The role of surgery in integrated therapies for non-small-cell lung cancer

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Summary

Surgery represents the best treatment for early-stage non-small-cell lung cancer (NSCLC). In selected cases, even locally-advanced cancers may be suitable for surgical treatment. The combination of chemotherapy (with or without radiotherapy) and surgery has proved potentially useful in improving survival, but pre-operative treatment may represent a risk factor for the onset of post-operative complications. Studies performed to date indicate the need for further multidisciplinary research with a view to identifying more advantageous treatment modalities, particularly for locally-advanced NSCLC.

Key words: combined modalities, non-small-lung cancer, surgery

Introduction

Surgery remains the only curative treatment for patients with non-small lung cancer (NSCLC) [1]. It offers the best chance of long-term survival and cure providing the tumor is confined to the chest and is resectable.

The survival for stage I and II resected disease ranges from 38% to 76% [2]. Surgery is the best treatment for early stage disease. However, it is important to adopt the appropriate procedure to remove the tumor and the loco-regional nodes. Lobectomy remains the most appropriate resection for most lung cancers, since it is an anatomical resection that removes the regional lymph nodes coursing along the lobar bronchus. However, in patients with borderline pulmonary function, a lesser resection may offer the best alternative. Even today, pneumonectomy carries a peri-operative mortality rate of at least 5%, so an entire lung should only be removed when it is strictly necessary [3]. Sleeve resection or bronchoplastic procedures, when technically feasible, are methods that enable radical removal of the tumor, while avoiding pneumonectomy and preserving lung tissue. Even with proximal involvement of the pulmonary artery, partial resection or sleeve resection of the artery is feasible to avoid having to remove the entire lung. Our experience with bronchoplastic procedures demonstrates that these techniques represent safe and effective therapies for selected patients with pulmonary malignancies [4].

The optimal treatment for patients with locally advanced NSCLC, which accounts for about 40% of cases of NSCLC, remains open to debate [5]. Since a large number of patients have stage III disease, even small improvements in treatment can reduce the high rate of mortality recorded for lung cancer.

The term 'locally advanced' (stage III) covers situations with the involvement of structures outside the lung parenchyma, whether by direct extension (T-factor) or nodal involvement (N-factor). Stage III NSCLC is further divided into stage IIIA (T3 and/or N2), which designates potentially resectable tumors, and stage IIIB (T4 and/or N3) which includes tumors that are usually considered unresectable. In stage IIIA and selected cases of stage IIIB disease, there are groups of patients with a genuine chance of cure by surgery, i.e., patients with T3N0/N1 disease, carefully selected patients with T4No/N1 disease and patients with N2 'minimal disease'.

Five-year survival rates for resected T3N0/N1 patients with NSCLC have reportedly ranged from 33% to 59% [6–10] and surgery remains the treatment of choice in stage IIIA (T3) patients. Postoperative treatment for patients who have undergone chest wall resection with pulmonary resection remains controversial. There are no randomized studies comparing postoperative radiation therapy with no further treatment after complete resection.

Patients with T4 disease by extension to the mediastinum may benefit from radical surgical treatment. This is true when partially infiltrated structures (such as the vena cava, left atrium and carina) can be resected. However, it is important to recognize that, despite the apparent feasibility of removing some of these invasive lesions, the prognosis for long-term survival remains poor. Nonetheless, a combined-modality approach to patients with T4 disease may produce survival results comparable with those observed for T3 disease. N2 disease in combination with a T3 or T4 primary is associated with five-year survival of less than 10%, however, even when resection is performed [11].

Surgical results with stage IIIA (N2) patients are unfavorable and surgery is not considered as a standard treatment for this group of patients, though there is a
chance of long-term survival in selected patients with N2 disease.

Martini and Flehinger observed in a group of 151 N2 patients submitted to radical surgery that the best survival was obtained in patients who were thought preoperatively, on the basis of chest radiography, to have N0 or N1 disease: they achieved a five-year survival rate of 35% as opposed to 0% for those diagnosed as having N2 disease prior to the operation [12]. Moreover, patients who had lower mediastinal node metastases confined to a single nodal station experienced a 30% five-year survival rate after complete resection [13–15]. Surgical resection is still an accepted treatment for this latter group of patients, but they represent only a quarter of all patients with N2 disease [16].

By contrast, extracapsular mediastinal node disease, superior mediastinal node metastases, and multiple levels of mediastinal node involvement are associated with a five-year survival rate of less than 10%, even after complete surgical resection. The prognosis for stage IIIA patients who have bulky or multi-level N2 disease is so poor that surgical resection is no longer considered appropriate initial therapy. This has led to investigations on the potential role of preoperative induction (neo-adjuvant) chemotherapy, either alone or with radiotherapy. For N2 clinical disease, both local control and overall survival were influenced by radiation (five-year survival rate 10% [17]), but 50% to 80% of patients developed distant metastases during or shortly after treatment, emphasizing the need for systemic therapy in stage III NSCLC [18]. The rationale is that the addition of chemotherapy will control micrometastases as well as reduce the size of the primary tumor to facilitate the local control achieved by resection.

There are numerous reports on the successful use of neo-adjuvant chemotherapy for downstaging locally-advanced NSCLC. Perhaps the prototype phase II trial of neo-adjuvant therapy for N2 disease was begun by investigators at the Memorial Sloan-Kettering Cancer Center in 1986: only patients with N2 disease, and specifically those with bulky disease, underwent surgery after two or three cycles of chemotherapy with cisplatin, vinblastine, and mitomycin C (MPV). Complete resection was feasible in 65% of patients, with a median survival and five-year survival of 27 months and 26%, respectively [19]. The cumulative data in two other studies (Toronto Group and Lung Cancer Study Group [20, 21]) demonstrate that neo-adjuvant therapy with MVP is feasible and effective, though a risk of mitomycin-induced pulmonary toxicity, especially postoperative adult respiratory distress syndrome (ARDS), was observed. In a multi-institutional study conducted by the Cancer and Leukemia Group B (CALGB), patients with N2 disease received two cycles with cisplatin and vinblastine. Patients who showed no signs of progressive disease underwent resection followed by sequential chemotherapy and radiation therapy, with a median survival and three-year survival rate of 20.9 months and 23%, respectively [22]. In two randomized trials in highly-selected patients, survival was better among patients who received pre-operative cisplatin-based chemotherapy than among those who received surgery alone, but both of these trials included a heterogeneous patient population comprising cases of N2 disease as well as patients with T3N0 disease [23, 24].

Combination chemo/radiotherapy has also been feasible in stage III disease. Such combined modality regimens may be associated with potential additional benefits but also with toxicity problems. A recent extensive phase II neo-adjuvant trial was performed by the Southwest Oncology Group (SWOG) that studied concurrent induction chemotherapy with cisplatin + etoposide and radiation in stage IIIA and IIIB patients [25], with a median survival and three-year survival rate of 13 months and 27%, respectively, and an 8% incidence of postoperative death.

Our experience with locally-advanced NSCLC patients submitted to neo-adjuvant chemo- and/or radiotherapy between January 1990 and December 1997 consists of 91 patients. Twenty-eight had preoperative irradiation, thirty-one had preoperative chemotherapy and thirty-two had preoperative chemotherapy and irradiation. Our series does not belong to a homogeneous multi-modality therapy protocol because patients often come from different cancer centers and have not previously been evaluated at our Department. All patients had clinical stage IIIA or IIIB disease, according to the TNM classification. Histological examination revealed 44 adenocarcinomas, 37 epidermoid carcinomas and 4 large-cell carcinomas. Six patients had no evidence of tumor (before neo-adjuvant therapy, the diagnosis was epidermoid carcinoma for four patients and adenocarcinoma for two). The overall 30-day mortality was 3.3% (three patients died of cardiopulmonary failure). Sixteen patients (17.6%) had postoperative complications. The median survival and one-year and three-year survival rates were 20 months, 74% and 24%, respectively. Thirty-six patients are still alive (maximum 84 months).

In 1996 we published a phase II study with a view to evaluating the feasibility, response rate and effect on survival of full-dose polychemotherapy delivered concurrently with bifractionated radiotherapy at radical doses in a subset of patients with marginally resectable or unresectable stage IIIA–B NSCLC [26]. The adoption of a daily bifractionated irradiation scheme was based on the opportunity to administer a higher dose over a relatively short period of time, and thus to proceed with surgical treatment earlier. This study included 39 patients (24 with clinical stage IIIA and 15 IIIB disease): 19 were considered resectable and 20 were unresectable. Treatment consisted of two courses of cisplatin for one day plus etoposide for three days, delivered from day 1 to day 22, plus radiotherapy delivered in two cycles from day 3 to day 12 and from day 24 to day 33 (total dose 5120 cGy in 31 days). Four patients failed to complete the induction treatment (because of early death in three patients and refusal in one). The response rate was 67%. After induction treatment, patients with an objective
response or marginally resectable with stable disease underwent surgery, followed by three courses of adjuvant chemotherapy. Marginally resectable patients with disease progressing under treatment or inoperable patients with stable disease under treatment were not resected. So 21 patients underwent surgery (15 IIIA patients and 6 IIIB patients): 20 had radical resection and 1 had exploratory thoracotomy. Surgical specimens were tumor-free in 3 patients (14%); only microscopic tumor was found in 8 patients (38%), and macroscopic residual tumor was found in 10 (48%). Resected patients had a median survival of 21 months versus 10 months among unresected patients (P = 0.01). No significant difference emerged between stage IIIA and stage IIIB cases.

The study demonstrated the feasibility of our complex combined treatment and of the administration of a radical surgical treatment within a short period of time since the median time of induction therapy was 37 days. Moreover, said interval was too short to allow for the normal lung tissue to develop fibrotic changes and consequent surgical difficulties. The most important side effects observed during treatment were leukopenia (27%), thrombocytopenia (9%) and esophagitis with dysphagia (23%). Postoperative complications were frequent: 2 patients had pulmonary failure, 2 experienced cardiac arrhythmia, 1 had a lung abscess, 1 had a bronchopleural fistula, for a total of surgery-related complications in 6 patients (29%); surgery-related deaths were 2 of 21 (10%).

Trials on neo-adjuvant therapy have demonstrated the feasibility of combined modality treatment in stage III NSCLC: the resectability and survival rates appear to be at least 50% better than in the past with surgical treatment alone. In all trials reported to date, however, the most common form of relapse has been distant metastatic disease, which emphasizes the need for more effective systemic treatment. In our experience, for Pancoast's tumor with preoperative irradiation followed by resection of the tumor, chest wall and adjacent structures, the role of surgery is essential, but it is necessary not only to improve the results of radiotherapy, but even to utilize chemotherapy: in fact 33% of deaths were due to local recurrence, but 52% were due to multiple metastases [27].

With neo-adjuvant therapy there is an increased risk of postoperative complications. Various chemotherapeutic agents are associated with potential perioperative problems, e.g., the risk of exacerbating cisplatin-induced nephrotoxicity by volume depletion. It is important to avoid fluid overloading in patients whose pulmonary vascular bed may be compromised by preoperative therapy (at risk of ARDS due to mitomycin or radiation). Moreover, resection after preoperative therapy can be extremely difficult and hazardous because of the fibrosis that often results as a response to such therapy. Intraoperatively, it is often impossible to determine whether there is any residual active tumor within an area of dense fibrosis and difficult decisions must be taken as to the extent of bronchopulmonary resection [28]. Finally, preoperative treatment increases the risk of surgical complications affecting the bronchial stump and anastomoses. In our experience with bronchoplastic and tracheo-bronchoplastic procedures in patients with bronchogenic carcinoma, we found a significant difference in 30-day post-operative mortality between patients who had or had not received preoperative irradiation [4].

Despite numerous studies addressing preoperative therapy, be it chemotherapy alone or combined with radiation therapy, the question as to the role of surgical resection in the outcome of patients with N₂ disease remains unanswered. To date there have been no conclusive studies to demonstrate that surgery is superior to radiation therapy in controlling local disease in such patients.

References

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