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Lung cancer with chest wall involvement: Predictive factors of long-term survival after surgical resection

Luca Voltolini, Cristian Rapicetta*, Luca Luzzi, Claudia Ghiribelli, Tommaso Ligabue, Piero Paladini, Giuseppe Gotti

Thoracic Surgery Unit, University Hospital of Siena, viale Bracci 1, 53100 Siena, Italy

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Summary Multimodal management of lung cancer extending to chest wall and type of surgical procedure to be performed are still debated. The aim of this retrospective analysis was to analyze the predictive factors of long-term survival after surgery, focusing on depth of infiltration, type of surgical intervention and possible role of preoperative therapies, comparing survival of these patients with that of a group of patients affected by a Pancoast tumour and surgical treated in the same period.

Materials and methods: We reviewed records of 83 consecutive patients with NSCLC in stage T3 (owing to direct extension to chest wall), who underwent surgical resection in our Thoracic Surgery Unit between January 1994 and December 2003. Patients were classified in two groups: pancoast tumours (PT) or chest wall extending tumours (CW): survival and prognostic factors of each category were analyzed.

Results: In the CW group we had 68 patients: 45 were in stage IIB (pT3N0), 23 in stage IIIA (pT3-N1-2). Histology revealed adenocarcinoma in 23 cases, squamous cell carcinoma in 34, large cells anaplastic carcinoma in 8, adenosquamous carcinoma in 3. An involvement of chest wall tissues beyond the endothoracic fascia was found in 21 patients, while in the remaining 47 the invasion of chest wall tissues was confined to the parietal pleura. An extrapleural dissection was performed in 48 patients while combined pulmonary and chest wall en bloc resection was required in 20 patients. Resection was incomplete in three cases. In the PT group we had 15 patients: 11 were in stage IIB and 4 in stage IIIA. Histological type was adenocarcinoma in 10 cases, squamous cell carcinoma in 4 and adenosquamous carcinoma in 1.

A univariate analysis performed in the CW group showed that survival was significantly affected by nodal status, stage, extension of chest wall invasion, type of lung resection and residual disease. In a multivariate analysis we found that nodal status, completeness of resection and extension of chest wall involvement maintained a significant prognostic value. There was no difference between the survival curve of CW and PT group: considering the two subset of CW patients, on the basis of depth of infiltration, survival of PT patients was significantly better than that of CW patients with involvement of muscular tissues and ribs ($p = 0.02$).

* Corresponding author. Tel.: +39 0577 586140; fax: +39 0577 586736.
E-mail address: rapsody99@libero.it (C. Rapicetta).

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Conclusion: Nodal status, radical resection and depth of chest wall infiltration are the main predictive factors affecting long-term survival, while surgical procedure does not impact on it if margins of resection are free from disease. The better survival observed in PT patients let us to hypothesize that an induction chemo-radiation therapy, as routinely administered to PT patients, could have a potential benefit in survival of patients with CW tumour extending beyond parietal pleura.

1. Introduction

Surgery remains the cornerstone of treatment of lung cancer. The 5-year survival of patients treated for NSCLC varies from 80% in T1N0M0 to less than 10% in bulky N2-3 disease [1]. Invasion of chest wall is not rare, with a percentage of 5—8% of all resected NSCLC; nowadays the prognostic importance of this finding is controverse. Although neoplastic invasion of chest wall cancer has never been considered evidence of unresectability, early reports showed a very low long-term survival [1—3]. Recent studies have shown instead exceptional 5-year survivals, never reported before in literatures [4,5]. The authors of these studies advocated the en bloc chest wall resection in all patients with chest wall involvement and rejected extra pleural dissection, also in those patients with an isolated parietal pleural infiltration. However, although the objective of this policy should improve the prognosis reducing local recurrences, many series demonstrated that long-term survival is much more impaired by distant metastases than by recurrences on chest wall. Moreover, the possible role of induction and/or adjuvant therapy in the improvement of prognosis is still debated and no randomized trials have ever been reported until now. The aim of our study is to investigate the possible factors that could affect long-term survival after surgery in an homogenous group of patients affected by NSCLC invading chest wall.

In order to disclose a potential benefit of induction chemo- and radiation-therapy in these patients, they were compared with a group of patients affected by pancoast tumour who systematically underwent a combined preoperative treatment before surgery and were operated on during the same period.

2. Materials and methods

Between January 1994 and December 2004, 83 patients affected by NSCLC involving the chest wall underwent surgical resection at the Thoracic Surgery Unit, University Hospital of Siena, Italy. Sixty-eight out of these patients presented a chest wall invasion (CW), while 15 patients had a pancoast tumour (PT). Patients with metastatic cancer, occult pleural dissemination, positive bronchial stump and SCLC were excluded from this study.

Preoperative work up consisted of: physical examination, routine blood tests, bronchoscopy and total body CT scan in all patients. Bone scintigraphy was also performed on symptomatic patients or on those with high levels of serum phosphate. All patients affected by PT received a magnetic resonance (MR) in order to assess tumour extension to soft tissues or ribs and to exclude the infiltration of nervous and/or vascular structures of the upper thoracic inlet. Mediastinoscopy, anterior mediastinotomy or transbronchial biopsy were carried out in each case where CT-scan showed evidence of N2 disease. Patients with recent cardiac ischemia, congestive heart failure, unstable angina pectoris, malignant arrhythmia and severe lung failure were not candidate to surgery. Patients with impaired respiratory function (FEV1 < 60% predicted, DLCO < 60%, MVV < 50%) underwent perfusion pulmonary scintigraphy and cardiopulmonary test.

All the 15 patients affected by PT received induction radiation therapy (RT) associated with chemotherapy (CHT) in the last 7 cases, according to the American College of Chest Physician (ACCP) guidelines. No patients in the CW group received induction therapy, except for one with histologically proven N2 disease. In all patients radical mediastinal lymphadenectomy was performed. Resection was considered complete (R0) by demonstration of negative tissue margins at pathological examination. Survival rates were referred to 5-year follow-up from date of operation. Survival curves were computed using Kaplan—Meyer method and compared with the log-rank test.

At the univariate analysis the prognostic factors tested were: age, gender, hystology, extension of lung resection, type of surgical procedure (en bloc versus extrapleural dissection), grade of chest wall invasion (parietal pleural versus bone and muscular tissues) and completeness of resection. The multivariate analysis was carried out with the same variables using the Cox's proportional hazard test. The limit for statistical significance was a p-value less than 0.05. In two series of patients the chi-square test was used to establish the significance of different distribution of an event.

3. Results

Patients were divided into two groups: CW and PT group.

The CW group consisted of 68 patients (57 males and 11 females), whose the mean age was 69 years (range 48—81). In 17 of them (25%) cancer diagnosis was occasional. In the rest of them (51) the main symptoms were: chest pain in 29 cases (43%), cough in 12 (17%), dyspnoea in 5 (7%), fever in 3 (4%), asthenia and weight loss in 2 (3%). After surgery 45 patients (66%) were in pathological stage IIB and 17 (33%) in stage IIIA. Out of them, 10 patients were T3N1 and 7 patients T3N2 (4 of N2 patients were unforseen at the clinical staging). The histology revealed: squamous cell carcinoma in 34 cases (50%), adenocarcinoma in 23 (34%), anaplastic large cell carcinoma in 8 (12%), adenosquamous carcinoma in 3 (4%). The operative procedures performed were: 45 lobectomies (66%), 18 pneumonectomies (26%), 3 segmentectomies (4%) and 2 wedge resections (3%). Sublobar resections were preferred in patients with severe impairment of respiratory function. An extrapleural dissection was carried out

in 48 patients (70%) in which tumour was easily dissectable from chest wall contact plane. In the remaining 20 patients, ribs and/or intercostal muscles were affected and, therefore, an en bloc resection was mandatory. The mean number of resected ribs was 2.6 (range 1—4) with a size of chest wall resected between 4.7 and 5.9 cm. In three patients we found microscopic residual disease (R1) at the resection margin. Two patients had undergone en bloc chest wall resection while one patient had an extrapleural mobilization of the tumour (Table 1).

Among those patients who underwent en bloc resection the chest wall involvement was antero-lateral in 12 patients (60%) and posterior in 8 (40%).

As reported in literature [1] we performed reconstruction of the chest wall in thin patients with large (>5 cm in greatest length) and antero-lateral thoracectomies, in order to prevent chest flail during breathing (scapula and muscolar flap alone were considered sufficient for posterior defects). Chest wall repair with prothesis was required in six patients (29%); in the remaining 14 patients a muscle flap was used.

Average follow up was 27 months (range 8—144). The 30-day mortality was 4% (three patients). One patient died intraoperatively of acute myocardial infarction; the other two patients died of bronco-pleural fistula. Causes of death at follow up were: distant relapse in 15 cases (22%), local recurrence in 12 (17%), respiratory failure in 6 (9%), stroke in 2 (3%), pulmonary embolism in 2 (3%). Two patients received neo-adjuvant chemotherapy, one patient radiation therapy on the mediastinum. All of them showed an histologically proved N2 disease. Twenty-two patients received postoperative treatment (CHT in 5 cases, RT in 12 and both in 5). Only the three patients with R1 disease received RT as adjuvant treatment, while the remaining 19 received RT and/or CHT after developing local recurrence or distant metastases. The overall survival rate in all CW patients was 37% (mean 59, median 48, range 0—144 months).

In the subgroup of CW patients with isolated pleural involvement we reported a 5-year survival rate of 43%; in the subgroup with chest wall structures invasion 5-year survival rate was 8.7% ($p = 0.003$). Concerning nodal involvement, 5-year survival rate was 42% in patients in stage IIB and 17% in stage IIIA ($p = 0.002$). Considering the margins of resection, none of the three patients with residual disease were alive after 5-year of follow up, while patients with radical resection had a 5-year survival rate of 33% ($p = 0.0001$). All five patients who had undergone sublobar lung resection were dead after 9 months from date of surgery ($p = 0.001$). Finally, survival rates after extrapleural mobilization of tumour and after en bloc resection were 40 and 12%, respectively ($p = 0.036$). The survival curves of each group and log-rank test values are shown in Figs. 1—5.

In order to assess their indipendent predictive value, covariates were tested in a Cox-proportional hazard model (Table 2). From multivariate analysis, depth of chest wall invasion and nodal involvement resulted in two independent adverse prognostic factors with respectively $p = 0.011$ and 0.033. Completeness of resection, which is a well recognized factor worsening survival, failed to reach the statistical significance because of the small number of cases. Surgical procedures did not impact either in postoperative mortality or in long-term survival. No differences in terms of chest wall recurrences were found between extra pleural mobilization of the tumour and en bloc resection.

Among the PT patients there were 15 patients (11 males and 4 females) with mean age 61 (range 54—67). All

Table 1 Main demographic, clinical and pathological data of population

	CW pleural group	CW full thickness group	PT group	Total population
Age*	68.2	70.1	63.2*	67.9
Gender (male/female)	37/10	20/1	13/2	70/13
Stage (IIB/IIIA)	29/18	16/5	11/4	56/27
Pulmonary resection				
Lobectomy	30	15	13	58
Pneumonectomy	14	4	2	20
Segmentectomy	3	—	—	3
Wedge resection	—	2	—	2
Hystology				
ADK	13	6	10*	29
Squamous cell K	23	11	4*	38
Anaplastic	5	3	—	8
Other	6	1	1	8
Chest wall resection (yes/no)	1/46	19/2	15/—	34/49
Incomplete resection (R1)*	—	3*	1	3
Causes of death				
Distant metastasis	12	3	5	20
Local recurrence	8	4	2	14
Other	4	6	1	11

Age (PT patients vs. others); incomplete resection (CW patients vs. pleural); histology (PT patients vs. others).
* Significative difference ($p < 0.05$).

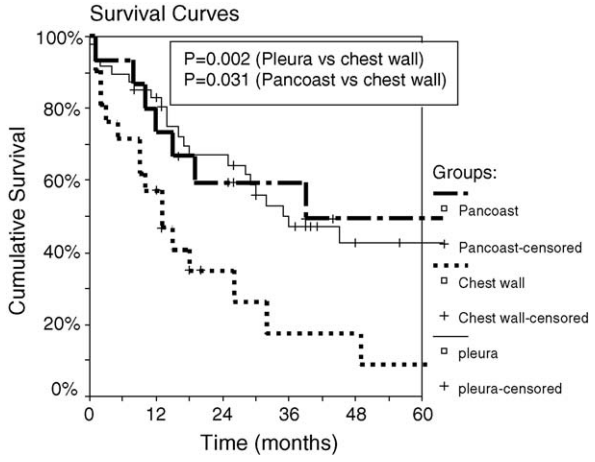

Fig. 1 Survival curves of the three groups.

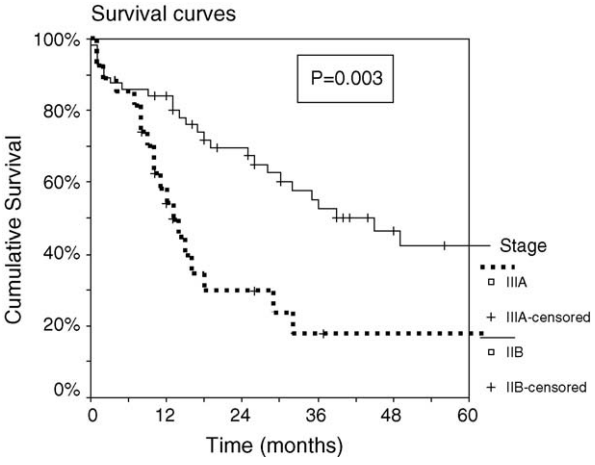

Fig. 2 Survival curves in CW group according to stage.

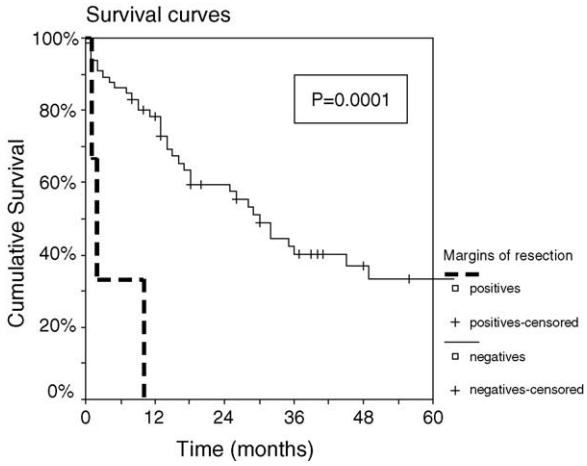

Fig. 3 Survival curves in CW group according to completeness of resection.

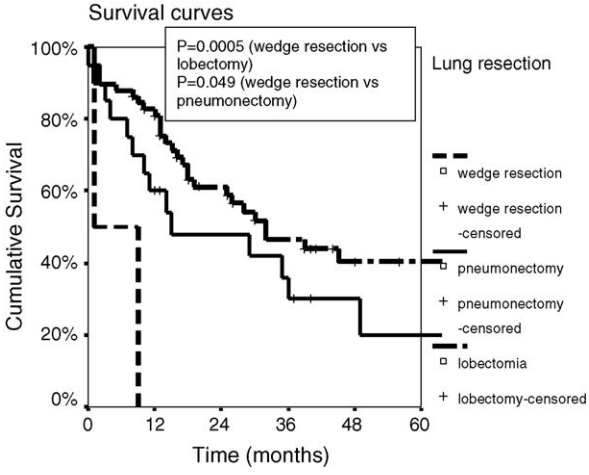

Fig. 4 Survival curves according to type of lung resection.

patients complained for pain. Postoperative staging showed 13 patients (87%) in stage IIB and 2 (13%) in stage IIIA. Histology revealed adenocarcinoma in 10 cases (67%), squamous cell carcinoma in 4 (27%) and adenosquamous carcinoma in 1 (6%). Pulmonary resections were lobectomy in 13 cases (87%), pneumonectomy in 1 case (6.6%) and sublobar resection in 1 case (6.6%).

In the group of PT patients 5-year survival rate was 49% (mean survival time 50, median 39 months). No postoperative fatal complications occurred. No predictive factors of survival were identified with statistical analysis, probably because of the small number of cases.

Comparing the overall 5-year survival of all CW patients with that of PT patients, we did not find any statistical difference. However, patients of the CW group with ribs or muscular invasion showed to have a significant lower survival than patients of the PT group ($p = 0.03$) Moreover, 5-year survival of PT group was higher than that of CW subgroup with

Table 2 Multivariate analysis—Cox regression (CW group)

Covariate	Comparing factor	Relative risk (95% CI)	Significance
Age	≥vs. < 70 years	1.37 (0.57—3.29)	$p = 0.47$
Gender	Male vs. female	0.74 (0.24—2.29)	$p = 0.60$
Lobectomy	Yes vs. no	2.41 (0.62—9.33)	$p = 0.23$
Pneumonectomy	Yes vs. no	2.94 (0.7—12.2)	$p = 0.13$
Pathological stage	IIB vs. IIIA	0.38 (0.16—0.89)	$p = 0.027$
Hystology	Squamous cell carcinoma vs. others	0.38 (0.13—1.13)	$p = 0.08$
Chest wall infiltration	Muscle and ribs vs. parietal pleura	35.2 (1.4—868.4)	$p = 0.029$
Surgical procedure	Chest wall resection vs. extrapleural dissection	12.08 (0.56—257)	$p = 0.11$
Margins of resection	Positive vs. negative	1.1 (0.10—12.07)	$p = 0.92$

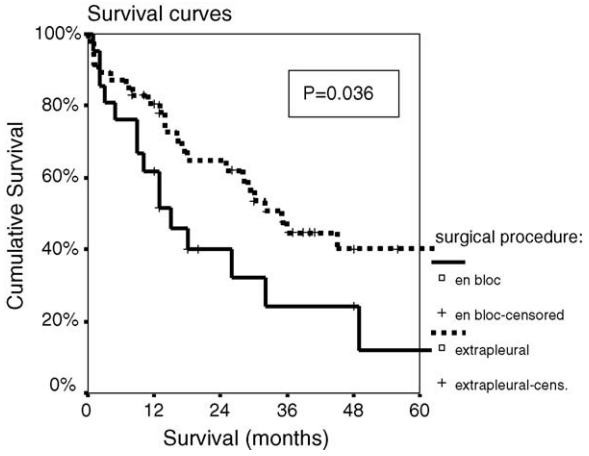

Fig. 5 Survival curves according to type of surgical procedure.

infiltration of chest wall structures (Fig. 1) and comparable to that of CW group with isolated pleural involvement.

4. Discussion

Involvement of chest wall occurs from 3 to 8% of all surgically treated NSCLC [1,6], and our series confirms this percentage (6.3%). The management of this particular group of patients remains a subject of interest especially for two reasons: the factors that may influence the prognosis and the role of induction and/or postoperative therapies in long-term survival. Chest wall invasion in NSCLC is no longer considered a controindication for surgical resection [2], and durable survival can be achieved with an acceptable operative mortality [1,6]. However, many factors concur to impair the long-term survival in these patients. In our study, standard survival predictors (such as completeness of resection, lymph nodal status, histology and extension of lung resection) were analyzed along with depth of chest wall invasion and type of resection (en bloc versus extrapleural), that are specific for this group of patients. All predictors were firstly assessed through a univariate analysis and then confirmed by a multivariate study. Lymphnodal infiltration and completeness of resection appear to be the main survival predictors in the univariate analysis: nodal status and not the completeness of resection (probably for the small number of R1 patients) maintained its significance in the multivariate analysis. These results have been observed also in the previous literature and are universally accepted [2,3,7]. However, the impact of these two factors on long-term survival is so important that secondary factors like extension of infiltration, surgical strategy and postoperative treatment were often difficult to define especially in a multivariate analysis. In his series of 104 surgically resected patients, Chapelier found that patients with a tumour infiltration confined to the parietal pleura had a significantly better 5-year survival than those with chest wall infiltration [3]. Deeper involvement was advocated as a predictor of worse prognosis also by Mischina et al. [9] and in a recent report by Facciolo et al. [4], who found that depth of tumour invasion affected prognosis in the sub-group of pN0 patients. In our series we found a statistical difference in 5-year survival between patients with a tumour infiltration confined to parietal pleura and those with infiltration of the chest wall ($p = 0.003$). We also found a better 5-year survival in patients who underwent extrapleural resection than in those who received an en bloc resection ($p = 0.003$). In our policy, in cases with minimal parietal pleural involvement should be resected by an extrapleural dissection without concomitant rib resection: intraoperative histological exam of margins could be useful for the surgeon. However, if in doubt, an en bloc resection should be carried out. Facciolo advocated the en bloc chest wall resection both in patients with a suspect of chest wall involvement and in those with tumour confined in the parietal pleura. With this approach, he obtained an extremely high 5-year survival rate (79.1%) in patients with parietal pleura invasion and in those with extrapleural chest wall involvement (54%). This exceptional survival, never reported before in literature for stage IIB, could justify an en bloc resection beforehand. However, a higher incidence of mortality and morbidity after chest wall resection is reported in literature [8]. Although in our series the extrapleural dissection was associated to a better 5-year survival at the univariate analysis, this significance was lost in the multivariate analysis when extension of infiltration was introduced among covariates. We can argue that the type of resection has no impact on long-term survival, whereas depth of infiltration is the most important independent prognostic factor after the N status and the completeness of resection.

Although induction and/or adjuvant therapy could play a role in CW patients, its usefulness is still debated. As far as postoperative radiation therapy is concerned, no randomized trials have ever been compared, and different conclusions have been reported in various retrospective reviews. Gould has recently concluded that even though adjuvant radiotherapy may reduce the local recurrence, it has no impact on long-term survival [10]. In our study no differences in survival have been observed between patients who underwent adjuvant treatment and those who did not. No patients received preoperative radiation therapy except for one (in the mediastinum for lymphadenopaty). To assess the possible advantages of induction therapy in CW patients, these patients were compared with the group of PT patients operated in the same period. Pancoast tumours are traditionally considered as a group of tumours with their own characteristics, especially for the particular symptomathology and surgical approach. However, they are included in TNM classification in stage T3 and, in our opinion, they can be properly compared with CW tumours if no concomitant vascular, nervous or vertebral infiltration (T4) is present. The PT group showed a better 5-year survival than CW subgroup with muscular or rib invasion ($p = 0.03$) and similar those with the isolated pleural infiltration ($p = $ n.s.). The difference remained significative ($p = 0.033$) even after excluding perioperative deaths, presence of R1 disease and sublobar pulmonary resections. The small number of cases did not allow to find significative prognostic factors in a univariate and a multivariate analysis. However, the two groups (CW and PT) were homogeneous in terms of age, gender, preoperative work up, surgical management and pathological stage. Histology revealed a higher percentage of adenocarcinomas among PT patients. We can argue that preoperative radiation therapy could improve the success of resection by circumscribing and reducing the infiltration of chest wall, thus, allowing to achieve a final condition closer to isolated

involvement of the parietal pleura. Since these conclusions have been deduced from two similar but not equal groups of patients, the potential benefit of induction therapy in CW patients remains an hypothesis. Today, it represents, however, a stimulus to set up, in our Institution, a randomized study which could provide objective data.

We conclude that the factors affecting long-term survival after complete resection are N-status and depth of chest wall involvement. Consequently any effort must be spent in achieving a preoperative accurate N-staging, avoiding surgery in N2 patients before an induction chemotherapy. The chest wall involvement should be assessed preoperatively by a videtoroacoscopic exploration as proposed by Roviaro et al. [5] or, as in our experience, by a high resolution TC study. To conclude, since the detection of ribs or muscular tumour invasion could be an indication to an adjuvant chemo-radiation treatment, the role of CT scan becomes crucial. Concerning chest wall extension, in addition to commonly used criteria (such as pleural contact area and chest wall-tumour angle), thin-sectional CT scan with specific software algorithms reconstruction can significantly improve the accuracy of CT to the level reached by MRI, as reported by Uhrmeister et al. [11].

The detection of an isolated parietal pleura infiltration by CT scan is not crucial because those patients are candidated for surgery as first therapeutic option if nodal involvement has been excluded.

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