

Pneumonectomy with *en bloc* chest wall resection: is it worthwhile? Report on 34 patients from two institutions[†]

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Abstract

OBJECTIVES: Pneumonectomy with *en bloc* chest wall resection is often denied because of the procedure-related high risk. We evaluated the short- and long-term outcome of this procedure.

METHODS: From January 1995 to October 2011, 34 patients (30 males and 4 females; mean age: 61.8 years) underwent pneumonectomy with *en bloc* chest wall resection for 33 non-small-cell lung cancer and 1 metastatic osteosarcoma in two institutions. Data were retrospectively reviewed.

RESULTS: Operative (30-day) mortality was 2.9% (1 of 34), and morbidity was 38.2% (13 of 34). There were 14 (41.1%) right-side procedures and 20 (58.8%) left-side procedures. Three (8.8%) patients developed bronchopleural fistulas. The mean number of resected ribs per patient was 2.7 ± 1.1 . In 13 (38.2%) patients, a prosthetic reconstruction of the chest wall was needed. In 3 (8.8%) cases, the bronchial step was buttressed. Preoperative pain was statistically significantly related to the depth of chest wall invasion ($P = 0.026$). The N status was N0 in 18 (52.9%) cases, N1 in 9 (26.4%), N2 in 6 (17.6%) and Nx in 1 (metastatic osteosarcoma). Patients were followed-up for a total of 979 months. The median survival was 40 months. The overall 5-year survival was 46.8% ($\pm 95\%$ confidence interval [CI]: 0.2–0.6): 45.2 ($\pm 95\%$ CI: 0.03–0.8) for right-side and 48.4% ($\pm 95\%$ CI: 0.2–0.7) for left-side procedures, respectively. According to the N status, the 5-year survival was 59.7 ($\pm 95\%$ CI: 0.3–0.8) in N0, 55.5 ($\pm 95\%$ CI: 0.06–1) in N1 and 16.6% ($\pm 95\%$ CI: 0–0.4) in N2. The subgroup N0 plus N1 (27 patients) showed a 58.08% ($\pm 95\%$ CI: 0.3–0.8) 5-year survival compared with 16.6% ($\pm 95\%$ CI: 0–0.4) in N2 (χ^2 : 3.7; $P = 0.053$).

CONCLUSIONS: Pneumonectomy with *en bloc* chest wall reconstruction can be safely offered to selected patients. The addition of *en bloc* chest wall resection to pneumonectomy does not affect operative mortality and morbidity compared with standard pneumonectomy. The pivotal additional effect of the chest wall resection should not be considered a contraindication for such procedures. Survival showed a clinically relevant difference by comparing N0 plus N1 with N2 (58.1 vs 16.6%), not confirmed by the statistical analysis ($P = 0.053$).

Keywords: Lung cancer • Pneumonectomy • Chest wall

INTRODUCTION

Pneumonectomy with *en bloc* chest wall resection is a rarely performed procedure because of the high perioperative surgical risk, which is related either to the pneumonectomy itself or to the resection of the chest wall, and to the combined effect of both procedures. The additional impairment of respiratory function related

to the combined procedure is as high as 27% as highlighted in a recent paper from Memorial Sloan Kettering Cancer Center, NY, USA [1]. Most of the papers addressing the issue of pneumonectomy with chest wall resection conclude that this procedure should be performed only in highly selected patients [1–6] and should not be routinely recommended. Such negative attitude denies some patients the chance of a potentially radical and curative procedure. Nevertheless, the total number of reported patients in the literature is very small, there are no clear data and no study on such topics exists up to now. In this paper, we sought to evaluate morbidity and mortality and the outcome of pneumonectomy with *en bloc* chest wall resection in a case series of 34 patients coming from two high-volume Italian institutions.

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MATERIALS AND METHODS

From January 1995 to October 2011, 34 patients (30 males and 4 females; mean age: 61.8 years, range 19–78) underwent pneumonectomy with *en bloc* chest wall resection, out of a total of 715 pneumonectomies performed in the same period (4.7%), in two Italian institutions, Carlo Forlanini Hospital, Azienda Ospedaliera San Camillo Forlanini, Rome (14 patients) and European Institute of Oncology (EIO), Milan (20 patients). Indications for surgery were in 33 patients with non-small-cell lung cancer (NSCLC) and in 1 patient with metastatic osteosarcoma. Data were retrospectively reviewed. Demographics are shown in Table 1. Preoperative workup included chest radiography and thoracic, abdominal and brain computed tomographic (CT) scan. Positron emission tomography - computed tomography (PET-CT) has been routinely performed since 2007. Preoperative workup also included routine biochemical profile, bronchoscopy, pulmonary function tests and arterial blood gas analysis at rest, as well as quantitative ventilation and perfusion scans in patients in whom predicted postoperative forced expiratory volume in 1 s (FEV1) could be estimated <1 l, or 40%. Patients with FEV1 that is greater than 80% predicted and without evidence of dyspnoea or interstitial lung disease are considered suitable candidates for pneumonectomy without further testing. Preoperative FEV1 and diffuse lung carbon oxide (DLCO) values are shown in Table 2. In some cases, an exercise test with the determination of maximum oxygen uptake (VO_2) was performed. Operative risk was considered acceptable if the maximum VO_2 was ≥ 20 ml/kg/min and unacceptable if it was ≤ 10 ml/kg/min. With values between 10 and 20 ml/kg/min, patients were considered at relatively high risk, and definitive decision was based on a complex evaluation taking into account the predictive postoperative FEV1, PO_2 , PCO_2 , maximum VO_2 , age and associated comorbidities. Mediastinoscopy was not routinely performed as part of the preoperative workup, except to rule out an N2 disease when suspected on the basis of positive nodes on PET-CT or enlarged mediastinal lymph nodes at CT scan (minimum diameter >1.0 cm). Indications for surgery were NSCLC in 33 patients and pulmonary metastasis from osteosarcoma in 1 patient. Pneumonectomy was needed because of: (a) bulky hilar nodal involvement (3 patients); (b) vascular involvement (5 patients); (c) bilobar (trans-fissure) involvement (22 patients); (d) completion pneumonectomy (4 patients). Surgical procedures were performed through postero-lateral thoracotomy. The bronchus was sectioned with a bronchial stapler in 33 cases (TA™ 30: 20 patients; TA55: 7 patients and EndoGIA™: 6 patients; Covidien, Norwalk, CO, USA). Systematic lymph node

Table 1: Demographics

Sex	
Male	30
Female	4
Mean age (range)	61.8 (19–78) years
Side	
Right	14
Left	20
Smokers	
Active ex-smoker	31
No	3

dissection was completed in all but 1 patient. NSCLC was staged according to the 7th edition of the *America Joint Cancer Committee (AJCC) Cancer Staging TNM AJCC Cancer Staging Handbook: TNM Classification of Malignant Tumours*. According to the new staging system, the descriptor Pleura (PL) was used for the evaluation of the depth of chest wall invasion: PL3 that indicates parietal pleura involvement was substaged into: (a) parietal pleura only; (b) parietal pleura + soft tissue; (c) bone invasion (full thickness involvement) [7, 8]. According to Shapiro *et al.* [9], major morbidity was defined as pneumonia, adult respiratory distress syndrome, empyema, sepsis, bronchopleural fistula (BPF), pulmonary embolism, ventilator support beyond 48 h, myocardial infarct, reoperation for bleeding and central neurological event. Hospital mortality was defined as death during the same hospitalization or within 30 days of the procedure. Informed consent was obtained from all patients.

Statistics

We retrospectively reviewed the medical records of these patients. Continuous variables are presented as mean \pm standard deviation unless otherwise noted. For univariate analysis, χ^2 test of the potential risk factors for postoperative complications was performed. Survival data were complete for all patients. Survival rates were calculated either from the date of surgery until death or from the date of the last follow-up by means of the Kaplan-Meier test and compared by using the log-rank test for univariate analysis. A *P*-value of ≤ 0.05 was considered significant.

RESULTS

Preoperative pain (Table 2) was statistically significantly related to the depth of chest wall invasion ($P = 0.026$), with 12 of 26 (46%) symptomatic patients being in substage 'PL3 c' (full thickness invasion of the chest wall). Fourteen patients underwent induction chemotherapy (41.1%). The mean hospital stay was 11.5 ± 4.8 (range: 6–24) days. The overall operative (30 days) mortality was 2.9% (1 of 34). The cause of the reported death was an early BPF complicated by respiratory insufficiency and sepsis. Major morbidity was 38.2% (13 of 34; Table 3). The incidence of early BPF was 2 of 34 (5.8%). Furthermore, 1 patient developed a late BPF 226 days after the surgical procedure. An

Table 2: Preoperative data

Preoperative FEV1	
80–100%	23
60–79%	9
52–59%	2
Preoperative DLCO	
80–100%	17
60–79%	12
52–59%	5
Preoperative pain	
Yes	26 (a: 6; b: 8; c:12)
No	8

FEV: forced expiratory volume in 1 s; DLCO: diffuse lung carbon oxide.

Table 3: Morbidity

Atrial fibrillation	3
Bronchopleural fistula	1
Bronchopleural fistula + sepsis	1
Bleeding	1
Renal failure	1
Atrial fibrillation + myocardial infarction	1
Neurological disorder	2
Cardiac failure	1
Respiratory insufficiency + cardiac failure	1
Respiratory insufficiency	1

Table 4: Pathological report

Chest wall resection	
1 rib	4
2 ribs	12
3 ribs	11
4 ribs	4
5 ribs	3
Depth of chest wall invasion (PL3)	
a	12
b	9
c	13
T staging	
T4	6
T3	28
N staging (33 of 34)	
N0	18
N1	9
N2	6
Histology	
Adenocarcinoma	13
Pleomorphic carcinoma	3
Squamous cell carcinoma	11
Adenosquamous carcinoma	2
Large-cell carcinoma	2
Large cell neuroendocrine carcinoma	1
Mixed sarcomatoid-large-cell carcinoma	1
Metastatic osteosarcoma	1

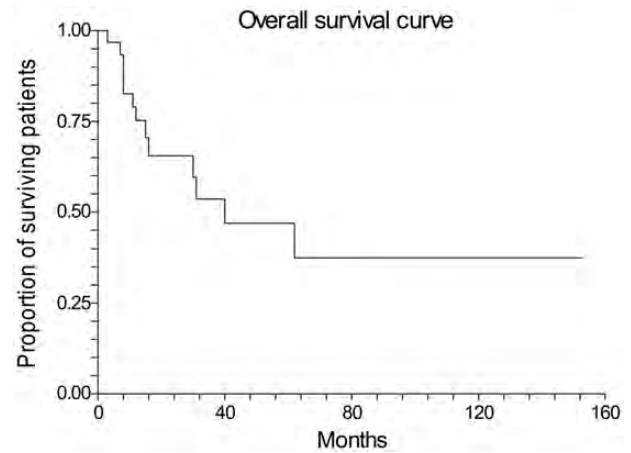
R0 resection was performed in 32 of 34 (94.1%) cases. A right-side pneumonectomy was performed in 14 (41.1%) patients, with an operative mortality rate of 7.1% (1 of 14). A left-side procedure was performed in 20 (58.8%) patients, with no mortality. The histological report with the depth of chest wall invasion is shown in Table 4. The mean number of resected ribs per patient was 2.7 ± 1.1 , and ranged from 1 to 5 (Table 4). In 13 (38.2%) patients, a prosthetic reconstruction of the chest wall was needed (Table 5): in 6 of 14 (42.8%) right-side procedures and in 7 of 20 (35%) left-side procedures. The most common prosthesis employed in our series (4 of 13) was bovine pericardium (Veritas, Synovis Life Technologies is a wholly owned subsidiary under Baxter International, Inc., USA). In 3 (8.8%) cases, the bronchial step was buttressed (Table 6). Thirty-one (94.1%) patients were active or ex-smokers (Table 1). Induction therapy did not show any statistically significant correlation with

Table 5: Prosthetic reconstruction

Veritas (bovine pericardium)	4
Gore-Tex (polytetrafluoroethylene)	3
Vicryl (polyglactin)	3
Marlex (crystalline polypropylene and high-density polyethylene-HDPE) + methacrylate mesh	2
Marlex + polyethylene mesh	1

Table 6: Bronchial buttress

Pericardial flap	1
Diaphragmatic flap	1
Mediastinal fat	1

**Figure 1:** Overall survival curve.

morbidity or with the need of postoperative ventilation. No statistically significant correlation was found between preoperative FEV1 and the morbidity rate. Smoking habits failed to show any statistically significant effect on postoperative complications of these cases and on the need for invasive postoperative ventilation. The N status was N0 in 18 (52.9%) cases, N1 in 9 (26.4%), N2 in 6 (17.6%) and Nx in 1 (metastatic osteosarcoma). Patients were followed up for a total of 979 months. The median survival was 40 months. The overall 5-year survival was 46.8% ($\pm 95\%$ confidence interval [CI]: 0.2–0.6; Fig. 1): 45.2 ($\pm 95\%$ CI: 0.03–0.8) for right-side and 48.4% ($\pm 95\%$ CI: 0.2–0.7) for left-side procedures, respectively (no statistically significant difference). According to the N status, the 5-year survival was 59.7 ($\pm 95\%$ CI: 0.3–0.8) in N0, 55.5 ($\pm 95\%$ CI: 0.06–1) in N1 and 16.6% ($\pm 95\%$ CI: 0–0.4) in N2. The subgroup N0 plus N1 (27 patients) showed a 58.08% ($\pm 95\%$ CI: 0.3–0.8) 5-year survival compared with 16.6% ($\pm 95\%$ CI: 0–0.4) in N2 (χ^2 : 3.74; $P = 0.05$). According to the depth of chest wall invasion, the 5-year survival was 47.6 ($\pm 95\%$ CI: 0.1–0.8), 43.2 ($\pm 95\%$ CI: 0.02–0.8) and 43.7% ($\pm 95\%$ CI: 0–0.8), respectively, in substages PL3 a, PL3 b and PL3 c; no statistically significant difference was found.

DISCUSSION

Pneumonectomy with *en bloc* chest wall resection has been seldom, if ever, reported in chest wall resection series with unclear data and a negative attitude. Doddoli *et al.* [7], out of a multicentre series of 309 NSCLC invading chest wall, reported 79 pneumonectomies, but the majority of these cases underwent extrapleural resection and not *en bloc* resection. Nevertheless, the overall mortality of the pneumonectomy group with extrapleural resection was remarkable: 12.7%. In a series of 107 NSCLC invading chest wall recently reported by Lee *et al.* [6], 45 pneumonectomies were performed, but the authors did not identify how many chest wall resections or extrapleural dissections were performed: an impressive 57% 1-year mortality was reported in the pneumonectomy group. Pneumonectomy itself showed to be a univariate prognostic factor for survival in the series ($P = 0.041$), and the authors concluded that pneumonectomy should be avoided whenever possible because not only cancer-related death but also respiratory-related death is significantly high. The present paper represents a unique effort to address the outcome of patients undergoing pneumonectomy with *en bloc* chest wall resections. The overall operative mortality in our series was 2.9% (1 of 34), a figure which compares favourably with the 8.5% mortality rate reported out of 1507 patients undergoing this procedure from the Commission on Cancer of the American College of Surgeons national hospital survey performed in 2001, and with the 5.6%, out of 1002 patients, recently reported by Shapiro *et al.* from the Society of Thoracic Surgeons (STS) database [9, 10]. It should be stressed that the selection bias of both multicentre series reported by the ACS and the STS which also include procedures performed by general surgeons and cardiovascular surgeons and may justify the higher mortality rates compared with board-certified thoracic surgeons series [8, 9, 10]. The overall morbidity in our series was 38.2% (13 of 34), a percentage which is in line with the 30.4% reported from the STS database [9]. It is well known that pneumonectomy itself is associated with the highest degree of pulmonary and functional status compromise [11–13]. Additional chest wall resection could potentially worsen pulmonary reserve in such patients and be the single most important factor for understanding the morbidity rate [14]. In our series, no statistically significant correlation was found between preoperative FEV1 and DLCO, and the morbidity rate. The bias of such observation is the selection criteria of our series, including a high number of patients with a normal or border-line respiratory function: 67.6% of our patients (23 of 34) had an FEV1 between 80 and 100%, and only 2 (5.8%) had an FEV1 <60% [15]; furthermore, 85.2% (29 of 34) had a preoperative DLCO value >60%. In our series, the extent of chest wall resection did not impact the morbidity rate: most of the procedures undertook the resection of two or three ribs (12 vs 11 patients, respectively). In agreement with Doddoli *et al.*'s series [7], we found no statistically significant difference between the two groups (two vs three ribs resection) in terms of morbidity and mortality rate. The overall 5-year survival in our series was 46.8% ($\pm 95\%$ CI: 0.2–0.6; Fig. 1). Survival was not affected by the side of the resection. According to the N status, survival was 59.7% ($\pm 95\%$ CI: 0.3–0.8) in N0, 55.5% ($\pm 95\%$ CI: 0.06–1) in N1 and 16.6% ($\pm 95\%$ CI: 0–0.4) in N2. Comparing the N2 group with the N1 plus N0 group (16.6%; $\pm 95\%$ CI: 0–0.4) vs (58.08%; $\pm 95\%$ CI: 0.3–0.8, $P = 0.053$), the N2 status failed to be a statistically significant prognostic factor even if the P -value was very close

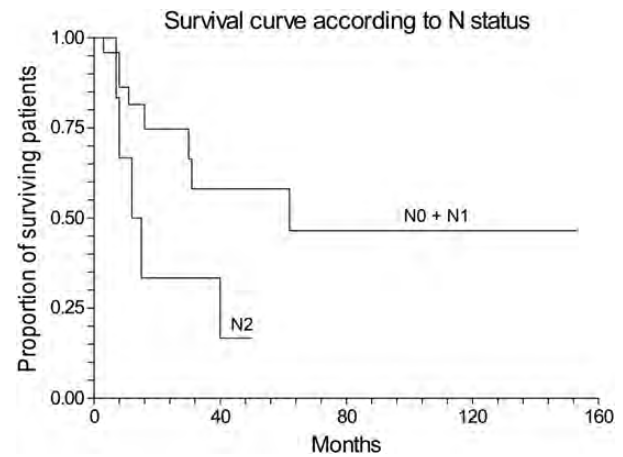


Figure 2: Survival according to the N status N0 + N1 vs N2.

(Fig. 2). In conclusion, pneumonectomy with *en bloc* chest wall reconstruction can be safely offered to selected patients. The addition of *en bloc* chest wall resection to pneumonectomy does not affect operative mortality and morbidity compared with standard pneumonectomy. The pivotal additional effect of the chest wall resection that jeopardizes the feasibility of the combined procedure should not be taken into account in approaching such operation in the light of the results reported in the present series. A careful knowledge of comorbidity and cardiorespiratory function can help to identify patients who are at increased risk for unfavourable outcomes. The critical factor is the experience of the institution in dealing with such complex resections. Survival is related to the nodal status. Large data are needed for a better evaluation of pneumonectomy with *en bloc* chest wall resection.

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Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr P. Van Schil (Antwerp, Belgium): In this retrospective study from 1995 until 2011, 34 patients underwent pneumonectomy with en bloc chest wall resection. Thirty-day mortality of these very extensive operations was only 3% and morbidity was 38%. Overall median survival time was 40 months. The authors nicely demonstrate that these demanding interventions can be performed safely in selected patients in centres having a large experience with difficult thoracic surgery. I have two questions. In 14 patients, or 41%, induction chemotherapy was given. What were the precise indications for induction chemotherapy, and how was restaging performed?

Second, looking at your last conclusion, mediastinoscopy was only selectively used in this study. Pathological N2 disease was found in almost 18% of patients. What were the specific sites of N2 involvement? As N2 disease is a major negative prognostic factor, should mediastinoscopy not routinely be performed in this subset of patients before embarking on such a large resection?

Dr Cardillo: I prefer to answer the second question first. First of all, I want to clarify that the surgical staging of the mediastinum is mandatory in patients undergoing such a big operation. It doesn't matter how you do the surgical

staging; it can be done by mediastinoscopy or by EBUS or by EUS. The most important factor is to stage the mediastinum. After we stage the mediastinum, we have to understand how we analyse the results, if it is a single zone or if it is multiple zone involvement. In single zone N2 disease, maybe a procedure can be done. Out of the six patients who had N2 disease, we found two patients with single zone N2 disease and in such patients we first performed the surgical procedure.

As regards postoperative therapy, according to our rule we very often give induction therapy in every patient with N2 disease. This is our rule. It doesn't matter if it is a single zone or a multiple zone. But in a patient with such major disease for which the alternatives are very few, maybe in the MDT meeting that should take place before the operation, even the single zone patient can undergo surgery. So the answer to the induction therapy is that we offer induction whenever there is single zone N2 disease; that is mandatory for us. But there are some points that should be discussed within the MDT, for example, single zone N2 disease. That is because we had six patients with N2 disease. Maybe in the near future when we further analyse the results of this study, we should be much more careful in offering this procedure to an N2 patient even if it is a single zone because of the high perioperative morbidity, although the mortality was very low. The lesson that we should take home is that whenever there is N2, single zone or multiple zone, it is better to deny the operation because the result is not good and because of the perioperative risk.

Dr Van Schil: Would you also consider induction therapy in patients with large-volume tumours to obtain a downstaging and probably to have a lesser extent of chest wall resection?

Dr Cardillo: Yes, but I think that in these patients, we have to consider the issue of the pain. These patients have a lot of pain and sometimes it is very difficult, even with first-class painkillers such as oral morphine, to control pain. These patients will ask for treatment even if they know that the results are not good.

Dr A. Chapelier (Suresnes, France): I have a comment and two questions. First, we at Marie Lannelongue in 2000 reported that for T3 lung cancer, the depth of chest wall involvement was a significant prognostic factor. My question is, for such an important resection, did you analyse this factor, the depth of chest wall involvement, in the survival?

Dr Cardillo: Yes. As I showed in one of my slides, we divided the PL3 factor (the level of the pleural involvement is called PL); PL3 means involvement of the parietal pleura. We divided PL3 into A, B, and C: PL3A means parietal pleura only, PL3B parietal pleura plus soft tissue, and PL3C, full-thickness. We found no statistically significant difference in this subset of patients. But it depends on the number of patients. In a previously published paper from Carlo Forlanini Hospital in Rome (*J Thorac Cardiovasc Surg* 2001;121:649), we have shown a difference between the different levels of chest wall involvement and survival. So it depends on the number of patients included in the study. This study involves only 34 patients whereas in our previous paper addressing the T3 group, the number was over 100, and we found a difference. We found no difference here maybe because the number was small for such a major and rare operation.

Dr Chapelier: Second, what is the rationale for chest wall reconstruction after this operation? You mentioned that a third of the patients had chest wall reconstruction.

Dr Cardillo: The rule for chest wall reconstruction is the same as every operation dealing with chest wall resection after lung cancer. It depends on the level of the chest wall involvement. For example, if the scapula can cover the defect, we don't use any prosthetic graft, of course; usually up to the fourth rib, we never use a prosthetic graft. When the defect is in the anterior part of the chest wall or is below the fifth rib, in that case we use prosthetic grafts. Usually we use a Gore-Tex soft tissue patch or, as we did most recently, we moved toward the biological patch, the Veritas bovine pericardial patch. These are the most commonly used in our experience.