvement of systematic therapy, in which prophylactic radiotherapy can be an integral part of, as an addition to systematic chemotherapy which lowers the risk of extracranial metastases, but not metastases in the brain [24].

Conclusion

Metastases in the brain are frequent site of relapse in patients with NSCLC (IIIA-N2). Autonomous risk factors for brain metastases in this group of patients are non-squamous cell lung carcinoma, N1-N2 nodal status and postoperative radiotherapy without preoperative radiotherapy.

REFERENCES

1. *Arriagada R, Dunant A, Pignon JP, Bergman B, Chabowski M, Grunenwald D,* et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010; 28(1): 35–42.
2. *Andre F, Grunenwald D, Pujol JL, Girard P, Dujon A, Brouchet L,* et al. Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? Cancer 2001; 91(12): 2394–400.
3. *Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E.* Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. Ann Oncol 2004; 15(7): 1042–7.

4. *Greco FA, Hainsworth JD.* Multidisciplinary approach to potentially curable non-small cell carcinoma of the lung. Oncology (Williston Park) 1997; 11(1): 27–36.
5. *Eberhardt WE, Hepp R, Stamatis G.* The role of surgery in stage IIIA non-small cell lung cancer. Hematol Oncol Clin North Am 2005; 19(2): 303–19.
6. *Eberhardt WE, Albain KS, Pass H, Putnam JB, Gregor A, Assamura H,* et al. Induction treatment before surgery for non-small cell lung cancer. Lung Cancer 2003; 42(Suppl 1): S9–14.
7. *Burdett S, Stewart LA, Rydzewska L.* A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol 2006; 1(7): 611–21.
8. *Kusumoto S, Hirose T, Fukayama M, Kataoka D, Hamada K, Sugiyama T,* et al. Induction chemoradiotherapy followed by surgery for locally advanced non-small cell lung cancer. Oncol Rep 2009; 22(5): 1157–62.
9. *Tieu BH, Sanborn RE, Thomas CR Jr.* Neoadjuvant therapy for resectable non-small cell lung cancer with mediastinal lymph node involvement. Thorac Surg Clin 2008; 18(4): 403–15.
10. *Betticher DC, Hsu Schmitz SF, Tötsch M, Hansen E, Joss C, von Briel C,* et al. Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. Br J Cancer 2006; 94(8): 1099–106.
11. *Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B,* 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(1): 247–53.
12. *Stinchcombe TE, Socinski MA.* The role of induction therapy for resectable non-small cell lung cancer. Drugs 2007; 67(3): 321–32.
13. *Felip E, Stahel RA, Pavlidis N.* ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer (NSCLC). Ann Oncol 2005;16(Suppl 1): i28–9.
14. *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. Eur J Cardiothorac Surg 1998; 13(1): 1–12.
15. *Van Zandwijk N, Smit EF, Kramer GW, Schramel F, Gans S, Festen J,* et al. Gemcitabine and cisplatin as induction regimen for patients with biopsy-proven stage IIIA N2 non-small-cell lung cancer: a phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC 08955). J Clin Oncol 2000; 18(14): 2658–64.
16. *Rinaldi M, Crinò L.* Induction chemotherapy with gemcitabine and cisplatin in stage III non-small cell lung cancer. Lung Cancer 2001; 34(Suppl 4): S25–30.
17. *Lorent N, De Leyn P, Lievens Y, Verbeken E, Nackaerts K, Dooms C,* et al. Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. Ann Oncol 2004; 15(11): 1645–53.
18. *Mamon HJ, Yeap BY, Jänne PA, Rehlando J, Shrager S, Jaklitsch MT, Mentzer S,* et al.. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. J Clin Oncol 2005; 23(7): 1530–7.
19. *Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ,* et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. J Clin Oncol 2005; 23(13): 2955–61.
20. *Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD.* Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. J Neurosurg 2002; 97(6): 1276–81.
21. *Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S,* et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999; 17(9): 2692–9.
22. *Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR.* Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 1996; 88(17): 1210–5.
23. *Machtay M, Seiferheld W, Komaki R, Cox JD, Sause WT, Byhardt RW.* Is prolonged survival possible for patients with supraclavicular node metastases in non-small cell lung cancer treated with chemoradiotherapy?: Analysis of the Radiation Therapy Oncology Group experience. Int J Radiat Oncol Biol Phys 1999; 44(4): 847–53.
24. *Stuschke M, Eberhardt W, Pöttgen C, Stamatis G, Wilke H, Stüben G,* et al. Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. J Clin Oncol 1999; 17(9):2700–9.
25. *Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara PN Jr,* et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 2003; 21(10): 2004–10.
26. *Cox JD, Scott CB, Byhardt RW, Emami B, Russell AH, Fu KK,* et al. Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. Int J Radiat Oncol Biol Phys 1999; 43(3): 505–9.
27. *Petrović M, Tomić I, Jovanović D.* Risk factors for brain metastases after definitive chemoradiation for locally advanced non-small cell lung cancer. Vojnosanit Pregl 2009; 66(11): 876–80. (Serbian)
28. *Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM.* Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. J Clin Oncol 2001; 19(5): 1344–9.
29. *Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ,* et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999; 341(7): 476–84.
30. *Arriagada R, Le Chevalier T, Borie F, Rivière A, Chomy P, Monnet I,* et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 1995; 87(3): 183–90.
31. *Gregor A, Cull A, Stephens RJ, Kirkpatrick JA, Yarnold JR, Girling DJ,* et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. Eur J Cancer 1997; 33(11): 1752–8.
32. *Le Péchoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C,* et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 2009; 10(5): 467–74.
33. *Pöttgen C, Eberhardt W, Grannass A, Korfee S, Stüben G, Teschler H,* et al. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. J Clin Oncol 2007; 25(31): 4987–92.

Received on February 1, 2010.
Revised on March 17, 2010.
Accepted on April 19, 2010.