

The impact of the sequence of pulmonary vessel ligation during anatomic resection for lung cancer on long-term survival – a prospective randomized trial

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ABSTRACT

Purpose: The aim of this prospective randomized trial was to assess the influence of the sequence of pulmonary vessel ligation, during anatomic resection, on long term survival in patients with NSCLC.

Material/Methods: This prospective randomized study included 385 patients treated surgically with lobectomy or pneumonectomy and standard lymphadenectomy between 1999 and 2003. Patients were randomly assigned to either primary ligation of the pulmonary artery or arteries (group A – 215 patients) or of the pulmonary vein or veins (group V – 170 patients). Patients were excluded if the sequence of vessel ligation was affected by technical difficulties or anatomic limitations. Univariate and multivariate analyses included: the sequence of vessel ligation, age, gender, tumor histology, stage (TNM), and cause of death (cancer related or non-cancer related).

Results: Median follow-up was 63 months. The groups were comparable regarding gender, histology, type of resection, and T, N, and overall stage. Overall, 5-year survival reached 50% in group A and 54% in group V ($p = 0.82$) and did not differ significantly in cancer related and non-cancer related deaths ($p = 0.67$ and $p = 0.26$, respectively). Univariate analysis identified higher T and N factors, advanced stage, pneumonectomy, male sex, and older age as negative prognostic factors. Multivariate analysis demonstrated that age, T3-4 disease, and nodal involvement were associated with inferior survival.

Conclusions: The sequence of pulmonary vessel ligation during anatomic resection for non-small cell lung cancer does not significantly affect long-term survival.

Key words: lung cancer, vessel ligation sequence, long-term survival

INTRODUCTION

Lung cancer (LC) is currently a major medical problem in Poland and throughout the world, as well as the most frequent cause of cancer-related mortality in men and women [1-6]. Despite advances in diagnostic and treatment methods, the results from curative treatment of lung cancer are still unsatisfactory. Treatment involves surgery in the majority of cases of non-small cell lung cancer (NSCLC), predominantly

in stage I and II. The efficacy of the treatment of lung cancer is dependent on many factors related and non-related to the surgical technique. The sequence of vessel closure by stapling or ligation during oncological resection may prevent blood-related metastases and influence long-term survival [7].

The aims of the analyses carried out in this study were to answer the following questions: Do prognostic factors, such as age at the time of diagnosis, gender, TNM stage, histological type of NSCLC, and the extent of resection of the pulmonary

tissue, influence the long-term results of surgical curative treatment of primary lung cancer (PLC)? Does the sequence of pulmonary vessel ligation, during anatomic resection in NSCLC, impact the long-term survival of patients operated on due to PLC and the occurrence of distant metastases in those patients?

MATERIALS AND METHODS

The analyzed group consisted of 385 patients diagnosed with PLC: 118 women and 267 men aged from 29 to 77 (the average age was 59.7 yrs and the median was 61 ± 8.36 yrs). The patients were radically operated on during the years 1999-2003 at the Thoracic Surgery Department in Szczecin-Zdunowo, Poland. The patients underwent anatomic resection (lobectomy or bilobectomy – 64% of cases, or pneumonectomy – 36%) and standard mediastinal lymphadenectomy. All patients were treated surgically in an open fashion by posterolateral thoracotomy. The average observation time was 61.5 months (the median was 63.5 ± 39.5 months). Forty-six (11.9%) patients underwent postoperative chemotherapy, 97 (25.1%) standard radiotherapy, and 57 (14.8%) palliative radiotherapy. All patients with pN2 (78 patients, 20.2%) received postoperative radiotherapy. Patients who underwent neoadjuvant therapy were excluded. This study was approved by Institutional Review Board (1/1997), all patients signed informed consent regarding surgery.

The sequence of vessel ligation was randomly chosen. Our randomization was achieved by a coin-toss performed by a person not involved into the study. At the beginning of our study in 1999 we were unable to perform computerized randomization. When it was available, we decided to continue traditional method to maintain the same randomization way for the entire group. Patients in whom the sequence of vessel ligation was forced, e.g. due to the extent or localization of tumor, technical problems, or other reasons, were excluded from the analysis. The techniques used for oncologic patients were used in all surgical procedures (avoiding touching and maneuvering the tumor, surgical margin free from malignancy, lymphadenectomy, etc.). In 215 patients (group A), the pulmonary artery or its branch providing blood flow to the tumor area was ligated first; whereas, in 170 patients (group V), the pulmonary vein or its branch was ligated first. Seventy-two (18.7%) patients lacked the preoperative histological diagnosis and the tumor located peripherally was resected by stapler for intraoperative pathologic examination before the proper resection. In that group, the pulmonary artery was ligated first in 42 patients; whereas, the pulmonary vein was ligated first in 30 patients. Data on the survival of patients were gathered directly from the patients, their families, or from the information collected by the West Pomeranian Department of the National Health Fund.

Statistical analysis was performed using Statistica 7.1 software and included Mann-Whitney U test, chi-square or Fisher exact test, univariate and multivariate analysis of survival (Cox proportional hazard model), and Kaplan-Meier survival curves. The statistical power for comparison of survival rates between patients in group A (n=215) and group V (n=170) was sufficient to detect with 80% probability the true difference equal to 15%. A p value <0.05 was considered significant.

RESULTS

Both groups, A and V, were comparable regarding gender, age, TNM stage, extent of resection, and time of observation (*Tab. 1*). The most frequent types of resection were right upper lobectomy (83 patients, 21.5%) and left pneumonectomy (78 patients, 20.2%). The dominant TNM stage was IB (40.2%) followed by IIB (25.7%) and IIIA (23.4%). Squamous cell carcinoma was diagnosed in 50.6% of patients and adenocarcinoma in 41.3%. Sixty-nine patients (17.9%) experienced distant metastases during follow-up. Overall, 5-year survival reached 50% in group A and 54% in group V ($p = 0.82$) and did not differ significantly between cancer related and non-cancer related deaths ($p = 0.67$ and $p = 0.26$, respectively) (*Fig. 1*, *Fig. 2*). The long term mortality rate at the end of observation for all patients was 13.2% for non-cancer related, 32.5% for cancer related, and 11.9% for unknown deaths. Overall, the long term survival rate was 42.3% (163 patients).

Factors that adversely affected survival in univariate analysis included more advanced T and N stage, male gender, older age (greater than 60 yrs at the time of diagnosis), and the more extensive type of resection (pneumonectomy) (*Fig. 3-7*). In multivariate analysis, only older age and more advanced T and N stage impacted worse survival for all groups (*Tab. 2*). It was observed that male gender, older age (more than 60 yrs), and advanced N stage (N1-2 vs N0) were independent factors of higher cancer-related mortality. Factors that had no significant effect on overall survival included histopathological type of NSCLC and the sequence of pulmonary vessel ligation (*Fig. 8*). The sequence of vessel ligation did not influence survival in the entire group as well as in the subgroups (TNM stage $p=0.81$, histology $p=0.67$, age < or > 60 years old $p=0.31$, sex $p=0.18$, type of resection $p=0.78$). It was noticed that in group V, fewer patients experienced blood-related metastases than in group A, but the difference was not statistically significant (14.7% vs. 20.5%, $p=0.18$) (*Fig. 9*). Blood – related or distant metastases in our study included brain, adrenal glands, bones, liver and opposite lung metastases. The non-significant difference between groups V and A was related to sequence of vessel ligation but not to tumor size or location. This finding suggests that ligating the

Figure 1. The influence of the sequence of pulmonary vessels ligation on the patients' survival considering cancer-related mortality ($p=0.67$).

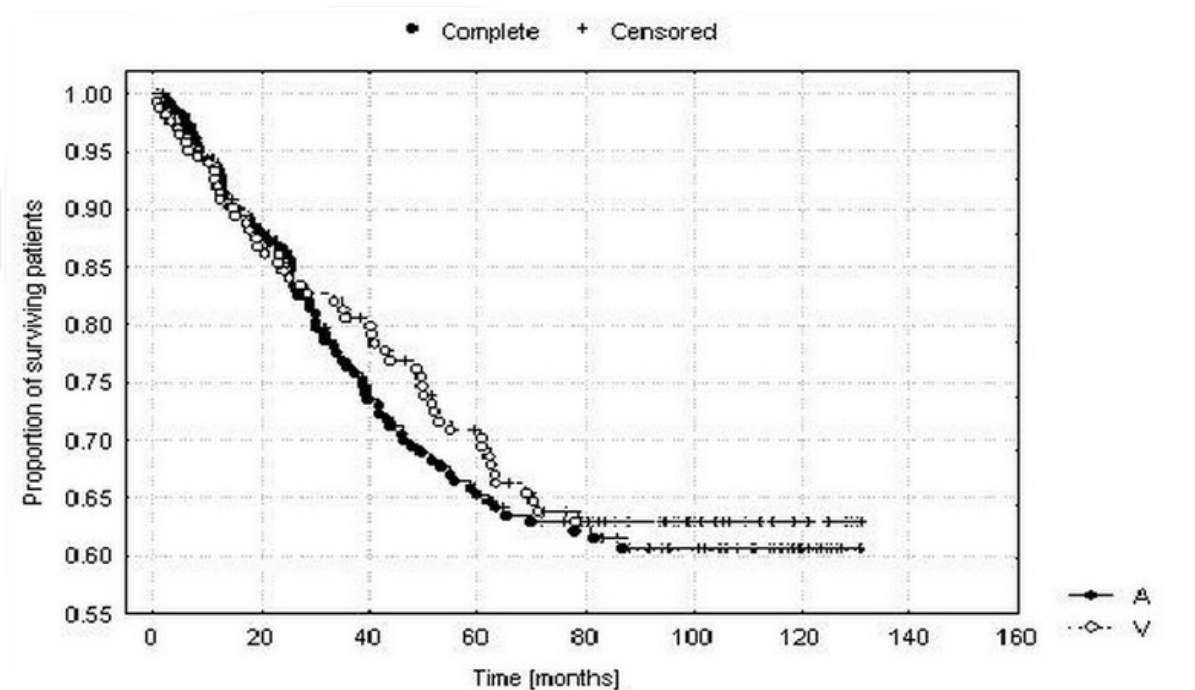
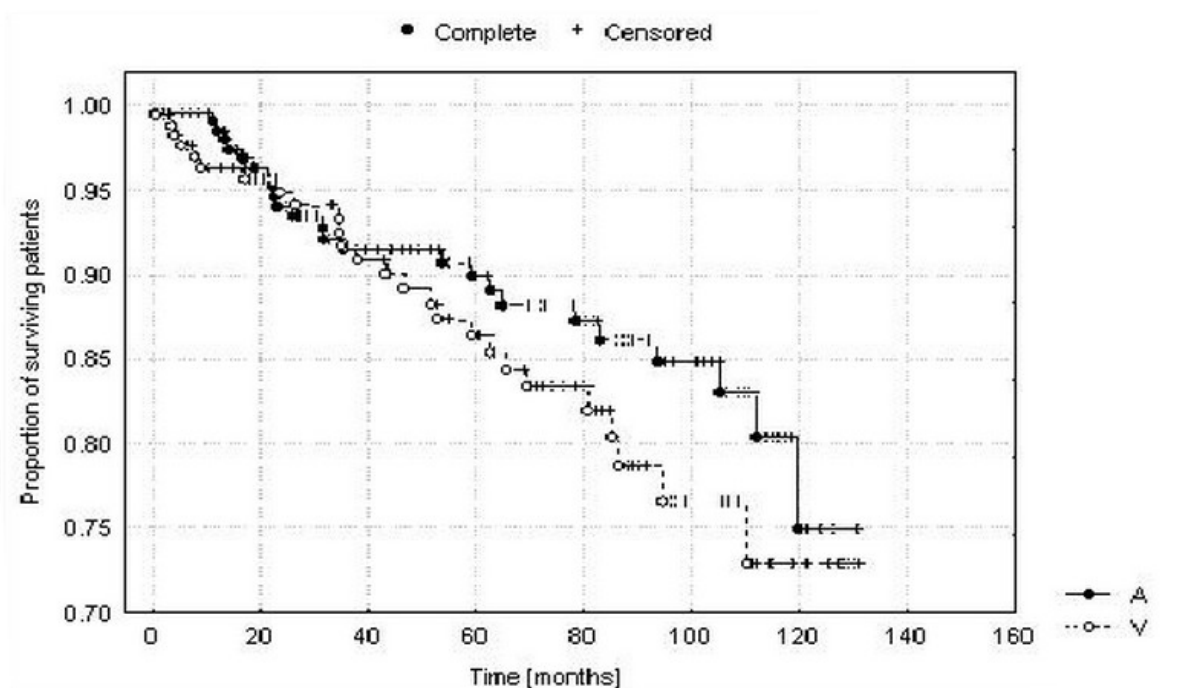


Figure 2. The influence of the sequence of pulmonary vessels ligation on the patients' survival considering non-cancer-related mortality ($p=0.26$).



pulmonary vein first may decrease the rate of hematogenous cancer cell dissemination and the occurrence of blood related metastases.

Last 50 specimens (lungs or lobes) resected from both groups (25 each) were weighted and we did not find significant

differences regarding weight for group V and A ($p=0.68$). We analyzed data regarding average blood loss, operating time, complication rate, pre- and postoperative hemoglobin level, length of stay and did not find significant differences between the groups (all differences $p>0.05$).

Figure 3. The influence of T factor on the patients' survival ($p=0.0030$).

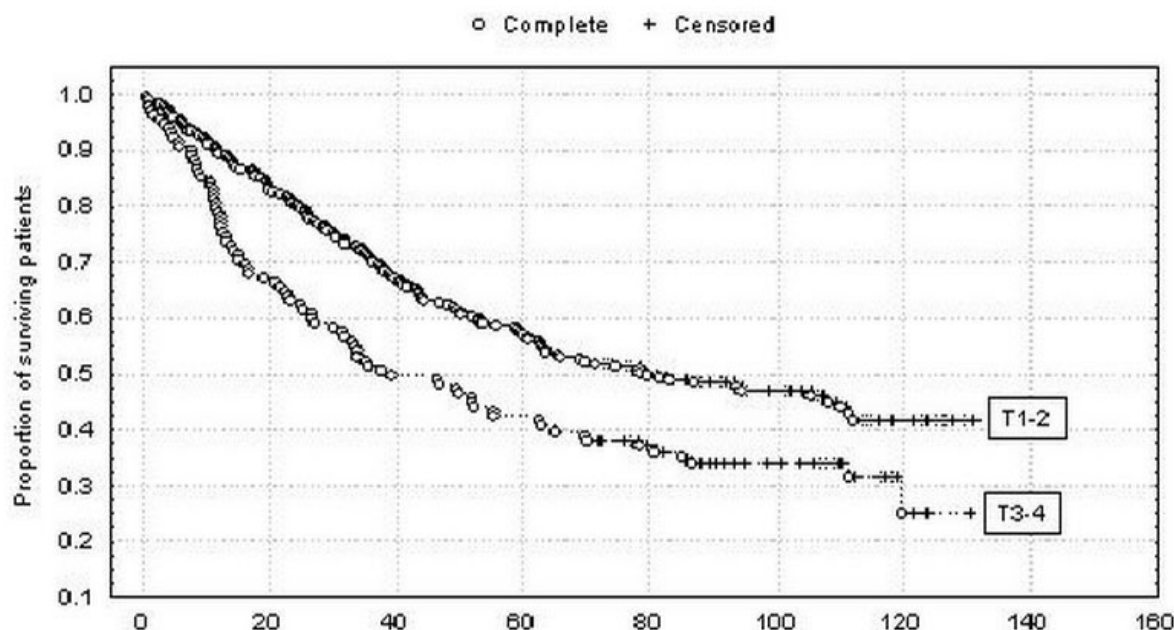
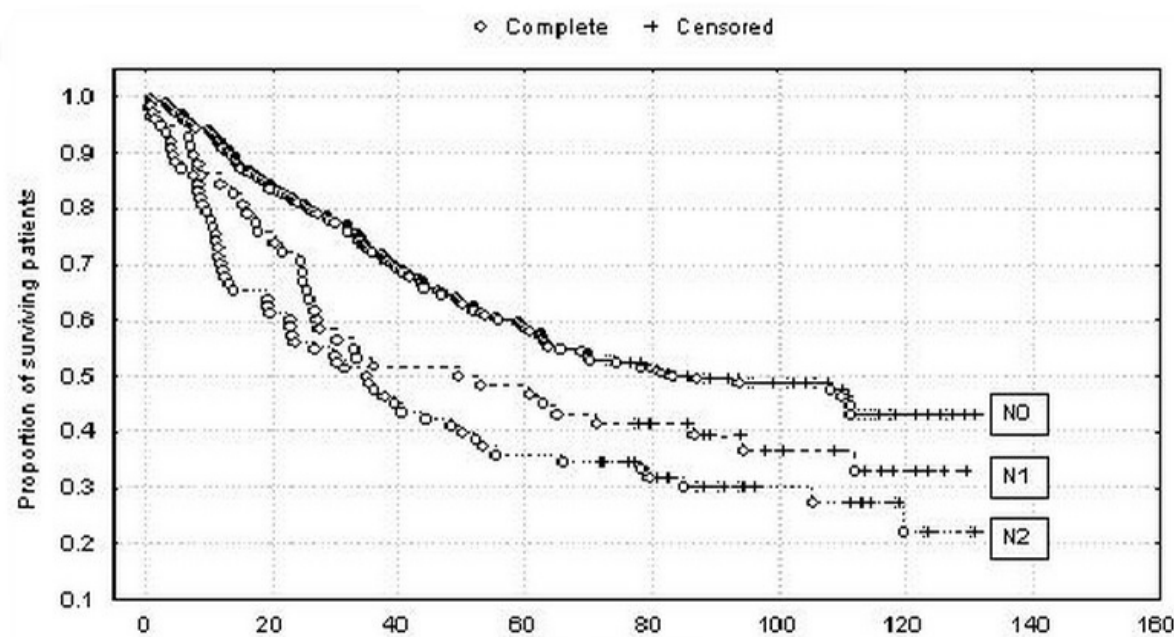


Figure 4. The influence of N factor on the patients' survival (N0 vs. N1: $p=0.065$, N1 vs. N2: $p=0.21$, N0 vs. N2: $p=0.00023$, N0 vs. N1-2: $p=0.00027$).



DISCUSSION

Lung cancer is the most common cause of cancer-related mortality in the world and usually requires combined treatments; yet, surgery remains the best curative option. It is disputable whether manipulation of the malignant tumor during resection may cause the release of cancer cells into the bloodstream and impact the occurrence of distant

metastases. Many thoracic surgeons recommend ligation of the pulmonary vein before the pulmonary artery.

This topic was analyzed by a few thoracic surgeons, but their conclusions varied. Their studies were not prospective randomized trials and also had other limitations. Refaely *et al.* [8] analyzed the results of surgical treatment of 279 patients who survived lobectomy for NSCLC from 1992 to 1998 and found 48% of patients had the vein interrupted before the artery and 52% had an artery ligated first. In multivariate

Figure 5. The influence of cancer clinical stage on the patients' survival (I vs. II: $p=0.00088$, I vs. III: $p=0.00003$; II vs. III: $p=0.42$).

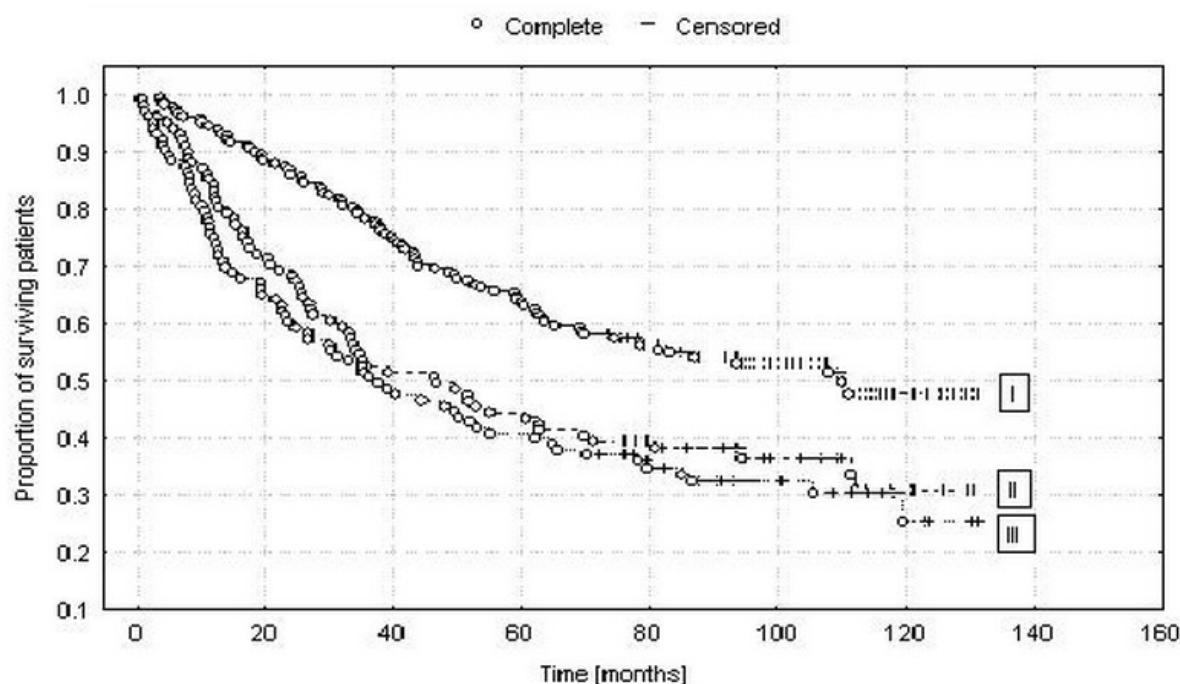
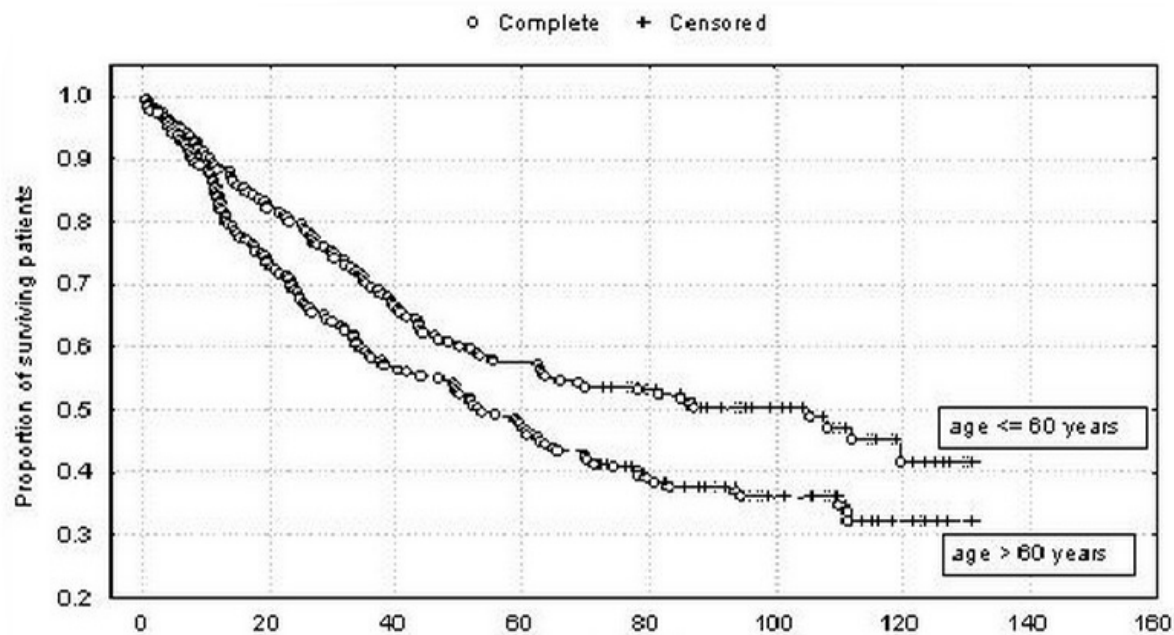


Figure 6. The influence of age on the patients' survival ($p=0.009$).



analysis, the total recurrence rates (artery-first 53%, vein-first 51%) were similar. Analysis revealed a risk for recurrence among patients with high disease stage and of male gender. Analysis by Refaely *et al.* [8] included a large group of patients but it was not a prospective randomized study. Grodzki *et al.* [9] analyzed whether the sequence of pulmonary vessel

ligation influences decreases in carcinoembryogenic antigen CEA serum levels in 155 anatomically and radically resected patients. CEA was measured before surgery and 7 days after. They concluded that the sequence of pulmonary vessel ligation does not influence the postoperative decrease in CEA serum levels. This study was not randomized either. Kurusu

Figure 7. The influence of extent of resection on patients' survival ($p=0.029$).

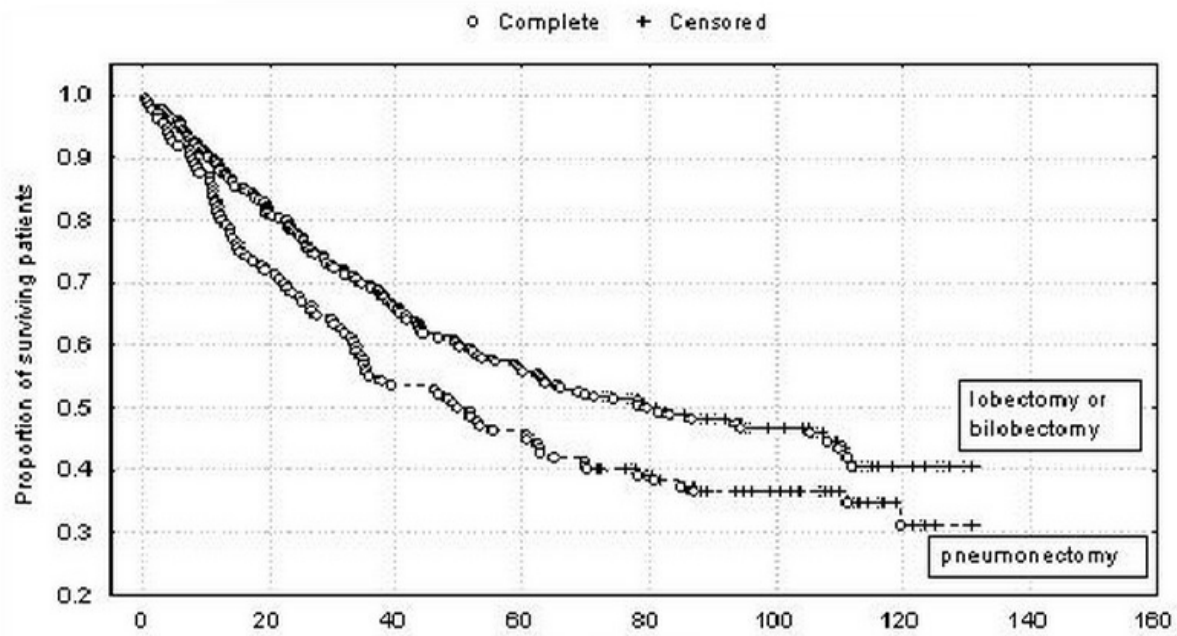
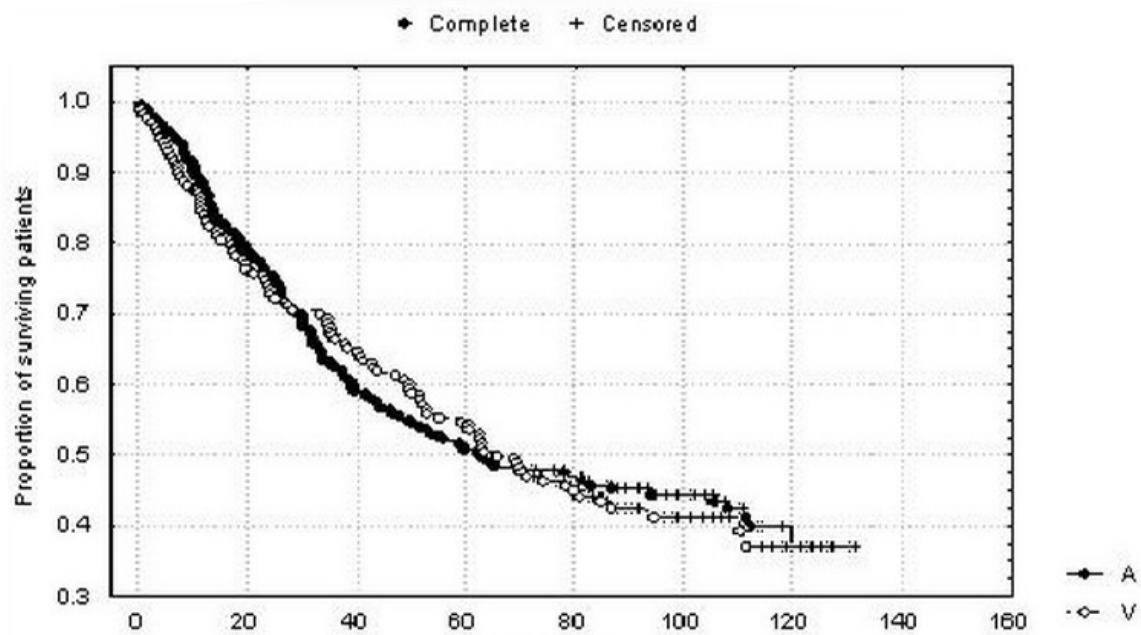


Figure 8. The influence of the sequence of pulmonary vessels ligation on the patients' survival ($p=0.82$).

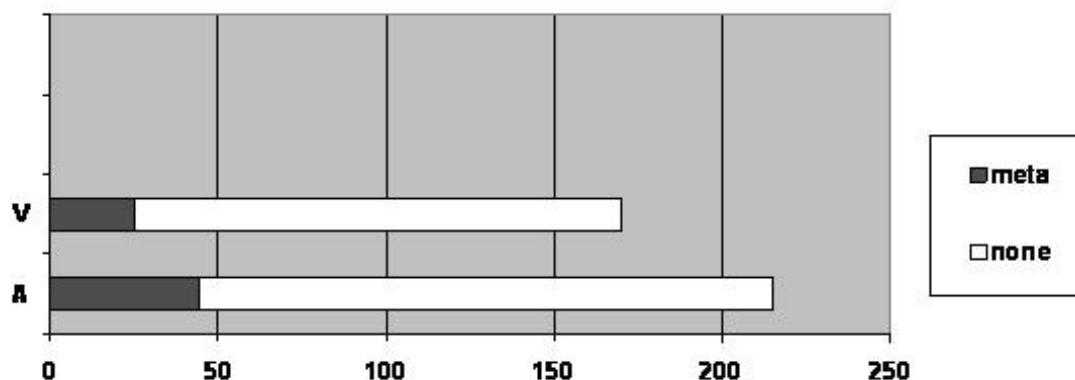


et al. [10] examined whether the sequence of vessel ligation during anatomical NSCLC resection affects the presence of circulating cancer cells, as reflected by CEA-mRNA. They assessed the presence of CEA-mRNA in peripheral blood samples taken before, during, and after the surgical procedure from 30 patients with NSCLC. They found 53% of patients had positive blood samples preoperatively, 85.7% had positive samples when an artery was ligated first, and 42.9% had positive samples when the vein was ligated first. These results suggest that many “operative” patients have disseminated

disease before operation and ligation of the vein first may prevent cancer cell dissemination intraoperatively. This study included a small group of patients. Ai and Zhang [11] assessed differences in pin1 mRNA expression, in blood samples from NSCLC patients, due to the sequence of pulmonary vessel ligation and found similar results.

In our study, age > 60 yrs. was a significant poor prognostic factor ($p=0.0090$), but we have to note that almost half of the deaths were non-cancer related; therefore, we should consider serious concomitant diseases in the long-term

Figure 9. The presence of blood-related metastases in A and V group ($p=0.18$).



prognosis. Similar conclusions were published by DeMaria *et al.* [12]. In contrast, Bryant *et al.* [13] found a significantly worse prognosis for patients younger than 45 yrs. suffering from NSCLC (51% vs. 62%; $p=0.037$). De Perrot *et al.* [14] examined three groups of patients (aged <60 yrs., 60 – 69 yrs., and > 70 yrs.) treated surgically due to NSCLC and did not find significant differences in survival ($p=0.19$). However, they observed more advanced disease and larger numbers of explorative thoracotomies and pneumonectomies in the groups older than 60 yrs. The long-term prognosis was better for the patients treated with lobectomy or bilobectomy vs. pneumonectomy in our study ($p=0.05$), which is in accordance with the studies by Rami-Porta *et al.* [15] and Puri *et al.* [16]. Currently, we are trying to perform segmentectomies in selected stage IA patients but lobectomy remains the “gold standard” for NSCLC patients in our department.

This was a completely prospective, randomized, large, and long-term study comparing two groups of patients comparable regarding gender, age, TNM stage, extent of resection, and time of observation. All patients in whom the surgeon’s decision regarding the sequence of vessel ligation was somehow forced, due to technical difficulties or the extent of the tumor, were excluded from the study. The potential limitations of our study are: the differences in the size of the groups A and V (215 vs 170) despite blind randomization, the relatively large number of patients with N2 disease confirmed postoperatively and treated with radiotherapy or radiochemotherapy, several surgeons performed the surgeries that were otherwise comparable regarding technique and oncologic principles, and a relatively large number of pneumonectomies.

CONCLUSIONS

We conclude that our results did not show statistically significant influence of the sequence of pulmonary vessel ligation, especially on the long term survival. It was noticed that in the group V (ligation of a pulmonary vein first), less

blood-related metastases were observed than in the group A (ligation of a pulmonary artery first) but these differences were not statistically significant ($p=0.18$). Negative prognostic factors for survival in NSCLC patients in this study were: older age, male gender, more advanced TNM stage and more extended type of resection.

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