VIA MEDICA

PRACA ORYGINALNA

Mariusz Chabowski[1], Tadeusz M. Orłowski[1], Daniel Rabczenko[2]

[1]Department of Surgery, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland
[2]Department of Medical Statistics, National Institute of Hygiene, Warsaw, Poland

Analysis of prognostic factors and efficacy of surgical treatment for non-small cell lung cancer: department of surgery NTLDRI (1998–1999)

Analiza czynników rokowniczych oraz ocena skuteczności chirurgicznego leczenia niedrobnokomórkowego raka płuca w Klinice Chirurgii IGiChP w latach 1998–1999

Streszczenie

Wprowadzenie: Postępowanie chirurgiczne stanowi podstawową metodę leczenia niedrobnokomórkowego raka płuca.
Materiał i metody: W pracy przeprowadzono retrospektywną analizę skuteczności tego leczenia w grupie 431 chorych operowanych w Klinice Chirurgii Instytutu Gruźlicy i Chorób Płuc w Warszawie w latach 1998–1999. W 218 (50%) przypadkach wykonano lobektomię, w 21 (5%) — bilobektomię, w 188 (44%) — pneumonektomię, a w 4 (1%) — resekcję klinową. U 70 (16%) chorych rozpoznano stadium zaawansowania pIA, u 112 (26%) — pIB, u 22 (5%) — pIIA, u 110 (26%) — pIIB, u 88 (20%) — pIIIA, u 13 (3%) — pIIIB i u 16 (4%) — pIV.
Wyniki: Wskaźnik 5-letniego przeżycia dla całej grupy wynosił 49,1%. Analiza statystyczna wykazała wyższy odsetek odległych przeżyć w grupie wiekowej do 50. rż. ($p = 0,03$), u płci żeńskiej ($p = 0,01$, HR = 0,63), w przypadku mniej rozległego zabiegu (lobektomia) ($p < 0,005$). Wskaźniki odległych przeżyć wykazywały znamienną zależność od stadium zaawansowania choroby nowotworowej ($p < 0,005$). Pięcioletnie przeżycie pacjentów w stadium IA wynosiło 81,7%, IB — 62,2%, IIA — 59,1%, IIB — 38%, IIIA — 21,3%, IIIB — 8,3% oraz IV — 8,3%. Typ histopatologiczny miał również znamienny wpływ na odległe przeżycia chorych ($p < 0,005$). Pięcioletnie przeżycie chorych na raka płaskonabłonkowego wynosiło 53,4%, na raka gruczołowego — 38,3%, na raka wielkokomórkowego — 37,5%, na rakowiaka — 94,7%, a na pozostałe typy raka — 39,1%. Wskaźnik odległego przeżycia zależał znamiennie od cechy T ($p < 0,005$). Obniżone wyjściowe stężenie hemoglobiny ($p < 0,005$, HR = 1,52) oraz przetoczenie masy erytrocytarnej w okresie pooperacyjnym ($p = 0,03$) były niekorzystnymi czynnikami rokowniczymi. Znamiennie gorsze rokowanie wykazano w przypadku cechy R1 lub R2 ($p = 0,01$) oraz cechy M1 ($p < 0,005$). Dodatkowo, w analizie wielowymiarowej Coxa wartość FEV1 poniżej 80% (HR = 1,46) była zmienną negatywnie wpływającą na odległe przeżycie, a brak objawów klinicznych choroby, z wyjątkiem kaszlu (HR = 0,73) — zmienną wpływającą korzystnie.
Wnioski: W analizie jednowymiarowej wyłoniono następujące czynniki ryzyka: płeć męska, wiek powyżej 50. rż., obniżone stężenie Hb, zabieg operacyjny o poszerzonym zakresie, zaawansowane stadium, utkanie raka gruczołowego i wielkokomórkowego, cecha T, N, R i M oraz przetoczenie ME w okresie pooperacyjnym. Analiza wielowymiarowa Coxa wykazała następujące negatywne czynniki prognostyczne: obniżone wyjściowe stężenie Hb, wartość FEV1 poniżej 80%, zabieg operacyjny o poszerzonym zakresie (pneumonektomia), zaawansowane stadium raka, utkanie raka gruczołowego oraz następujące korzystne rokowniczo czynniki: płeć żeńska i brak objawów klinicznych, z wyjątkiem kaszlu.

Słowa kluczowe: niedrobnokomórkowy rak płuca, czynniki prognostyczne, leczenie chirurgiczne, stadium zaawansowania
Pneumonol. Alergol. Pol. 2008; 76: 1–10

Corresponding author: Department of Surgery, 26 Plocka Street, 01–138 Warsaw, Poland, phone: (+ 48 22) 431 22 00, fax: (+ 48 22) 431 24 55, e-mail: m.chabowski@igichp.edu.pl

Praca wpłynęła do Redakcji: 19.06.2007 r.

ISSN 0867–7077

Abstract

Introduction: Surgical resection is the mainstay of curative treatment for non-small cell lung cancer.

Material and methods: A retrospective analysis of the efficacy of this treatment, based on 431 patients operated from 1998 to 1999 in the Department of Surgery of the National Tuberculosis and Lung Diseases Research Institute, was accomplished. In 218 cases (51%) lobectomy was performed, in 21 cases (5%) — bilobectomy, in 188 cases (44%) — pneumonectomy and in 4 cases (1%) — wedge resection. The pIA stage was diagnosed in 70 cases (16%), pIB — in 112 (26%), pIIA — in 22 (5%), pIIB — in 110 (26%), pIIIA — in 88 (20%), pIIIB — in 13 (3%) and pIV — in 16 (4%).

Results: The five-year survival rate for the whole group was 49.1%. Statistical analysis revealed better survival in patients younger than 50 ($p = 0.03$), in women ($p = 0.01$, HR = 0.63) and in cases with less extensive surgery, i.e. lobectomy, ($p < 0.05$). Long-term survival was significantly dependent on the disease stage ($p < 0.005$). Five-year survival of patients in stage IA was 81.7%, IB — 62.2%, IIA — 59.1%, IIB — 38%, IIIA — 21.3%, IIIB — 8.3% and IV — 8.3%. Tumour status ($p < 0.005$) and histological subtype ($p < 0.005$) had a significant influence on long-term survival. Five-year survival of patients with squamous cell carcinoma was 53.4%, with adenocarcinoma — 38.3%, with large cell carcinoma — 37.5%, with carcinoid — 94.7% and with other types of cancer — 39.1%. The decreased preoperative Hb level ($p < 0.005$, HR = 1.52), as well as blood transfusion in postoperative period ($p = 0.03$), were negative prognostic factors. Significantly worse prognosis was observed in the cases of R1 or R2 categories ($p = 0.01$) and M1 category ($p < 0.005$). Additionally, in multivariate Cox analysis, a decreased FEV1 lower than 80% (HR = 1.46) was a negative prognostic factor, and lack of symptoms, except cough (HR = 0.73), was a positive one.

Conclusions: Univariate analysis revealed several factors worsening prognosis: male sex, age older than 50 years, lowered preoperative Hb concentration, extended surgery, advanced stage, adenocarcinoma and large cell carcinoma, T status, N status, R status, M status and blood transfusion in postoperative period. In multivariate Cox analysis lowered preoperative Hb concentration, decreased FEV1 lower than 80% pred., extended surgery (pneumonectomy), advanced stage and adenocarcinoma were negative prognostic factors. Female sex and lack of symptoms, except coughing were positive prognostic factors.

Key words: non-small cell lung cancer, prognostic factors, surgical treatment, staging

Pneumonol. Alergol. Pol. 2008; 76: 1–10

Introduction

Lung cancer is the most lethal cancer in the world [1]. In 2004 in Poland 21 128 cases of lung cancer were recognized and it was the most frequent cancer in men [2]. In the US 173 000 new cases of lung cancer were diagnosed in 2004 [1, 3–5]. Lung cancer is responsible for approximately 30% of all cancer deaths [4]. In the US, lung cancer has been the leading cause of cancer mortality in both men and women since 1987 [1, 4]. The lung cancer death rate among men has continued to decrease since 1991 [1, 4, 6–8]. In women, most countries show a rising trend in incidence and mortality due to the custom of cigarette smoking [9, 10]. Lung cancer is unique among cancers by having a known etiology and therefore the possibility of risk reduction by means of smoking cessation [1, 5]. Tobacco smoking accounts for approximately 90% of the lung cancer risk, but only 20% of cigarette smokers develope lung cancer [1, 4, 6, 10, 11]. According to current WHO classification, there are four histological subtypes of lung cancer: squamous cell carcinoma (40–60% of lung cancers), adenocarcinoma (25–30%), the incidence of which has increased since the 1990s, large cell carcinoma (10–15%) and small cell carcinoma (20%) [10, 11]. First three types are defined as non-small cell carcinoma (NSCLC) and constitute 80% of all lung cancer cases [8, 12, 13]. In North America, unlike in Europe, adenocarcinoma has become the predominant type of NSCLC [1, 10, 14]. In 1968 the international tumour-node-metastasis (TNM) system for cancer staging was accepted by the Union Internationale Contre le Cancer (UICC). Since then the revision of the TNM classification had been repeated every 4–10 years until the fifth edition based on Mountain's database (5319 cases) was finally enacted in 1997 [11]. In 1999 the Staging Committee of the International Association for the Study of Lung Cancer (IASLC) was formed to submit its recommendations to the UICC for the next revision of the International Staging System for Lung Cancer. It managed to develop an international database including 100 869 lung cancer cases treated between 1990 and 2000 from 45 centres in 20 countries around the globe [15]. The presented material represents our contribution to the IASLC worldwide database in order to enact the sixth revision of the TNM staging system for NSCLC in 2009. The choice of therapy of NSCLC depends on the stage of the disease (cTNM). In Poland 20% of patients are in stage I or II at diagnosis, 40% — in stage IIIA or IIIB and the remaining 40% — in stage IV [13, 16]. In early stages of NSCLC (stages I and II) radical surgery is the treatment of choice [12, 17, 18].

The best therapeutic option is lobectomy with regional lymph node dissection [12, 17, 19]. Chemotherapy and radiotherapy are applied as neoadjuvant or adjuvant therapy in early stages and constitute substantial treatment in advanced stages of lung cancer. In 2004, 3631 out of 21 128 new cases of primary NSCLC were operated (resection rate — 17.2%) in Poland. This means that the remaining patients were offered only non-surgical therapy [2]. Similar resection rates in Sweden in 1999 were 9.8%, and in Norway in 2002 — 17% [14, 18]. In the US about 35 000 patients with lung cancer a year were offered surgery [7]. Early detection may be the best way to improve prognosis, but mass screening including low-dose spiral chest CT screening remains controversial [7, 17, 19]. The prognosis in lung cancer is very poor and disappointing with a 5-year survival of about 10–15%. It has remained unchanged over the last two decades [1, 8, 11, 12, 14, 18–20]. Relapse of the disease occurs in about half of the resected cases [7, 13]. Failure of treatment is caused by distant metastases in 75% of cases and by local recurrences in 25% [16]. We aimed to assess the prognostic factors of NSCLC after surgery as well as to evaluate the results of surgical treatment.

Material and methods

The study included 431 consecutive patients who underwent radical surgery for NSCLC in the Department of Surgery of the National Tuberculosis and Lung Diseases Research Institute between January 1998 and December 1999. The following data from medical records were retrospectively analysed:

- age, gender, smoking status, symptoms, comorbidity and performance status;
- blood group and Rh-factor, preoperative Hb, albumin, Ca and serum alkaline phosphatase level;
- site of tumour: right or left lung; peripheral or central; upper, middle or lower lobe;
- bronchoscopic examination (presence or lack of endobronchial lesions);
- presence or lack of preoperative histological diagnosis;
- preoperative lung function (baseline VC and FEV1 above 80% of pred; 50–80% of pred and lower than 50% of pred);
- mediastinoscopy;
- extent of surgery (limited resection, lobectomy or pneumonectomy);
- postoperative complications;
- postoperative blood transfusion;
- postoperative histological examination: histological subtype of tumour; tumour size (T status); mediastinal lymph nodes status (N disease); pathological stage of disease (pTNM) and completeness of resection (R status) according to TNM system in Mountain modification (5th edition) from 1997 [12];
- neoadjuvant and adjuvant chemotherapy.

Detailed patient characteristics are presented in Table 1. Concomitant diseases were: cardiovascular — 144 (33%) patients, peptic ulcer — 41 (9.5%), diabetes — 15 (3.5%), emphysema — 15 (3.5%), CNS — 9 (2%) and renal — 4 (1%). Two hundred and two (47%) patients did not suffer from any accompanying disease. The performance status of all patients was satisfactory, i.e. 0 or 1 according to ECOG scale. Blood groups were as follows: A — 168 (39%) cases, 0 — 139 (32%), B — 86 (20%) and AB — 38 (9%). Normal albumin concentration was observed in 422 (98%) patients. Calcium levels were examined in 130 (30%) patients, and were within normal limits in the majority of cases (1.03–1.3 mmol/l). Serum alkaline phosphatase concentrations were examined in 187 (43%) patients, and were within limits (91–258 U/l) in 147 (34%) cases, and in 7 cases (1.6%) — even lower than 91 U/l. Only 30 (7%) patients had elevated concentrations of alkaline phosphatase. In 315 (73%) patients, preoperative VC was higher than 80% of pred., and in 93 (21%) it was lower than 80% of pred. In 23 (5%) cases it was not possible to obtain a spirometry report. Endobronchial lesions occurred in 194 (45%) patients. Due to mediastinal lymph node enlargement prior to lung surgery, 153 (35%) patients underwent mediastinoscopy, which was positive in four cases. Thirty-one (20.8%) out of 149 patients with negative mediastinoscopy had metastases in mediastinal lymph nodes (pN2) in postoperative histological reports. Four patients with positive mediastinoscopy received neoadjuvant chemotherapy and then underwent surgery (three pneumonectomies and one lobectomy). In three cases, there were still metastases in mediastinal lymph nodes. In total, 23 (5%) patients received neoadjuvant therapy due to both cN1 and cN2. Men underwent a similar number of pneumonectomies and lobectomies, 152 (47%) and 155 (48%), respectively. Women underwent twice as many pneumonectomies as lobectomies, 63 (58%) and 36 (33%), respectively. There was a predominance of squamous cell carcinoma in males (62%) with only 28% of adenocarcinoma. A higher proportion of females was found to have adenocarcinoma (49%), and only 27% — squamous cell carcinoma. In the pN2 group, metastases to the following lymph nodes were revealed: subcarinal in 62 cases, AP window in 14, lower paratracheal in 13, paraoesophageal in 6, upper paratracheal in 6, para-aortic in 6,

Table 1. Patient characteristics

Tabela 1. Charakterystyka pacjentów

	N = 431		N = 431
Gender/*Płeć*		Type of surgery/*Rodzaj zabiegu*	
Men/*Mężczyźni*	323 (75%)	Wedge (sublobar) resection/*Resekcja klinowa*	4 (1%)
Women/*Kobiety*	108 (25%)	Lobectomy/*Lobektomia*	218 (50%)
Wiek/Age		Bilobectomy/*Bilobektomia*	21 (5%)
< 40 years old	15 (3.5%)	Pneumonectomy/*Pneumonektomia*	188 (44%)
40–49	46 (10.7%)	Extension of disease/*Stadium*	
50–59	118 (27.3%)	IA	70 (16%)
60–69	182 (42.2%)	IB	112 (26%)
> 70	70 (16.2%)	IIA	22 (5%)
Smoking status/*Palenie tytoniu*		IIB	110 (26%)
No-smokers/*Niepalący*	67 (16%)	IIIA	88 (20%)
Smokers/*Palący*	273 (63%)	IIIB	13 (3%)
Not available/*Brak danych*	91 (21%)	IV	16 (4%)
Symptoms/*Objawy*		Histology/*Utkanie histopatologiczne*	
Without symptoms/*Bezobjawowo*	138 (32%)	Squamous carcinoma/*Rak płaskonabłonkowy*	229 (53%)
Cough/*Kaszel*	176 (41%)	Adenocarcinoma/*Rak gruczołowy*	144 (33%)
Hemoptoe/*Krwioplucie*	89 (21%)	Large cell carcinoma/*Rak wielkokomórkowy*	16 (4%)
Chest pain/*Bóle w klatce piersiowej*	47 (11%)	Carcinoid/*Rakowiak*	19 (5%)
Weight loss/*Utrata masy ciała*	42 (10%)	Other NSCLC/*Rak niedrobnokomórkowy — inne*	23 (5%)
Pneumonia/*Zapalenie płuc*	41 (10%)	pT status/*Cecha T*	
Hb levels/*Hemoglobina*		T1	112 (26%)
14–16 g/dl — normal/*w normie*	196 (45%)	T2	254 (59%)
< 14 g/dl — decreased/*obniżona*	236 (55%)	T3	51 (12%)
FEV1		T4	14 (3%)
Over 80% of pred./*Powyżej 80%*	208 (48%)	pN disease/*Cecha N*	
Below 80% of pred./*Poniżej 80%*	200 (46%)	N0	220 (51%)
Site of tumour/*Lokalizacja*		N1	129 (30%)
Peripheral/*Obwodowa*	294 (68%)	N2	82 (19%)
Central/*Centralna*	137 (32%)	M status/*Cecha M*	
Right upper lobe/*Płat górny prawy*	127 (29,4%)	M0	415 (96.2%)
Middle lobe/*Płat środkowy*	21 (5%)	M1	16 (3.7%)
Right lower lobe/*Płat dolny prawy*	111 (25,7%)	R status/*Cecha R*	
Left upper lobe/*Płat górny lewy*	99 (22,9%)	R0	420 (97.4%)
Left lower lobe/*Płat dolny lewy*	73 (16,9%)	R1	9 (2.1%)
Mediastinoscopy/*Mediastinoskopia*		R2	2 (0.5%)
No/*Nie*	278 (65%)		
Yes/*Tak*	153 (35%)		

pulmonary ligament in 5 and pretracheal in 2. Sixteen (3.7%) patients presented simultaneous M1 disease as brain or ipsilateral non-primary lobe metastasis. Complete resection (R0) was performed in 420 cases (97.4%), and incomplete resection: R1, in 9 cases (2.1%) and R2 in 2 cases (0.5%). Seventeen (4%) patients underwent adjuvant radiotherapy, and 31 (7%) — adjuvant chemotherapy. Survival curves were calculated by the Kaplan-Meier method, and significant differences in probability of survival were evaluated by log-rank test. P-values less than 0.05 were considered statistically significant. Confidence interval (CI) of 0.95 was accepted. Univariate and multivariate analysis were performed using Cox proportional hazards regression model to determine factors potentially predicting postoperative survival.

Results

Having excluded 30-day operative mortality, 49.1% of the 431 patients survived for five years. The median of the whole group was 58.5 months (95% CI: 41–81). In 307 (71%) cases, the postoperative period was uneventful. One hundred and twenty four (29%) patients developed the following postoperative complications: cardiovascular — in 30 (7%) cases, respiratory — in 26 (6%), bleeding — in 16 (4%), empyema — in 16 (4%), wound disruption — in 13 (3%), renal — in 6 (1%) and psychotic — in 5 (1%). Cardiovascular complication rates of 6% and 10% were noted for lobectomy and pneumonectomy, respectively. No bronchopleural fistula occurred in lobectomy patients compared to 4% of those undergoing pneumonectomy. For pneumonectomy, higher posto-

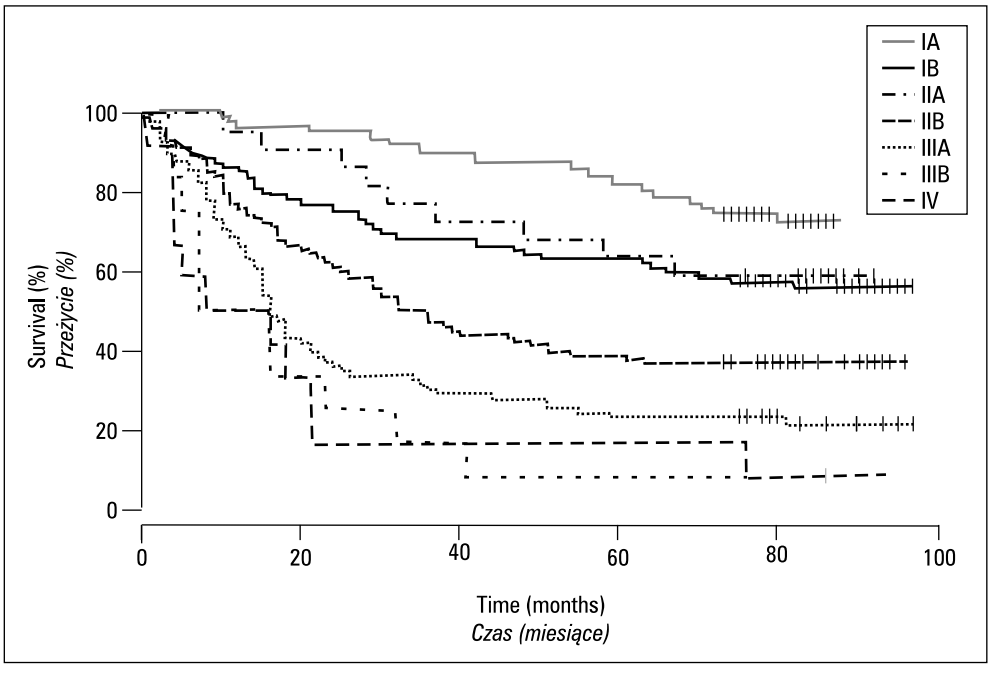

Figure 1. Kaplan-Meier survival curves for patients stratified on the basis of staging

Rycina 1. Krzywe przeżycia Kaplana-Meiera w zależności od stadium zaawansowania

perative bleeding rates of 7% were observed. For lobectomy, postoperative air leak rate was 11%. Postoperative transfusion was administered in 160 (37%) cases. Postoperative death, i.e. death within 30 days following operation, occurred in five (1.2%) cases. Death after lobectomy happened in one (0.4%) case, and after pneumonectomy — in four (2.1%) cases. The status of all patients (alive or deceased) was confirmed thanks to precise information from the City Hall registry. Two hundred and forty-two (56%) patients died, and 189 (44%) are still alive. Survivors were: in stage IA — 51 (27%) patients, IB — 63 (33%), IIA — 13 (7%), IIB — 40 (21%), IIIA — 19 (10%), IIIB — 1 (0.5%) and IV — 2 (1%). Favourable survival was observed in patients less than 50 years old ($p = 0.03$). There were significant differences in survival ($p=0.01$) between females (5-year survival, 58.9%) and males (5-year survival, 45.4%). Reduced preoperative Hb levels were a negative prognostic factor ($p < 0.005$). A significant difference in survival according to the extent of surgery was demonstrated ($p < 0.005$). Five year survival rate was 56.7% and 38.0% for lobectomy and for pneumonectomy, respectively. The prognosis depended also on stage of tumour ($p < 0.005$), the 5-year survival was: 81.7% in stage IA, 62.2% — IB, 59.1% — IIA, 38% — IIB, 21.3% — IIIA, 8.3% — IIIB and 8.3% — IV (Fig. 1). Subtype of chest tumours significantly influenced long-term survival ($p < 0.005$). Five year survival of patients with squamous cell carcinoma was 53.4%, adenocarcinoma — 38.3%, large cell carcinoma — 37.5%, carcinoid — 94.7% and other subtypes — 39.1% (Fig. 2). T status significantly influenced prognosis ($p < 0.005$). Five year survival for patients with T1 was 67.6%, T2 — 42.4%, T3 — 24.5% and T4 — 7.7% (Fig. 3). There were significant differences in N factor group ($p < 0.005$). Five year survival for patients with N0 was 57.3%, N1 — 35% and N2 — 10.2% (Fig. 4). The following parameters did not influence survival in univariate analysis: smoking ($p = 0.33$), symptoms — cough ($p = 0.19$), hemoptoe ($p = 0.39$), pneumonia ($p = 0.99$), weight loss ($p = 0.72$) or pain ($p = 0.13$), comorbidity ($p = 0.16$), blood group ($p = 0.40$), Rh-factor ($p = = 0.74$), serum alkaline phosphatase level ($p = 0.57$), left or right site of tumour ($p = 0.50$), central or peripheral tumour localization ($p = 0.79$), upper, middle or lower lobe tumour localization ($p = = 0.11$), presence of endobronchial lesion ($p = 0.74$), presence of preoperative histological diagnosis ($p = 0.98$) and performance of mediastinoscopy ($p = 0.17$). Postoperative blood transfusion was a negative prognostic factor ($p = 0.03$). Worse prognosis was combined with incomplete resection ($p = 0.01$) and M1 disease ($p < 0.005$). Five year survival for R0 was 49.8%, for R1 — 25%, and for R2 — 0% (Fig. 5). Five year survival for M0 was 50% and for M1 — 18.8%. Multivariate analysis revealed the following negative prognostic factors (Tab. 2): preoperative Hb level lower than 14 g/dl

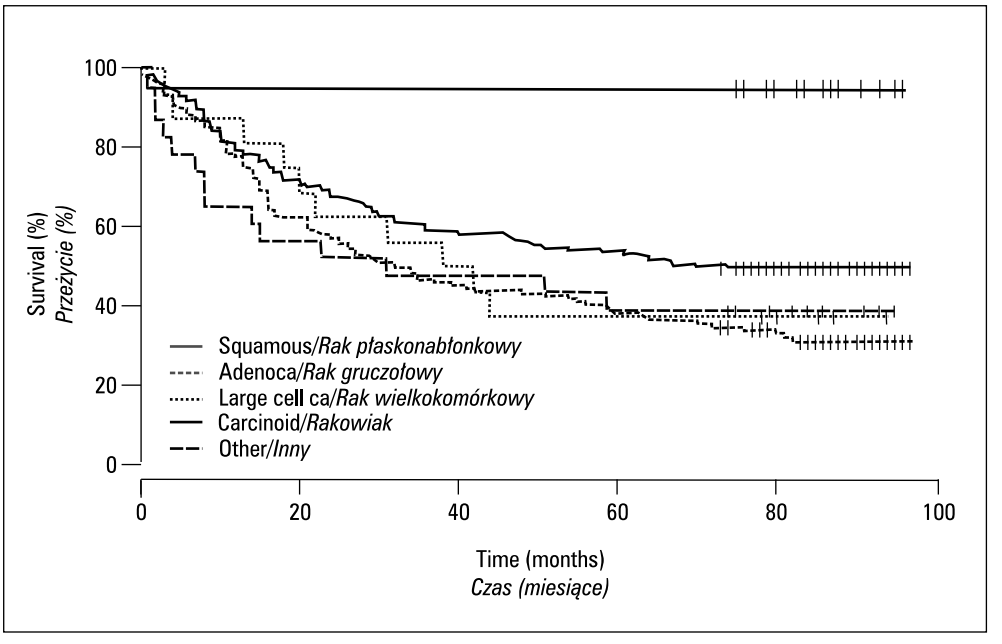

Figure 2. Kaplan-Meier survival curves for patients stratified on the basis of histological type

Rycina 2. Krzywe przeżycia Kaplana-Meiera w zależności od typu histologicznego guza

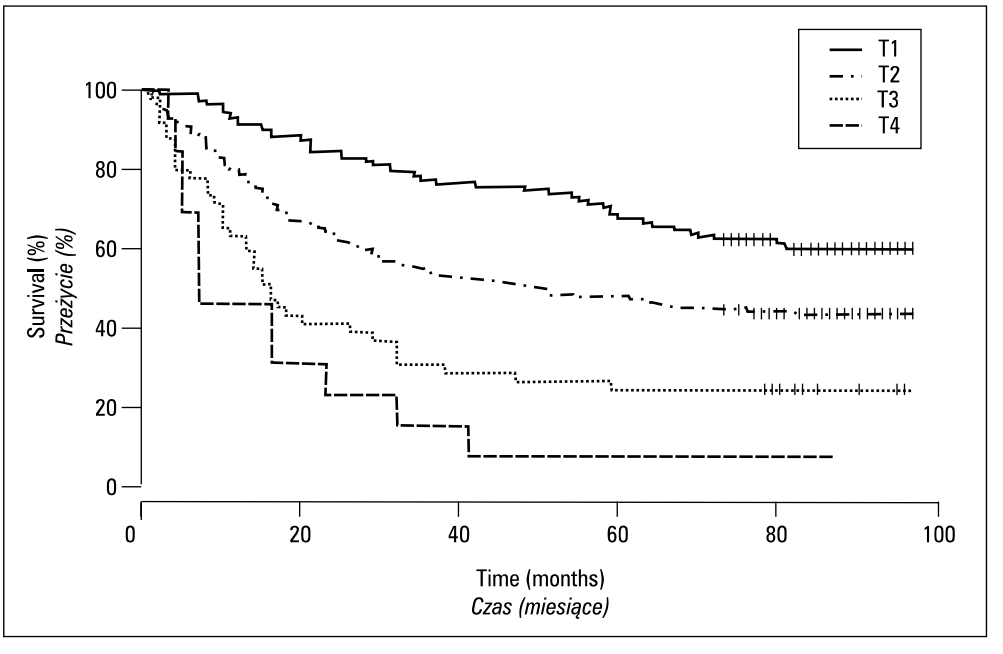

Figure 3. Kaplan-Meier survival curves for patients stratified on the basis of T status (pT)

Rycina 3. Krzywe przeżycia Kaplana-Meiera w zależności od cechy pT

(HR = 1.52), decreased FEV1 lower than 80% of pred. (HR = 1.46), extended surgery (pneumonectomy) (HR = 1.42), adenocarcinoma (HR = 1.99) and advanced tumour stage pTNM (HR = 2.01). According to Cox analysis, it was proven that positive prognostic factors were: gender (women far better) (HR = 0.63) and lack of clinical symptoms, except cough (HR = 0.73).

Discussion

The 5-year survival rate of 49.1% of 431 lung cancer patients who underwent surgery was similar to those reported in other studies, which generally range between 30–40% [8, 12, 21, 22]. British authors noted 5-year survival rate of 30.8% in 329 lung cancer patients, Norwegian — 43.7% in 536

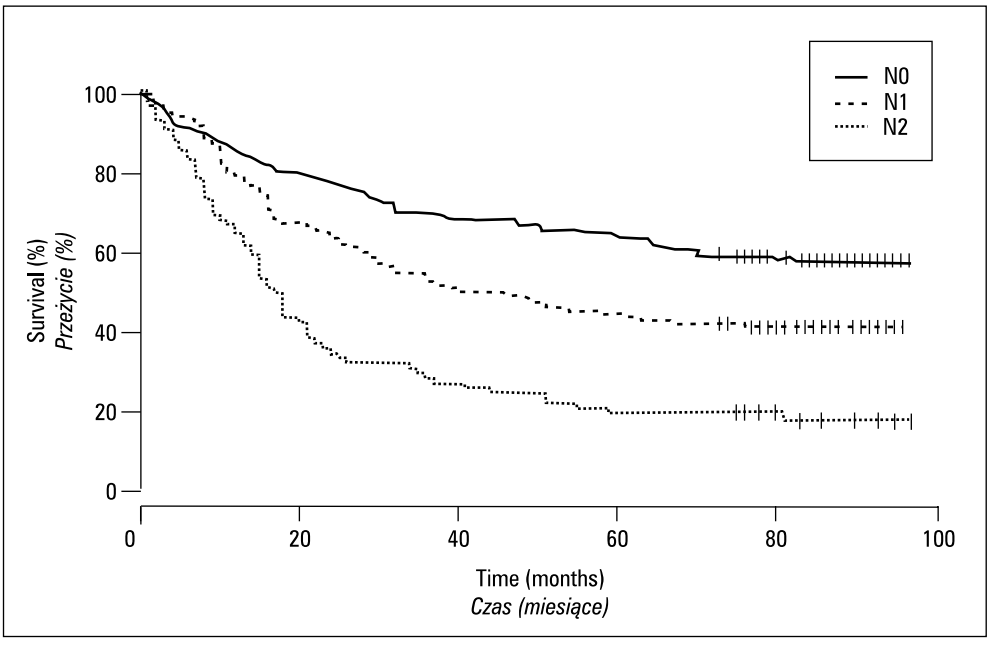

Figure 4. Kaplan-Meier survival curves for patients stratified on the basis of N disease (pN)

Rycina 4. Krzywe przeżycia Kaplana-Meiera w zależności od cechy pN

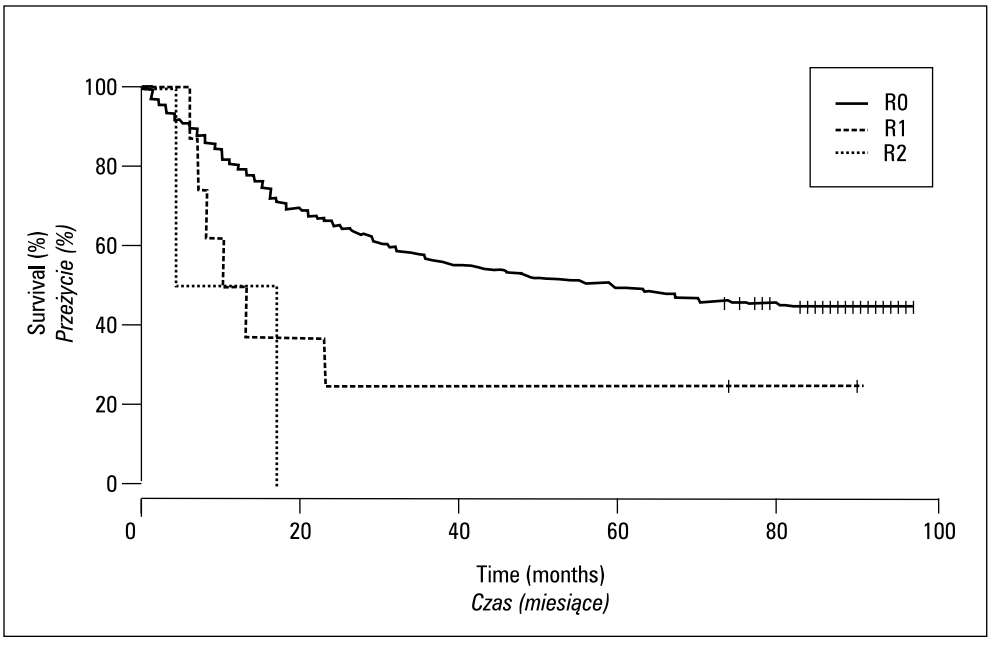

Figure 5. Kaplan-Meier survival curves for patients stratified on the basis of R status

Rycina 5. Krzywe przeżycia Kaplana-Meiera w zależności od cechy R

patients and Japanese — 52.6% in 6,644 patients [9, 18, 23]. Similar to our observations, the percentage of males and females with NSCLC was 70% and 30% in the Japanese study, respectively [23].

Damhuis et al. reported a 30-day operative mortality rate of 3.1%, Ghosh et al. — 3.9%, Doddoli et al. — 2.8% and Wada et al. — 1.3% [9, 22, 24–26]. We observed a similar postoperative mortality rate of 1.2%. Alpard et al. noticed mortality rates of 2.7% and 7.8% for lobectomy and pneumonectomy, respectively [12]. Japanese researchers noted 30-day operative mortality rates of 1.2% and 3.2% for lobectomy and pneumonectomy, respectively [25]. Our data showed 30-day operative mortality rates

Table 2. Model of multivariate Cox analysis (hazard ratio, confidence interval)

Tabela 2. Model wielowymiarowej analizy Coxa (iloraz ryzyka, przedział ufności)

Parameter *Parametr*	Hazard ratio *Iloraz ryzyka*	95% confidence interval *95% przedział ufności*	p value *Wartość p*
Female sex/*Płeć żeńska*	0.63	0.43–0.91	0.01
Lack of clinical symptoms, except coughing *Brak objawów klinicznych, z wyjątkiem kaszlu*	0.73	0.55–0.97	0.03
Hb < 14g/dl	1.52	1.15–2.01	< 0.005
FEV1 < 80%	1.46	1.10–1.92	0.01
Pneumonectomy/*Pneumonektomia*	1.42	1.05–1.92	0.02
Adenocarcinoma/Rak gruczołowy	1.99	1.44–2.75	< 0.005
Stage IB/*Stadium IB*	2.01	1.14–3.55	0.02
Stage IIA/*Stadium IIA*	1.48	0.62–3.55	0.38
Stage IIB/*Stadium IIB*	3.06	1.74–5.39	< 0.005
Stage IIIA/*Stadium IIIA*	5.26	3.01–9.20	< 0.005
Stage IIIB/*Stadium IIIB*	7.38	3.39–16.08	< 0.005
Stage IV/*Stadium IV*	5.98	2.75–13.02	< 0.005

of 0.4% and 2.12%, for lobectomy and pneumonectomy, respectively. Such satisfying results were achieved mainly due to careful surgical technique (little blood loss) and accurate postoperative care.

Paroxysmal atrial fibrillation is the most common complication other than air leak. It occurs in about 20% of patients after lung cancer resection with peak onset on the second postoperative day. Its occurrence is associated with longer hospital stay, higher costs and higher in-hospital mortality [27]. Alpard et al. reported cardiovascular complication rates of 8.5% and 40% for lobectomy and pneumonectomy, respectively. Bronchopleural fistula occurred in 0.3% of lobectomy patients compared to 6.2% of those undergoing pneumonectomy [13]. In our material, the rates of cardiovascular complications and bronchopleural fistula were slightly lower than in literature, and these complications occurred more frequently after pneumonectomy (extended operation).

Van Zandwijk et al., Goya et al. and other authors demonstrated better long-term survival in women, also confirmed by our univariate and multivariate analysis [10, 21, 23, 26, 28]. This phenomenon might be explained by the reduced life expectancy of men due to their higher incidence of cardiovascular diseases, and extended procedures (pneumonectomy) due to centrally located squamous cell carcinoma [4, 18]. Olak et al. underlined women's increased susceptibility to lung cancer, which might be the result of increased susceptibility to the carcinogens in tobacco smoke, differences in nicotine metabolism, higher frequency of gene mutations, reduced capacity to repair damaged DNA and hormonal factors (oestrogen) [1, 4, 5].

Berardi et al., Doddoli et al., Goya et al., Radzikowska et al. and Wada et al. demonstrated worse prognosis in older patients, which was also confirmed in the presented study [22, 23, 26, 28–30]. However, Ghosh et al. did not prove that age influenced survival [9]. Surprisingly, our results were opposite to the Turkish observations that smoking had a negative influence on survival in Cox analysis [31]. In the present study, coughing was the main presenting symptom of lung cancer (41%) which made the patients visit family doctors. This was in accordance with other authors (33–46%) [14].

Cangir et al., similar to our data, confirmed the significant influence of reduced lung function (FEV1 < 60% of pred.) on prognosis in univariate and multivariate analysis [31]. Wassawa-Kintu et al. pointed out that reduced FEV1 was a significant risk factor for lung cancer, probably due to impaired ability to clear inhaled carcinogens from airways in lung dysfunction [5]. Many authors recommended a predicted postresectional FEV1 of 1.0 L [10].

Our observations were similar to the study carried out by Wada et al., which confirmed that pN and R status had prognostic significance [29]. Rostad et al. also noted better survival in patients of free resection margins [18]. Other authors also underlined the prognostic value of N status [30, 31]. In the literature two different techniques of lymphadenectomy were applied: a systematic lymph node dissection (MLND), consisting of all media-

stinal fatty tissue with lymphatics, and systematic lymph node sampling (MLNS), consisting of the removal of at least six lymph nodes from different stations. The arguments in favour of MLND were: more accurate staging, eradication otherwise undetected micrometastases, better local control and even improved survival [26, 32]. The argument against MLND was possibility of higher morbidity, e.g. bronchopleural fistula, phrenic and recurrent laryngeal nerve injury, chylothorax and hemothorax. In our department, different surgeons applied different methods of lymphadenectomy, but this issue was not separately analyzed.

T status is an unquestionable factor determining survival, confirmed by many authors such as Ghosh et al., Cangir et al., Doddoli et al. and Berardi et al. [9, 26, 30, 31]. In the present study we took the definition of T category from the Mountain 5th edition of TNM from 1997. However, many authors proposed re-definition of T1 criteria as tumours smaller than 2 cm and upgrading lesions larger than 5 cm to T3 according to Carbone's suggestion or to T2B according to Watanabe's ideas [31]. It was also suggested that tumours invading only the parietal pleura should be classified as T2, and tumours invading the phrenic nerve or vagus nerve, subclavian vessels or brachial plexus should be upgraded to T4 designation [33]. In our material, the influence of the exact size of tumour on survival was not analysed. It was only proven that the better survival rate was associated with tumours up to 3 cm in size (pT1).

In terms of prognosis, tumour stage as summarized in the TNM-system is the most important prognostic factor in the opinion of many authors [3, 10, 12, 18, 21, 22, 28, 31]. Increasing stage correlates with a worse prognosis. Similarly to our results, Naruke et al. demonstrated overlapping prognoses of patients with neighbouring stages: IB — 59.9% and IIA — 57.2% [3, 33]. In addition, Goya et al. revealed very similar long-term survival rates of patients in stages IB and IIA (60.1% and 59.9%, respectively), and in stages IIIB and IV (19.3% and 20.0%, respectively) [23]. Many authors noticed the relatively small number of patients in stage IIA, this observation was confirmed also in the present study [22, 33, 34]. These findings indicate the need to revise the stage grouping. Naruke et al. and Ikeda et al. showed a favourable 5-year survival rate of 80% in stage IA, contrary to the figure of 24% in stage IIIA [3, 19]. Alpard et al. and Dancey et al. reported the following 5-year survival rates: 70––75% in stage I, 30–40% — II and 10–20% — III [8, 12]. Considering the poor prognosis in NSCLC, except for stage IA, some authors suggested a multidisciplinary approach (chemo and radiotherapy) in early stages of disease, i.e. IIA and IIB [3, 8, 35].

In our material, females developed mainly adenocarcinoma (49%), while squamous cell carcinoma predominated in males (62%), similar to the prospective trial of Koyi et al. and to the study by Rostad et al. [14, 18]. Van Zandwijk et al. and Naruke et al. revealed better long-term survival in cases of squamous cell carcinoma, similar to our univariate and multivariate results [3, 21]. The observations of Alpard et al., Ghosh et al. and Beadsmoore et al. are alike [9, 11, 12, 22]. Contrary to our results, Japanese researchers have demonstrated better prognosis in patients with adenocarcinoma [23].

Wada et al. reported 8.3% pneumonectomies and 79% lobectomies in a group of 7 099 patients with NSCLC [25]. In the literature, the current percentage of pneumonectomies stands at approximately 20% [12]. However, Ponn et al. reported 23––53% pneumonectomies in patients with N2 disease treated by induction therapy [36]. In our retrospective material, the extent of the lung cancer forced the surgeons to perform pneumonectomy in 44% of cases as 32% of patients had centrally located lesions and 45% of them had endobronchial lesions. Almost half of all the patients were in stages IIB or IIIA. Rostad et al. underlined that pneumonectomy was associated with increased rate of postoperative complications and mortality in comparison with lobectomy [18]. Many authors suggested that pneumonectomy, as an extended resection, was a negative prognostic factor [31].

Italian researchers concluded that Hb levels lower that 10 g/dl were a negative prognostic factor in resected lung cancer patients [30]. Similar results were obtained in univariate and multivariate analyses of the presented study. Authors reported that about 40% of operated patients require postoperative blood transfusion, which was in accordance with our results (37%). As allogenic blood transfusion can, to a certain extent, expose patients to blood-borne viruses such as HBV, HCV and HIV, care should be taken to limit the amount of blood given perioperatively [9]. Ghosh et al. noted worse survival in patients with adenocarcinoma who underwent radical resection and required blood transfusion due to frequent relapse [9]. Contrary to our data, Berardi et al. did not observe any association between blood transfusion and survival after lung cancer resection, and did not advise preoperative correction of anaemia [30, 37].

Conclusions

Univariate analysis revealed several factors worsening prognosis: male sex, age older than 50 years, lowered preoperative Hb concentration, extended surgery, advanced stage, adenocarcinoma and large cell carcinoma, T status, N status, R status, M status and blood transfusion in postoperative period.

In multivariate Cox analysis: lowered preoperative Hb concentration, decreased FEV1 lower than 80% pred., extended surgery (pneumonectomy), advanced stage and adenocarcinoma were negative prognostic factors. Female sex and lack of symptoms, except coughing were positive prognostic factors.

The five-year survival rate for the whole group was 49.1%. Five-year survival of patients in stage IA was 81.7%, IB — 62.2%, IIA — 59.1%, IIB — 38%, IIIA — 21.3%, IIIB — 8.3% and IV — 8.3%.

References

1. Ginsberg M.S. Epidemiology of lung cancer. Semin. Roentgenol. 2005; 40: 83–89.
2. Orłowski T., Rudziński P. Torakochirurgia 2004 — raport. Kardiochirurgia i Torakochirurgia Polska 2005; 2: 146–158.
3. Naruke T. Surgery in locally advanced non-small cell lung cancer. Lung Cancer 2003; 42: S11–S15.
4. Olak J., Colson Y. Gender differences in lung cancer: Have we really come a long way, baby? J. Thorac. Cardiovasc. Surg. 2004; 128: 346–351.
5. Wassawa-Kintu S., Gan W.Q., Man S.F., Pare P.D., Sin D.D. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax 2005; 60: 570–575.
6. Kosacka M., Jankowska R. The epidemiology of lung cancer. Pneumonol. Alergol. Pol. 2007; 75: 76–80.
7. Bilfinger T. Surgical aspects in the treatment of lung cancer. Curr. Opin. Pulm. Med. 2004; 10: 261–265.
8. Dancey J., Le Chevalier T. Non-small cell lung cancer: an overview of current management. Eur. J. Cancer 1997; 33: S2–S7.
9. Ghosh S., Ahmed K., Hopkinson D.N., Vaughan R. Pulmonary adenocarcinoma is associated with poor long-term survival after surgical resection. Cancer 2004; 101: 2058–2066.
10. Hoffman P.C., Mauer A.M., Vokes E.E. Lung cancer. Lancet 2000; 355: 479–485.
11. Beadsmoore C.J., Screaton N.J. Classification, staging and prognosis of lung cancer. Eur. J. Radiol. 2003; 45: 8–17.
12. Alpard S.K., Zwischenberger B. Staging and surgery for non-small cell lung cancer (NSCLC). Surg. Oncol. 1999; 7: 25–43.
13. Ptaszek B., Chabowski M., Wiatr E. i wsp. Analysis of the treatment (neoadjuvant chemotherapy and surgery) in IIB and IIIA stages of non-small cell lung cancer. Pneumonol. Alergol. Pol. 2006; 74: 171–178.
14. Koyi H., Hillerdal G., Branden E. A prospective study of a total material of lung cancer from a county in Sweden 1997–1999: gender, symptoms, type, stage and smoking habits. Lung Cancer 2002; 36: 9–14.
15. Goldstraw P., Crowley J.J. The International Association for the Study of Lung Cancer. International Staging Project on Lung Cancer. J. Thorac. Oncol. 2006; 1: 281–286.
16. Marciniak M., Kolodziej J., Pawelczyk K. The place of surgery in multimodal therapy of lung cancer. Adv. Clin. Exp. Med. 2004; 13: 1073–1077.
17. Watanabe S., Oda M., Go T. i wsp. Should mediastinal nodal dissection be routinely undertaken in patients with peripheral small-sized (2 cm or less) lung cancer? Retrospective analysis of 225 patients. Eur. J. Cardiothorac. Surg. 2001; 20: 1007–1011.
18. Rostad H., Naalsund A., Strand T.E. i wsp. Results of pulmonary resection for lung cancer in Norway, patients older than 70 years. Eur. J. Cardiothorac. Surg. 2005; 27: 325–328.
19. Ikeda N., Hayashi A., Miura Y. i wsp. Present strategy of lung cancer screening and surgical management. Ann. Thorac. Cardiovasc. Surg. 2005; 11: 363–366.
20. Junker K. Prognostic factors in stage I/II non-small cell lung cancer. Lung Cancer 2001; 33 (supl. I): S17–S24.
21. Van Zandwijk N., Mooi W.J., Rodenhuis S. Prognostic factors in NSCLC. Recent experiences. Lung Cancer 1995; 12 (supl. I): S27–S33.
22. Van Rens M., Riviere A., Elbers H. i wsp. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. Chest 2000; 117: 374–379.
23. Goya T., Asamura H., Yoshimura H. i wsp. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. Lung Cancer 2005; 50: 227–234.
24. Damhuis R.A.M., Schutte P.R. Resection rates and postoperative mortality in 7899 patients with ling cancer. Lung Cancer 1996; 15: 151.
25. Wada H., Nakamura T., Nakamoto K., Maeda M., Watanabe Y. Thirty-day operative mortality for thoracotomy in lung cancer. J. Thorac. Cardiovasc. Surg. 1998; 115: 70–73.
26. Doddoli C., Aragon A., Barlesi F. i wsp. Does the extent of lymph node dissection influence outcome in patients with stage I non-small cell lung cancer. Eur. J. Cardiothorac. Surg. 2005; 27: 680–685.
27. Roselli E.E., Murthy S.C., Rice T.W. i wsp. Atrial fibrillation complicating lung cancer resection. J. Thorac. Cardiovasc. Surg. 2005; 130: 438–444.
28. Radzikowska E., Głaz P., Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. Ann. Oncol. 2002; 13: 1087–1093.
29. Wada H., Fukuse T., Hitomi S. Long-term survival of surgical cases of lung cancer. Lung Cancer 1995; 13: 269–274.
30. Berardi R., Brunelli A., Tamburrano T. i wsp. Perioperative anemia and blood transfusions as prognostic factors in patients undergoing resection for non-small cell lung cancers. Lung Cancer 2005; 49: 371–376.
31. Cangir A.K., Kutlaz H., Akal M., Gungor A., Oydemir N., Akaz H. Prognostic value of tumor size in non-small cell lung cancer larger than five centimeters in diameter. Lung Cancer 2004; 46: 325–331.
32. Lardinois D., Suter H., Hakki H., Rousson V., Betticher D., Ris H.B. Morbidity, survival and site of recurrence after mediastinal lymph node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann. Thorac. Surg. 2005; 80: 268–275.
33. Watanabe Y. TNM classification for lung cancer. Ann. Thorac. Cardiovasc. Surg. 2003; 9: 343–350.
34. Jassem J., Skokowski J., Dziadziuszko R. i wsp. Results of surgical treatment of non-small cell lung cancer: validation of the new postoperative pathologic TNM classification. J. Thorac. Cardiovasc. Surg. 2000; 119: 1141–1146.
35. Ginsberg R.J. Surgical resection for non-small cell lung cancer: the impact of chemotherapy. Lung Cancer 1997; 18 (supl. 2): 79–80.
36. Ponn R.B., LoCicero J., Daly B.D.T. Surgical treatment of non-small cell lung cancer. 1548–1581. W: Shields T.W., LoCicero J., Ponn R.B., Rusch V.W. (red.). General thoracic surgery. 6th edition. Lippincott Williams & Wilkins. Philadelphia, 2005.
37. Rzyman W., Dziadziuszko R., Skokowski J. i wsp. The influence of blood transfusion on survival in operated non-small cell lung cancer patients. J. Thorac. Cardiovasc. Surg. 2003; 126: 755–760.