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# The impact of cardiovascular *comorbidity* on the outcome of surgery for stage I and II non-small-cell lung cancer☆

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**Abstract**

**Objective**: The association between lung malignancy and cardiovascular disease has been frequently reported though its therapeutic and prognostic implications not thoroughly analyzed. This study aims at assessing the possible impact of coexisting cardiovascular disease on the outcome of surgical treatment of non small cell lung cancer (NSCLC). **Methods**: Among 247 consecutive patients undergone surgery for stage I and II NSCLC between 1990 and 1997, 34 (13.7%) had a cardiovascular *comorbidity* going to be treated by surgery, namely coronary artery disease ($n = 14$), carotid stenosis ($n = 21$), abdominal aortic aneurysm ($n = 9$) and lower limbs arteriopathy ($n = 7$). Among 22 patients (64.7%) who underwent cardiac/vascular surgery first, operation was performed after a median interval of 4.5 weeks. In five of this subset lung cancer was incidentally detected. In the other patients the cardiovascular disease was diagnosed and treated after the lung cancer had been detected and operated with a median interval of 3.5 months from thoracic procedure. Surgical procedures for lung cancer were three pneumonectomies, 12 lobectomies, 19 wedge resections. Uni and multivariate analysis for risk factors was carried out. **Results**: In the group with cardiovascular comorbidity overall postoperative mortality was 9%, while morbidity rate was 58.8%, both of them primarily caused by cardiovascular disease and significantly higher for major resections. The 3- and 5-year survival rates were 54.8% and 35.5% compared to 69.2% and 56.4% among patients without cardiovascular comorbidity ($P = 0.01$) while the timing of vascular surgery (before or after thoracic procedure) did not significantly affect survival. Multifocal vascular disease resulted the only positive factor at multivariate analysis ($P = 0.005$, Odd Ratio = 3.51, 95% Confidence Interval = 1.4–8.4). **Conclusions**: Cardiovascular disease seems to have significant impact on survival and morbidity in patients undergone surgery for lung cancer, especially in presence of multifocal vascular disease and following major resections. The timing of vascular surgery and the extension of resection should rely on the severity of vascular disease, anaesthesiologist's and surgeon's final evaluation.


*Keywords:* Lung cancer; Vascular disease; Surgery

## 1. Introduction

The presence of concomitant diseases (comorbidity) in non-small cell lung cancer (NSCLC) is not infrequent and has always been considered as a significant prognostic factor yet in an anecdotic fashion. Theoretically it can result in a greater probability of death in the initial stages of NSCLC. As a matter of fact between 19 and 30% of pT1N0M0 NSCLC patients that undergo surgery die as a result of other diseases [1,2].

The need for evaluating prognostic factors that are independent of the anatomic extension of the tumour (TNM) and the type of surgical procedure has been already recognised [3]. The presence of clinical data and/or symptoms of comorbidity has been evaluated repeatedly as an additional prognostic factor [4] and specifically in patients with NSCLC an increasing proportion of comorbidity in relation to age has been found [5].

In patients with lung cancer the likelihood of also having other disorders such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease is statistically significant, given the association of both disorders with the

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main etiologic factor (i.e. tobacco) and the greater probability that patients with COPD have of developing NSCLC. Significantly, among patients who are operated upon for peripheral vascular disease lung cancer has been found in up to 3.25% [6] while concomitant coronary artery disease is present in 13.2–28% of cases [7–9].

The advantage of knowing about the existence of cardiovascular comorbidity may provide the clinician with the ability to select poor prognosis patients and establish a better treatment strategy. Studied prognostic factors in the evaluation of the outcome of surgery for such a subgroup of patients include the timing of surgical procedure, the extension of lung resection, the type of cardiovascular procedure and additional general risk factors [10].

The timing of surgical approach may be concomitant or staged, the latter being controversial between vascular or thoracic procedure as first step. A few studies dealt specifically with the timing of cardiac surgery in patients with NSCLC while, to our knowledge, no report exists approaching the issue of the timing for vascular surgery [9, 11].

This study aims at analyzing possible risk factors related to shorter survival rate in patients with NSCLC and cardiovascular *comorbidity*, and the possible impact of such comorbidity on the outcome of surgery for stage I and II NSCLC. In our series we pooled out a subset of patients that required surgical treatment also for a cardiovascular *comorbidity*.

Furthermore the effect of the surgical timing was also taken into consideration in order to find out a more suitable therapeutic approach. To this purpose 247 patients undergone surgery for stage I and II NSCLC were retrospectively evaluated in a single thoracic surgery university centre over an 8 year period with a minimum 5-year follow up.

## 2. Patients and method

### 2.1. General population

At the Thoracic Surgery Department of the Tor Vergata University of Rome, from January 1990 to June 1997, 247 consecutive patients underwent radical surgery for stage I (T1-T2N0M0) or II (T1N1M0 and T2N1M0 and T3N0) NSCLC. The patients were staged according to operative and pathological findings based on AJCC/UICC-TNM classification and stage grouping [12].

Preoperative staging always included complete clinical history and physical examination, blood cell count with differential, serum biochemistry, urinalysis, plain chest roentgenogram, respiratory functional tests, electrocardiogram and cardiac examination, total body computed tomography (CT) scan and fibrobronchoscopy. Only enlarged (greater than 1.5 cm in the maximal diameter) [13] mediastinal lymph nodes were preoperatively sampled, either by mediastinoscopy or video-thoracoscopy.

Bone scan was performed only when symptoms were present or alkaline phosphatase level was 50% greater than normal limits.

In the presence of symptomatic or previously documented cardiovascular disease, echocardiography, cardiopulmonary stress test, neck and lower limb ultrasound studies were always performed. When necessary, the evaluation also included angiographic examinations.

Postoperative follow up included clinical exam, blood biochemistry, serum tumour marker assay and chest x-ray, to be performed every 3 months for the first 2 years and thereafter twice per year. Total body CT-scan was done twice per year for the first 2 years and then yearly.

### 2.2. Selection criteria

Data regarding the presence of cardiovascular *comorbidity* were retrieved by patient records. Considered cardiovascular diseases were those susceptible of surgical treatment and were defined as follows: (a) cardiac ischemia suspected by electrocardiogram and ascertained by coronarography showing critical obstruction of left main coronary artery or triple-vessel disease, intractable or unstable angina. (b) Abdominal aortic aneurysm diagnosed at CT scan with a diameter equal or greater than 5 cm. (c) Critical unilateral carotid stenosis without compensatory circuit or evidence of irregular potentially embolising atheromatous plaque. (d) Critical iliac or femoral artery stenosis with angiographic evidence of a patent distal circuit.

According to the severity of the symptoms of both diseases the patients were categorized into three classes: (1) patients with neglected or ignored disease discovered during workup for NSCLC; (2) patients with both symptomatic diseases; (3) patients with occult NSCLC diagnosed during a workup for a cardiovascular disease. History and symptoms related to cardiovascular disease were myocardial infarction, angina, cerebral ischemia, and claudication due to limb ischemia. Symptoms related to NSCLC were chest pain, cough, bronchopneumonia, fever, dyspnoea, weight loss, haemoptysis, and anaemia.

We analysed generic (i.e. age and sex) as well as specific risk factors related to extension and severity of the tumour (i.e. stage, histology, grading), and to extension of surgical resection (i.e. minimal vs. anatomical). Specifically investigated comorbidity factors were: total cholesterol level greater than or equal to 220 mg/dl, diastolic blood pressure greater than or equal to 90 mmHg, blood glucose greater than or equal to 110 mg/dl, total bilirubin level greater than or equal to 1.5 mg/dl, serum creatinine level greater than or equal to 1.5 mg/dl, COPD (FEV1/FVC lower than or equal to 87%) [14], alcohol or drug abuse, multifocal cardiovascular disease, and smoking.

Finally, timing of both thoracic and cardiovascular procedures was taken into account; staged thoracic before cardiovascular procedure and vice versa were investigated as specific factors capable of influencing short and long-term survival.

### 2.3. Study population

According to our review 34 out of the 247 patients (13.7%) had a significant cardiovascular *comorbidity*. Distribution for generic and specific risk factor is reported in Table 1, while characteristics of the cardiovascular patients are summarized in Table 2. Coronary artery disease was present in 14 patients (41.1%), carotid stenosis in 21 (61.7%), abdominal aortic aneurysm in nine (26.4%) and lower limbs arteriopathy in seven (20.5%).

Patients with multifocal cardiovascular disease were 17. Twelve patients (35%) had no history of cardiovascular disease, 17 (50%) had a previous history of cardiovascular disease and the tumour was symptomatic, and only five (15%) had occult tumour.

Twenty-two patients (64.7%) underwent the cardiovascular procedure as first. Lung cancer was operated after a median interval of 4.5 weeks (interquartile 2–17). In the other patients the cardiovascular disease was operated after a median period of 12 (interquartile 2–52) weeks.

### 2.4. Statistical analysis

Univariate analysis was conducted among factors capable of conditioning intergroup differences. All tests were two-tailed with a 0.05 level of significance.

Survival curves were estimated using the Kaplan–Meier method [15] and the significance test was based on the log-rank test as given by Mantel [16]. The survival time was counted from the day of thoracic surgery. Recurrence was considered any new neoplastic lesion, second primaries included. All causes of death were treated as final events. Major factors capable of influencing recurrence or death were entered in a regression Cox's proportional hazards model [17] for a multivariate analysis.

## 3. Results

Thirty-day postoperative mortality after the thoracic procedure was 3/34 (9%), significantly higher than post-operative mortality reported in the entire group (5/213, 2.5%) ($P = 0.0001$). All three patients had undergone a major resection and the cause of death was related to cardiovascular disease. No postoperative mortality was recorded after the vascular surgery as second procedure.

Postoperative morbidity was significantly higher 20/34 (59%) than that found in the overall group 46/213 (21%) ($P = 0.0001$). Moreover morbidity rate was significantly related to the extension of the resection, namely in 12 out of 15 major resections (80%) versus eight out of 19 minimal resections (41%) respectively ($P = 0.0001$). Causes of

Table 1
Distribution of generic and specific comorbidity risk factors among patients with ($n = 34$) and without ($n = 213$) cardiovascular disease[a]

| Risk factors | General | Cardiovascular | *P* value* |
|---|---|---|---|
| Age mean ± SD | 63 ± 9.6 | 70 ± 6.7 | < 0.0001 |
| Age > 70 years (%) | 53 (25%) | 18 (53%) | < 0.0001 |
| Sex (male vs. female) | 169 vs. 44 | 31 vs. 3 | NS |
| Stage IA (%) | 98 (46%) | 11 (32%) | |
| Stage IB-IIA (%) | 90 (42%) | 15 (44%) | NS |
| Stage IIB (%) | 25 (12%) | 8 (24%) | |
| Histology (squamous vs. non) | 105 vs. 108 | 15 vs. 19 | NS |
| Grading (1 vs. 2 vs. 3) | 68 vs. 102 vs. 43 | 10 vs. 15 vs. 9 | NS |
| Minimal (%) | 37 (18%) | 19 (56%) | |
| Lobectomy (%) | 124 (57%) | 12 (35%) | 0.001 |
| Pneumonectomy (%) | 54 (25%) | 3 (9%) | |
| FEV1$^3$75% (%) | 90 (42%) | 16 (47%) | NS |
| Glicemia mean ± SD | 106 ± 26 | 113 ± 18 | NS |
| Hyperglicemia ≥ 110 mg/dl (%) | 64 (39%)* | 23 (70%) | 0.002 |
| Cholesterol mean ± SD | 196 ± 38 | 218 ± 35 | 0.002 |
| Hypercholesterolemia ≥ 220 mg/dl (%) | 63 (38%)* | 24 (71%) | 0.001 |
| Creatinine mean ± SD | 1.00 ± 0.3 | 1.17 ± 0.6 | NS |
| Hypercreatinine ≥ 1.5 mg/dl (%) | 17 (10%)* | 8 (24%) | 0.03 |
| Bilirubin mean ± SD | 0.90 ± 0.4 | 1.07 ± 0.5 | NS |
| Hyperbilirubin ≥ 1.5 mg/dl (%) | 19 (12%)* | 9 (26%) | 0.02 |
| Blood diastolic pressure mean ± SD | 82 ± 10 | 86 ± 7 | 0.01 |
| Diastolic hypertension ≥ 90mmHg (%) | 61 (37%)* | 19 (55%) | 0.04 |
| Alcohol or drug abuser (%) | 18 (8%) | 5 (15%) | NS |
| Smoke abuser (%) | 170 (80%) | 30 (88%) | NS |
| Median survival (months) | 78 | 44 | 0.01 |

[a] *164 pts.

Table 2
Main features of patients with cardiovascular disease

| N | Age | Sex | Cardio-vascular disease | Cardio-vascular surgery | Surgical interval[a] (weeks) | Cancer surgery | Histology | Stage | Outcome from cancer surgery |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 78 | M | Carotid | Endoarterectomy | 2 | Wedge | Squamous cell | Ia | Dead at 44 months for cerebral stroke |
| 2 | 57 | M | Heart Carotid | Cardiac bypass Endoarterectomy | 8 | Lobectomy | Large cell | Ib | Dead early for infection |
| 3 | 71 | M | Heart Limb | Cardiac bypass Aorto-femoral graft | 2 | Lobectomy | Adenocarcinoma | Ib | Dead at 4 months for local recurrence |
| 4 | 71 | F | Carotid | Endoarterectomy | 2 | Wedge | Squamous cell | Ia | Dead at 36 months for generalized disease |
| 5 | 51 | M | Limb | Aorto-femoral graft | 2 | Wedge | Large cell | IIa | Alive at 84 months |
| 6 | 67 | M | Heart Carotid | Cardiac bypass Endoarterectomy | −12 | Lobectomy | Squamous cell | Ib | Dead at 6 months for pulmonary edema |
| 7 | 69 | M | Heart Aortic aneurysm | Cardiac bypass off-pump Prosthesis substitution | 26 | Lobectomy | Adenocarcinoma | IIa | Dead early for cardiac ischemia |
| 8 | 69 | M | Carotid | Endoarterectomy | −24 | Lobectomy | Large cell | Ib | Dead at 15 months for brain metastases |
| 9 | 80 | M | Heart Carotid | Cardiac bypass Endoarterectomy | −2 | Wedge | Squamous cell | Ia | Dead at 7 months for cardiac ischemia |
| 10 | 71 | F | Heart Aortic aneurysm | Cardiac bypass Prosthesis substitution | 4 | Lobectomy | Adenocarcinoma | Ia | Dead early for multi organ failure |
| 11 | 68 | M | Heart Carotid | Cardiac bypass off-pump Endoarterectomy | 4 | Lobectomy | Adenocarcinoma | Ia | Dead early for cardiac ischemia |
| 12 | 58 | M | Limb Carotid | Aorto-femoral graft Endoarterectomy | −2 | Wedge | Large cell | IIa | Dead at 56 months for generalized disease |
| 13 | 69 | M | Carotid | Endoarterectomy | −2 | Wedge | Squamous cell | Ib | Alive at 71 months |
| 14 | 78 | M | Limb Heart | Aorto-femoral graft Cardiac angioplasty | −4 | Wedge | Squamous cell | Ib | Dead at 7 months for generalized disease |
| 15 | 69 | M | Limb | Aorto-femoral graft | −4 | Wedge | Squamous cell | IIa | Alive at 87 months |
| 16 | 77 | M | Carotid Heart | Endoarterectomy Cardiac angioplasty | −2 | Wedge | Adenocarcinoma | Ib | Dead at 12 months for cerebral stroke |
| 17 | 74 | M | Aortic aneurysm | Prosthesis substitution | 17 | Wedge | Squamous cell | Ib | Dead at 47 months for cardiac ischemia |
| 18 | 71 | M | Carotid Aortic aneurysm | Endoarterectomy Prosthesis substitution | 34 | Pneumonectomy | Adenocarcinoma | Ia | Dead at 51 months for brain metastases |
| 19 | 69 | M | Aortic aneurysm | Prosthesis substitution | −52 | Lobectomy | Squamous cell | Ib | Dead at 20 months for brain metastases |
| 20 | 73 | F | Limb | Aorto-femoral graft | −108 | Lobectomy | Squamous cell | IIa | Alive at 80 months |
| 21 | 60 | M | Carotid | Endoarterectomy | −148 | Lobectomy | Adenocarcinoma | Ia | Alive at 98 months |
| 22 | 65 | M | Limb Carotid | Aorto-femoral graft Endoarterectomy | 2 | Pneumonectomy | Adenocarcinoma | Ib | Dead at 76 months for cardiac ischemia |
| 23 | 76 | M | Aortic aneurysm | Prosthesis substitution | 13 | Wedge | Squamous cell | Ib | Dead at 26 months for local recurrence |
| 24 | 73 | M | Heart Aortic aneurysm | Cardiac bypass Prosthesis substitution | −40 | Lobectomy | Large cell | Ia | Dead at 73 months for generalized disease |
| 25 | 76 | M | Heart Carotid | Cardiac bypass Endoarterectomy | 3 | Wedge | Large cell | IIa | Dead at 54 months for local recurrence |
| 26 | 74 | M | Carotid | Endoarterectomy | 4 | Wedge | Adenocarcinoma | Ib | Alive at 84 months |
| 27 | 64 | M | Carotid | Endoarterectomy | 36 | Wedge | Adenocarcinoma | IIa | Alive at 105 months |
| 28 | 82 | M | Heart Aortic Aneurysm | Cardiac angioplasty Prosthesis substitution | 3 | Wedge | Squamous cell | Ib | Dead at 36 months for cardiac ischemia |
| 29 | 71 | M | Carotid | Endoarterectomy | 31 | Lobectomy | Adenocarcinoma | Ia | Alive at 74 months |
| 30 | 73 | M | Heart Carotid | Cardiac bypass off-pump Endoarterectomy | 26 | Wedge | Squamous cell | Ib | Dead at 3 months for local recurrence |
| 31 | 70 | M | Heart Carotid | Cardiac bypass off-pump Endoarterectomy | 5 | Pneumonectomy | Adenocarcinoma | Ia | Dead at 25 months for generalized disease |
| 32 | 78 | M | Limb | Aorto-femoral graft | 13 | Wedge | Squamous cell | Ib | Alive at 62 months |
| 33 | 65 | M | Carotid | Endoarterectomy | 2 | Wedge | Adenocarcinoma | Ia | Dead at 13 months for local recurrence |
| 34 | 66 | M | Carotid | Endoarterectomy | 6 | Wedge | Squamous cell | IIa | Dead at 50 months for generalized disease |

[a] Cardiovascular operation−lung operation.

morbidity were cardiac arrhythmia ($n = 18$), myocardial infarction ($n = 4$), transient ischemic cerebral attack ($n = 9$), lower limb acute ischemia ($n = 4$), renal insufficiency ($n = 4$), and medullary ischemia ($n = 1$).

The cardiovascular patients were followed for a minimum period of 5 years and a maximum of 10 years. Nine patients are still alive while 15 died of progression of neoplastic disease and ten following cardiovascular complications (Table 2). Median survival was 44 months for all patients, in the patients with multifocal cardiovascular disease it went down to 20 months, and to barely 7 months for patients with cardiac disease.

The 3- and 5-year survival rates in patients with cardiovascular *comorbidity* were 54.8% and 35.5% respectively. On the other hand 69.2% and 56.4% were the 3 and 5 year survival rates among patients without any cardiovascular *comorbidity* ($P = 0.01$) (Fig. 1). The same survival analysis was conducted for the specific cause of death (Fig. 2): as expected a highly significant difference was found for cardiovascular-related cause of death in the group with comorbidity, whereas no difference resulted for cancer-related death. When reorganized for stage, in patients with stage IA the 55.6% 3-year and 33.3% 5-year survival rates were significantly lower than those recorded in patients without cardiovascular disease ($P = 0.003$) (Fig. 3). Significant differences were also demonstrated for stage IB-IIA in which survival was 35.7% and 28.6% at 3 and 5 years ($P = 0.04$), respectively (Fig. 4).

Generic, tumour-related, surgery-related and comorbidity risk factors described in the Section 2 were examined. Factors resulted significantly related with survival were only stage ($P = 0.001$) and multifocal cardiovascular disease ($P = 0.002$). Timing of the surgery for the cardiovascular disease did not significantly affect survival.

At multivariate analysis by the Cox regression multifocal vascular disease was the only positive factor affecting significantly the survival rate ($P = 0.005$, Odd Ratio $= 3.51$, 95% Confidence Interval $= 1.4$–$8.4$).

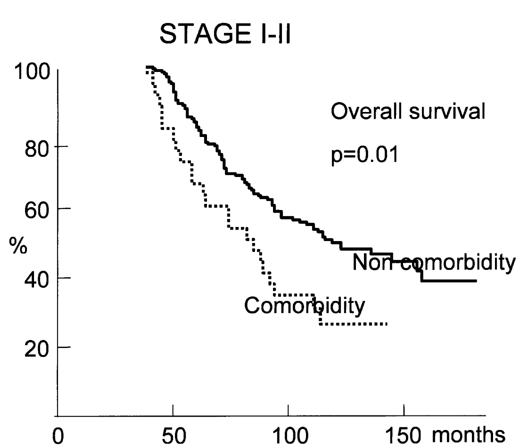


Fig. 1. Kaplan–Meier curves of the whole study population stratified for presence (dotted line) or absence (continuous line) of the cardiovascular disease. The 5-year overall survival rate was 56.4% vs. 35.5% ($P = 0.01$).

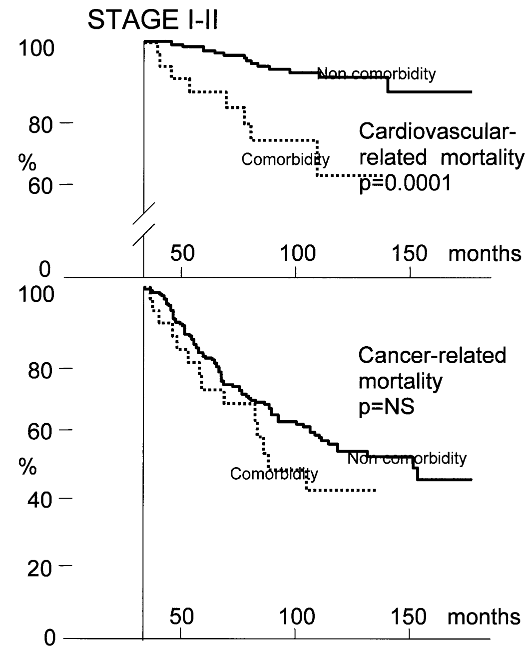


Fig. 2. Kaplan–Meier curves of the whole study population stratified for presence (dotted line) or absence (continuous line) of the cardiovascular disease according to cardiovascular-related ($P = 0.0001$) and cancer-related (not significant) cause of death.

## 4. Discussion

For patients with NSCLC surgical resection remains the only curative option. This is true especially for those cases in which the tumour has not overcome the limits of localized disease. Comorbidity defines the occurrence of bronchogenic carcinoma in association with other disorders [4]. The consistent rate of coexistent medical conditions in these patients not only may jeopardize their selection for a surgical treatment but also may worsen the final outcome. The surgeon is often faced with the issue of planning lung resection in a patient with significant coexisting disease.

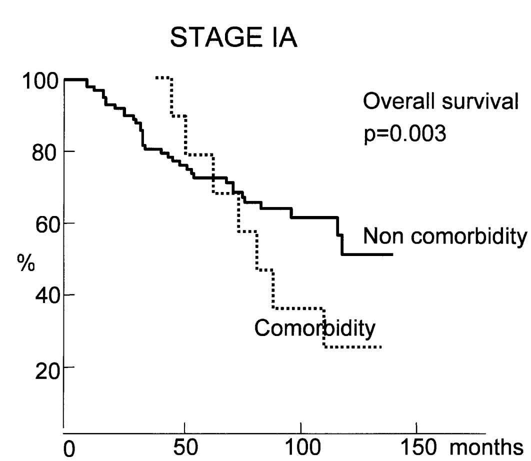


Fig. 3. Kaplan–Meier curves for stage IA population. The 5-year overall survival rate was 71.9% for group without cardiovascular disease (continuous line) and 33.3% for the group with cardiovascular disease ($P = 0.003$).

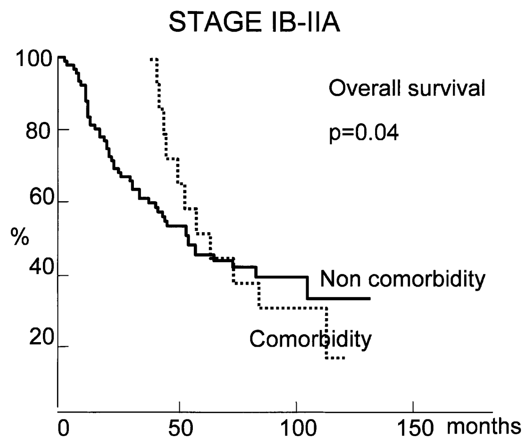


Fig. 4. Kaplan–Meier curves for stage IB-IIA population. The 5-year overall survival rate was 43.5% for group without cardiovascular disease (continuous line) and 28.6% for the group with cardiovascular disease ($P = 0.04$).

As a matter of fact, cigarette smoking is highly associated with the development of lung carcinoma but the incidence increases further in smokers who are also affected by COPD [5]. Both smoking and chronic respiratory disorders are associated with atherosclerotic vascular disease, making these conditions prevalent in patients with lung carcinoma. For this reason the prevalence of lung carcinoma in patients admitted for elective vascular surgery has been evaluated [18]. Moreover the coexistence of vascular disease in patients with lung cancer has been investigated [8]. Yet no author, to our knowledge, has thoroughly assessed the impact of cardiovascular comorbidity on morbidity and mortality of lung cancer patients undergone surgical treatment.

In our series of Stage I and II NSCLC patients we pooled out a subset that required surgical treatment also for a concomitant cardiovascular disease. Thereafter generic as well as specific risk factors related to extension and severity of the tumour and to extension of surgical resection and timing of both thoracic and cardiovascular procedures were analysed.

Both postoperative mortality and morbidity after thoracic procedure resulted increased in this subgroup of patients when compared to others ($P = 0.0001$). Interestingly, all deaths occurred in patients who had undergone a major resection and the cause of death was related to cardiovascular disease. This might bring to the consideration that the same principle applied in preferring conservative resections in patients with respiratory imbalance [19,20] may be extended to patients with concomitant cardiovascular disease.

The same findings were recorded for postoperative morbidity, in that most patients with cardiovascular comorbidity undergone major resection had a significantly higher postoperative morbidity. This confirms that the extension of resection is an independent prognostic factor in all patients with coexisting disease and that a careful selection of patients must be carried out to prevent 'unexplained' postoperative deaths [21–23]. To this purpose the presence of symptoms related to all type of cardiovascular disease should not go underestimated and a thorough preoperative assessment should be planned.

Both 3- and 5-year survival would significantly differ whether a concomitant cardiovascular disease was present or not and even the overall analysis by stage would confirm a worse outcome for co-morbid cases. Moreover the impact of cardiovascular-related cause was relevant as showed by the analysis for cause of death. Among risk factors taken into consideration only stage and multifocal cardiovascular disease were related with survival while the timing for vascular surgery was not. At multivariate analysis by the Cox regression multifocal vascular disease was the only positive factor affecting significantly the survival rate.

From the analysis of our data it appears evident that coexistent cardiovascular diseases beyond the cancer can strongly increase the risk of morbidity and perioperative mortality. It may also affect the patient's survival and orientate the options for treatment. Peripheral vascular disease is generally not analyzed as an isolated risk factor but together with cardiovascular diseases and often considered as a non prognostic comorbidity as mild hypertension, myocardial infarction or congestive heart failure more than 6 months old [7,8]. On the contrary, we found it responsible for a significant increment in the morbidity and mortality rates, especially if multifocal. Therefore, we think that it is necessary to also evaluate the severity of the disease, whatever its location, in order to achieve a correct preoperative assessment in such patients.

As far as the timing of the operations is concerned we found that it did not significantly affect overall mortality. Despite to the relative small sample size and retrospective, non-randomized nature of the study we really think that timing is not a major point in the discussion. Therefore surgeons may have to decide which disorder to treat first, vascular or pulmonary, after making a cost/benefit evaluation. We often privileged cardiovascular operation as first because of the potential reduction of perioperative risk and the relative less priority of an early stage slow-growing NSCLC in elderly people. However, despite the specific treatment, the risk of cardiovascular related morbidity and mortality was still significant in our series.

According to the same considerations we prefer to avoid one stage cardiovascular-thoracic operation: perioperative risks may reach an unbearable level and this may have consequences also on postoperative immune response impairment. Furthermore, due to potentially increased risk of metastatic embolisation during extra-corporeal circulation, we privileged, whenever available, off-pump procedures in performing cardiac surgery especially if accomplished before thoracic surgery.

In conclusion cardiovascular disease, especially multifocal, significantly affects both survival and morbidity in patients undergone surgery for lung cancer in which major resections seems to have a prognostic significance. On the other hand we believe that the timing of vascular surgery should be based upon the severity of vascular disease and both anaesthesiologist's and surgeon's evaluation.

Moreover it should be emphasized that apart from direct effects on survival, severe comorbidity can also have a prognostic impact by altering therapeutic strategy. Namely, if a patient is not able to tolerate the planned treatment due to a comorbid status he may be given a less aggressive or even merely palliative treatment. The direct consequence of this should be that of classifying patients not only by the extension of the disease (TNM) but also by the presence of prognostic comorbidity. The risk of not including comorbidity data in cancer statistics is a growing imprecision in categorizing patients that will certainly jeopardize the evaluation of 5-year survival and therapeutic effectiveness.

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