Extended pneumonectomy for non small cell lung cancer – should we still do it?

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The aim of the study was to assess the early and late results of extended pneumonectomies in lung cancer patients with T3 and T4 disease.

Between Jan. 1995 and Dec. 1999 – 445 pneumonectomies were performed in patients with lung cancer. In 37 patients without preoperative N2 involvement a standard pneumonectomy was extended to include the following additional resections: chest wall (10), pericardium (9), diaphragm (5), VCS (3), descending aorta (2), left atrium (5), esophagus (1) and tracheal bifurcation (2). The effect of various factors on general mortality and morbidity was analyzed with the use of binary logistic regression.

There were two early postoperative deaths (6.8%). Major complications occurred in 10 patients (29%). Overall survival rates at 1, 2, and 3 years were 43, 30 and 24%, respectively. The survival rates for the subgroup with chest involvement only were 50, 42 and 30%, respectively. Eight patients survived beyond the 36 month follow-up. The only factor significantly affecting mortality was incomplete resection, as revealed by postoperative microscopic examination (R1, $p<0.05$).

Extended operations are justified by a relatively low mortality rate and low number of severe postoperative complications, specially in patients with chest wall involvement only. The result of this treatment predominantly depends upon the completness of the resection.

Key words: locally advanced lung cancer, extended surgical resection

Pulmonary resection is still the preferred treatment for patients with non small cell lung cancer (NSCLC). As lung cancer grows it may invade various thoracic structures and organs such as: the chest wall (the most frequent at approximately 5% of cases), vertebral body, superior vena cava, thoracic aorta, pericardium, diaphragm and esophagus. The prognostic value of this finding is still unclear and remains controversial. In patients with chest wall involvement a 5 year survival rate of between 20–40% can be expected [2, 6]. However, the prognosis for patients with tumors invading mediastinal organs is as poor as 10% [4, 9, 16]. From the surgical point of view some of these patients may benefit from extended surgery, but the question remains, whether the potential gain in survival rate counter-balances the higher operative risk. Therefore, the main aim of this study was assessment of the risk-benefit ratio of the extended pneumonectomy in patients with locally invasive lung cancer.

Material and methods

A retrospective study of the data obtained from 445 patients who underwent pneumonectomy between January 1995 and December 1999 was carried out to determine the pattern of failure and overall survival rate. All the patients received standard pneumonectomies including the dissection of the hilar and mediastinal lymph nodes. In 37 patients, this procedure was extended to include the following, additional resections: chest wall (10), pericardium (9), diaphragm (5), vena cava superior (3), descendending aorta (2), left atrium (5), esophagus (1) and tracheal bifurcation (2). This subgroup forms the basis for the current study and consisted of 29 males and 8 females with an age-range of patients 49–71 years (mean – 64). Their main symptoms were as folows: cough (24%), pain in the chest (21%) and hemoptysis (10%), 15% of the patients were symptom free.

Preoperative diagnostic procedures included clinical histories, physical examination, complete blood cell count, liver function tests, chest x-ray, spirometry of the lung, ultrasonography of the abdomen, fiberoptic bronchoscopy with cytology and histology of the biopsy specimens, transthoracic or transbronchial needle biopsies, CT of the chest and mediastinoscopy, whenever required (enlargement of mediastinal nodes). Patients with marked deterioration of respiratory function (VC<40%, FEV/VC<35%, FEV<1.5 L) or cardiac function (NYHA class III, CCS III) were not referred to surgery.

Preoperative lung cancer staging based on clinical, pathological and laboratory findings was used in accordance with the New International System for Staging Lung Cancer. Seven patients were assigned to stage II b, 17 to stage IIIa and 13 to IIIb. Patients with N2 disease were excluded from this study.

Following surgery, the operative, histopathological and hospital reports were analyzed for the following factors: tumor size and location, histology, patients age and sex and the type of additional surgical resection.

In the 10 patients with chest wall involvement this was predominantly on the antero-lateral aspect. In 9 of these patients "en bloc" resection of the tumor and chest wall was required. The number of resected ribs varied from 2–4. The mean size of chest wall defect was 7x8 cm. In 4 patients repair was achieved by muscle transposition while in 6 chest reconstruction was not necessary.

Tumor invasion to the pericardium was found to be resectable in 9 cases. In these patients the pericardium was usually dissected first, maintained "en bloc" with the resected lung and finally removed. To prevent extrusion of an atrial appendage or torsion of the heart the pericardium was reconstructed in 4 cases (one on the right and three on the left side) using pleura or a Teflon patch. In the remaining cases there was either no need for a pericardial repair or the heart was left free in the left pleural space.

Lung cancer infiltration of the diaphragm occurred in 5 patients, two on the left and three on the right side. Initially an incision was made through the full thickness of the diaphragm, completely encircling the tumor and then a routine pneumonectomy was carried out. Reapproximation of the cut surface of the diaphragm was possible in all cases.

An operable NSCLC invading the superior vena cava (SVC) was found in 3 patients. In two of these patients invasion of the SVC was partial and the tumor could be surgically managed by simple lateral resection of the vessel wall and primary suture. In the third case circumferential invasion precluded this technique and venous reconstruction with a PTFE graft was carried out. A PTFE graft was also used for one reconstruction of part of the descending aorta. After tumor dissection the descending aorta was cross-clamped below the left subclavian artery and 3 cm of the aorta with neoplastic infiltration, and was then excised. In the other patient with aortic involvement only a lateral resection of the aortic wall was required to remove the tumor completely.

Partial resection of the left atrium, due to lung cancer spread, was carried out on 5 patients prior to performing a right pneumonectomy. After clamping the left atrium below the level of the right pulmonary veins, the atrial "roof" with the associated veins was excised and two running sutures were used to close the atrium.

Carinal pnemonectomies were carried out on two patients with direct tumor spread from the right main bronchus to the trachea. These procedures consisted of removing the right lung and the tracheo-bronchial bifurcation followed by "end to end" anastomosis of the left bronchus with the trachea.

In one patient the mid-portion of the esophagus was affected by tumor spread and a short resection and reanastomosis of the cut ends was performed.

In all patients the following data were analyzed postoperatively: morbidity, any major complications, mortality, survival rate up to 3 years, histopathology of removed tissues (margin of oncological safety, lymph-node involvement). Those patients who had had a visual complete gross resection at surgery, but with positive margins at pathology, were defined as patients with microscopically incomplete resection (R1). Patients who underwent grossly incomplete resection (R2) were exluded from this study.

For statistical analysis the 5.0 statistica package was used. The effect of various factors on general mortality was analyzed with the use of binary logistic regression. Survival was estimated by the Kaplan-Meier product-limit method. Comparison of survival in relation to various factors was calculated using the Wilcoxon-Gehan method. To compare other factors between the groups the Fisher exact test was used.

Results

There were two early postoperative deaths (6.8%). One was related to hemorrhage and one to the herniation of the

Table 1. Major postoperative complications occuring in 10 patients after extended pneumonectomy

Patients	Postoperative complication
No. 1	Hemorrhage, atrial fibrillation
No. 2	Bronchopleral fistula, pyothorax
No. 3	Atrial fibrillation, pulmonary edema
No. 4	ARDS, bronchopneumonia
No. 5	Ventricular tachycardia, pulmonary edema
No. 6	Hemorrhage
No. 7	Pleuropneumonia, pyothorax
No. 8	Respiratory failure (mechanical ventilation)
No. 9	Transient cerebral ischemia
No. 10	Congestive heart failure

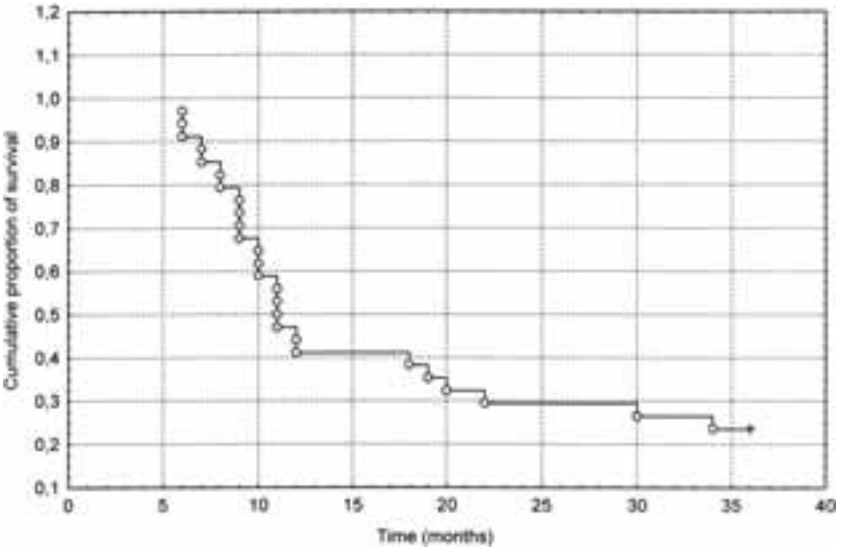

Figure 1. Cumulative proportion of survival (Kaplan-Meier method) of 34 patients who had extended pneumonectomy for lung cancer.

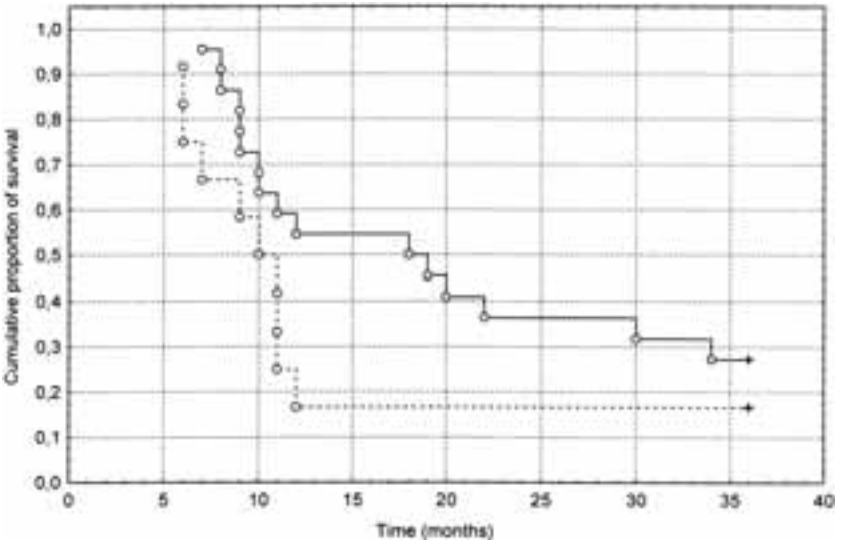

Figure 2. Cumulative proportion of survival (Kaplan-Meier method) comparing patients with tumor T3 stage (running line) and patients with tumor T4 stage (dotted line).

heart after right pneumonectomy. Major complications occurred in 10 patients (29%) and were as follows: massive bleeding (demanding rethoracotomy), severe cardiac rhythm disturbances, ARDS, pulmonary edema, bronchopleural fistula and pyothorax. Details of these complications are shown in Table 1.

Postoperative histopathological examination revealed squamous cell carcinoma in 27 patients, adenocarcinoma in 9 patients and large cell carcinoma in one patient, findings which were in complete accordance with the preoperative biopsy results. In three patients N2 involvement was found and they were given platin based standard adjuvant chemotherapy. One of these patients was preoperatively assigned to stage IIIa and the other two to stage IIIb. These patients were excluded from further investigation and the final number of cases studied was 34. Eighteen patients were classified as stage IIIa (T3,N1), sixteen as IIIb (T4,N0 – 5 and T4,N1 – 11). Of these, an oncological margin of safety resection (R0) was achieved in all but five cases.

Four patients with involvement of mediastinal organs such as the pericardium (1), VCS (1), esophagus (1) and diaphragm (1) and one after chest wall resection were proved to have residual (microscopic) R1 disease at the postoperative examination of the removed tissue. All five were subjected to standard radiotherapy, but died within the first year of clinical observation.

The mean follow-up period for all patients in this analysis including those who died, was 18 months. Overall survival rates at 1, 2 and 3 years were 43, 30 and 24%, respectively. When the subgroup with only chest wall involvement or mediastinal organ involvement was analyzed separately these rates were: 50%, 42%, 30% and 44%, 24%, 20%, respectively (statistical significance occured only in the second year of follow up: 42% vs 24%, $p<0.05$, Fisher's exact test).

Eight patients survived beyond the 36-month follow-up. Logistic regresion analysis revealed that the only factor significantly affecting mortality was incomplete resection at the microscopic level (R1, $p<0.05$). None of the other factors studied showed any significant impact on mortality. Analysis of survival in relation to various factors such as histopathology, size and location of tumor (T), nodal involvement and mediastinal organ involvement showed that there was only a trend in favor of survival of patients with T3 compared to T4 (Wilcoxon-Gehan, $p<0.1$)

Post mortem examination revealed distant metastases in 8 patients and local recurrence of the disease was detected in 6 patients.

In 65% of the patients the cause of death was directly related to the local or general spread of the disease. In the remaining patients, death was either indirectly related or not related at all to lung cancer (the causes being ischemic heart disease, stroke, pulmonary edema, pulmonary embolism or respiratory failure).

Discussion

In general, patients with T4 disease (IIIb) are not candidates for surgery alone [4, 8, 10]. One of the main issues to be addressed is how to choose, and when to refer to surgery candidates from this subgroup of patients. Sometimes, even with modern imaging techniques, it is hard to decide preoperatively whether the mediastinum is invaded by the tumor or not. An experienced radiologist collaborating closely with the thoracic surgeon can establish an accurate diagnosis in about 90% of cases. The remainder are usually patients examined during surgery and in some a radical resection is achieved. The group of patients discussed in this study consisted of those who were either underestimated preoperatively as T2 and intraoperatively found to be T3 (2 patients), patients with T3 involving the chest wall, pericardium and diaphragm or those in whom the tumor had spread to VCS, aorta, esophagus, tracheal bifurcation or the pulmonary vein in proximity to the left atrium. Our patients were operated on between 1995 and 1999 and in this period of time neoadjuvant therapy in IIIb disease was not used in Poland as a standard procedure. Therefore, those with T3 and T4 disease did not receive induction chemo- or radiotherapy in contrast to the patients with N2 involvement, but these latter patients were excluded from retrospective analysis. Some recent studies suggest that induction chemotherapy or radiotherapy in patients with T3 or T4 may improve late results but there is still no metaanalyzed randomized study which could confirm this thesis [13].

We agree with the findings of other authors that chest wall involvement in patients with NSCLC carries a better prognosis than cancerous spread to any mediastinal organs and the survival rate for the former is markedly higher than for those with mediastinal involvement [2, 6, 11, 16]. We can also confirm the results of some studies suggesting, that the only factor significantly affecting mortality was incomplete resection on the microscopical level (R1, $p<0.05$). None of the other factors studied showed any significant impact on mortality.

The mortality rate of 6.8% was within the generally accepted range for standard pneumonectomies, which is between 2 and 16%. Major complications occurred more frequently after extended pneumonectomies than following the standard operation, a finding which is in accordance with the results of other published studies [4, 7, 9]. However, the complications which occurred in our patients had fatal consequences in two cases only. These results may argue for extended surgical procedures in patients with locally advanced lung carcinoma. Extended operations were, and still are, attractive to many surgeons for two reasons. Firstly, the results of medical treatment for stage IIIb are very poor and, secondly, improvements in surgical technique and perioperative intensive care result in better postoperative survival rates [3, 4, 14, 15]. Therefore, the number of surgical patients who may have a greater chance of long-term survival has increased. The surgical management of patients presenting with a T4 disease involving direct invasion of mediastinal organs carries a risk of incomplete resection and a greater risk of complications due to the extended procedures [1, 7, 14, 16]. We can confirm that, in patients with tumor stage T4 microscopical, residual cancerous spread (R1) was found more frequently than in patients with T3 disease. In addition, we can confirm the failure of adjuvant radiotherapy in this subgroup of patients [11, 12], all of whom died within the first year of clinical observation. The decision whether to use surgery as a single treatment modality, remains therefore controversial [9]. Currently, the number of studies which confirm a survival benefit afforded by cisplatin-based induction chemotherapy followed by radiotherapy and finally by surgery is increasing [10, 13]. This may lead us to establish this combined treatment as a new standard form of therapy for locally advanced, resectable NSCLC [8]. However, individually, all these therapeutic options are associated with high local and distant failure rates, indicating that both local and systemic therapies need to be improved. The use of induction chemotherapy must be considered very carefully because of the higher incidence of postoperative complications, which have been recently reported [5, 10, 13].

It is difficult to draw firm conclusions from a retrospective study on such a relatively small group of heterogenous patients. Nevertheless, we would like to emphasize that, in our opinion, extended operations in lung cancer patients with T3 or T4 disease are justified by a relatively low mortality rate and low number of severe postoperative complications. Late results of this treatment depend mainly on the completeness of the surgical resection.

References

[1] BERNARD A, BOUCHOT O, HAGRY O, FAVRE JP. Risk analysis and long-term survival in patients undergoing resection of T4 lung cancer. Eur J Cardiothorac Surg 2001; 20: 344–349.

[2] CHAPELIER A, FADEL E, MACCHIARINI P, LENOT B, LADURIE F et al. Factors affecting long-term survival after "en block" resection of lung cancer invading the chest wall. Eur J Cardiothorac Surg 2000; 18: 513–518.

[3] DARTAVELLE PG. Herbert Sloan Lecture. Extended operations for the treatment of lung cancer. Ann Thorac Surg 1997; 63: 12–19.

[4] DODDOLI C, ROLLET G, THOMAS P, GHEZ O, SEREE Y et al. Is lung surgery justified in patients with direct mediastinal invasion? Eur J Cardiothorac Surg 2001; 20: 339–343.

[5] DODDOLI C, THOMAS P, THIRION X, SEREE Y, GIUDICELLI R, FUENTES P. Postoperative complications in relation to induction therapy for lung cancer. Eur J Cardiothorac Surg 2001; 20: 385–390.

[6] ELIA S, GRIFFO S, GENTILE M, COSTAIBLE R, FERRANTE G. Surgical treatment of lung cancer invading chest wall: a retrospective analysis of 110 patients. Eur J Cardiothorac Surg 2001; 20: 356–360.

[7] FUKUSE T, WADA H, HITOMI S. Extended operations for non-small cell lung cancer invading great vessels and left atrium. Eur J Cardiothorac Surg 1997; 11: 664–669.

[8] GORDON GS, VOKES EE. Chemoradiation for locally advanced, unresectable NSCLC. New standard of care, emerging strategies. Oncol (Huntingt) 1999; 13: 1075–1088.

[9] KODAMA K, HIGASHIYAMA M, YOKOUCHI H, TAKAMI K, YASUDA T, KABUTO T. Survival and postoperative complications after extended surgery for non small lung cancer. A retrospective study. J Thorac Cardiovasc Surg 1999; 47: 546–551.

[10] MACCHIARINI P, CHAPELIER AR, MONNET I, VANNETZEL JM, REBISCHUNG JL et al. Extended operations after induction therapy for stage IIIb (T4) non small cell lung cancer. Ann Thorac Surg 1994; 57: 966–973.

[11] PAIROLERO PP. Extended resections for lung cancer. How far is too far? Eur J Cardiothorac Surg 1999; 16 Suppl 1: S48–S50.

[12] PORT META-ANALYSIS TRIALIST GROUP. Postoperative radiotherapy in non small cell lung cancer: systemic review and meta-analysis of individual patient data from nine, randomized controlled trials. Lancet 1998; 25: 257–263.

[13] RENDINA EA, VENUTA F, DE GIACOMO T, CICCONE AM, RUVOLO G et al. Induction chemotherapy for T4 centrally located non small cell lung cancer. J Thorac Cardiovasc Surg 1999; 117: 225–233.

[14] SHIRAKUSA T, KAWAHARA K, IWASAKI A, OKABAYASHI K, SHIRAISHI T et al. Extended operation for T4 lung carcinoma. Ann Thorac Cardiovasc Surg 1998; 3: 110–118.

[15] SPAGGIARI L, THOMAS P, KONDO H, ROLLET G, REGUARD JF et al. Superior vena cava resection with prosthetic replacement for non small cell lung cancer: long-term results of a multicentric study. Eur J Cardiothorac Surg 2002; 21: 1080–1086.

[16] TAKAHASHI T, AKAMINE S, MORINAGA M, OKA T, TAGAVA Y, AYABE H. Extended resection for lung cancer invading mediastinal organs. J Thorac Cardiovasc Surg 1999; 47: 383–387.