



Controversies in oncology: surgery for small cell lung cancer? It's time to rethink the case

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Small cell lung cancer (SCLC) is a devastating disease, which owns the poorest prognosis of all different types of lung cancer. There has been only modest progress in its treatment over the last decades, and 5-year survival rates still are as low as 5%–7%.¹ Main reasons for these disappointing results are the early and rapid spread of the tumour and the high recurrence rate after initial response to chemotherapy. Both these features of SCLC have at the same time been used as strong arguments against the use of surgery as part of any treatment algorithm. However, over the last two decades, we have seen major improvements in diagnosis, precision of staging and development of more sophisticated multimodality-based treatment strategies, which have changed the therapeutic standards in many fields of oncology. It therefore seems to be timely and appropriate to also rediscuss the treatment algorithm for SCLC, especially with regard to a potential contribution of surgery for limited-stage SCLC.

Although surgery was in fact the treatment of choice in patients who were diagnosed at an early limited-stage of SCLC, many decades ago, chemotherapy and radiation therapy soon became the only accepted treatment modalities, mainly based on the findings of three randomised studies which, seen from today's perspective, did all not fulfil modern quality requirements.

In 1973, the medical research council trial² compared surgery and radiotherapy for the primary treatment of SCLC. Patients treated in the surgery group had a significantly inferior mean survival (199 vs 300 days, $p=0.04$) compared with the radiotherapy group. However, the study included patients in an advanced disease stage, who were diagnosed by rigid bronchoscopy, since modern staging techniques such as high-quality CT and PET scans, as well as endobronchial sonography, were not available, with the result that many patients had exploratory thoracotomy or

incomplete R2 resection and that an unusual high perioperative mortality rate and pneumonectomies was observed. Even more important, chemotherapy was not used as a standard treatment in this study at all.

In 1994, a second prospective randomised trial by Lad *et al*³ compared surgery plus adjuvant thoracic and whole brain irradiation versus thoracic and whole brain irradiation alone. In this study, all patients were treated with induction chemotherapy (cyclophosphamide, doxorubicin and vincristine), and the responders were randomised into two treatment arms. Since the survival rates were not different between the treatment groups (median overall survival (OS) 15.4 months surgical arm vs 18.6 months non-surgical arm, $p=0.78$), the authors concluded that the use of surgery within a multimodality protocol for treatment of limited disease (LD)-SCLC cannot be supported.

However, this first multimodality study had major limitations such as including advanced stages that were diagnosed by rigid bronchoscopy with biopsies from central visible tumours, 10% of the patients in the surgical arm not undergoing a surgical procedure at all and, even more important, a considerable number of patients having bulky mediastinal nodal involvement.

The third prospective randomised study that became available derived from China in 1995. Forty patients with stage III SCLC were treated with chemotherapy first and then randomised in a surgical and chemotherapy arm or radiotherapy and chemotherapy arm.⁴ Survival rates were higher in the surgical-chemotherapy group compared with the radiotherapy-chemotherapy group, but this difference did only reach statistical significance at 2 years.

Because of the low number of included cases and the lack of information on staging of these patients, the results of this study were difficult to interpret.

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Based on these results, combined chemotherapy and radiotherapy became the widely accepted standard treatment for all stages of SCLC, and surgery was only performed as an individual treatment option in very selected early-stage SCLC cases.

In recent years, however, the place for surgery in the treatment of SCLC started to be rediscussed, since data from larger retrospective observational studies and cancer registries became available, which suggested a potential role and benefit for surgery in well-selected patients with early-stage SCLC.⁵⁻¹¹

An analysis of the US National Cancer Database (NCDB) investigated 954 patients with stage pT1-2N0M0 SCLC treated with primary surgery with or without adjuvant therapy.¹¹ Overall, 5-year survival rate was 47%, and patients treated with primary surgery followed by adjuvant chemotherapy and brain radiation achieved an even more remarkable 5-year OS of 67%. Furthermore, a clear survival benefit for patients treated with lobectomy compared with other types of lung resection was demonstrated.

In another recent analysis of the NCDB, Combs *et al*⁹ reported on 2476 patients who had primary surgery for stage I-IIIa SCLC by curative intent. Five-year OS was 51% in stage I and 25% in stage II. The addition of chemotherapy to surgery resulted in further improvement of OS (HR 0.57). Similar to other trials, lobectomy was found to be associated with a 5-year OS of 40% compared with 21% and 22% for sublobar resection and pneumonectomy, respectively.

Importantly, the results from both trials are well comparable with survival rates described for pathologically staged IB-IIB (5-year OS ranging from 68% (IB) to 53% (IIB)) NSCLC from the most recent International Association for the Study of Lung Cancer (IASLC) TNM Classification of Malignant Tumours 8 (TNM-8) staging proposals.¹²

A third large cancer registry study has investigated the role of surgery in SCLC from data obtained by the Surveillance, Epidemiology and End Results (SEER) database.⁷ This study involved 2214 patients with stage I and II SCLC, diagnosed between 1988 and 2005, of whom 584 cases were treated with surgery. Interestingly, the use of surgery peaked at 47% in 1990 but declined to 16% by 2005, most likely as a result of the previously published randomised trials that did not support the routine use of surgery in early-stage SCLC. Despite that, the authors of this study reported a favourable outcome of patients treated with lobectomy (median OS 50 months (4.2 years)), which was significantly superior to patients with sublobar resections (30 months) or radiotherapy alone (20 months). Furthermore, the addition of local radiotherapy to resection provided no additional survival benefit, suggesting that one local treatment modality (ie, radical resection) might be adequate for treating patients with operable stage I-II SCLC.

A second SEER database analysis especially focused on the extent of surgery in early-stage SCLC.⁶ In 863 patients

who underwent surgery, lobectomy was associated with a median OS of 65 months and a 5-year OS rate of 53%. The use of pneumonectomy or sublobar resections resulted in less favourable outcome.

These findings have resulted in a general reconsideration of the role of surgery for treatment of SCLC. Although there are still no prospective randomised trials available, which have been performed under modern diagnostic and treatment standards, recent clinical guidelines have already adapted the new paradigm and recommend surgery for patients with early-stage SCLC,^{13 14} as well as adjuvant chemotherapy after first-line resection for stage T1-2N0M0 tumours, as this was associated with favourable outcome in most retrospective series.^{9 11}

Treatment of SCLC in the third decade of the 21st century will therefore most likely significantly differ from the uniform chemotherapy/radiotherapy approach of the past. For well-staged early disease, local tumour control by surgery, either upfront or after chemotherapy induction, is expected to become the standard of care.

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