

# Multimodality Therapy and the Role of Surgery for Small Cell Lung Cancer

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## Abstract

This study aimed at exploring the multimodality therapy and the role of surgery for small cell lung cancer in all its stages. The researchers proceeded to a review of the Medline PUBMED (January 1980 to Week 1, January 2016) and EMBASE (January 1980 to Week 1, January 2016) literature focusing on retrospective studies where the impact of surgery on survival was evaluated as a stage dependent event. Studies reporting survival rates less than 5 years were excluded. Bibliographies, reference lists of identified studies and review articles were hand-searched. And the study concluded that since a control randomized trial between chemo radiotherapy and primary surgery is difficult to be obtained among patients with limited SCLC, the question how to best integrate surgery into a multimodality approach treatment will remain unclear. We still need to further define and clarify our treatment strategy.

## 1.1 Introduction

Small cell carcinoma of lung (SCLC) constitutes about 15% of the lung cancers and due to its clinical and biologic characteristics is considered distinct from other lung carcinomas, collectively termed as non-small-cell lung carcinomas (NSCLC) (*see figure 1*). SCLC exhibits an aggressive behavior that is characterized by rapid growth, early metastasis to distant sites, and exquisite sensitivity to chemotherapeutic agents and radiation. Currently combined chemotherapy and thoracic radiation therapy is the standard treatment for patients with limited-stage disease SCLC (LD): the combination of platinum and etoposide with thoracic radiation therapy being the most widely used regimen with clinical trials consistently having achieved median survivals of 18 to 24 months and 40% to 50% 2-year survival rates with less than a 3% treatment-related mortality (Koul, 2012).

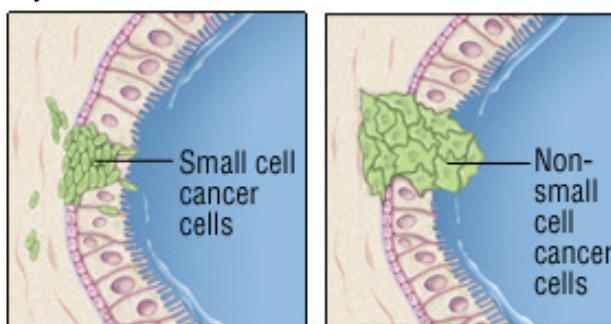


Figure (1): Small cell cancer cells and Non-small cell cancer cells

Small cell lung cancer (SCLC) is distinct from non-small cell carcinoma (NSCLC) both biologically and clinically. SCLC comprises approximately 15 percent of all lung cancers. It occurs almost exclusively in cigarette smokers; in one series, only 2 percent of 500 patients with SCLC did not have a smoking history (Albain, Swann, Rusch, Turrissi, Shepherd, Smith & Fry, 2009).

SCLC is also the most common histologic subtype among uranium miners, probably due to exposure to radioactive radon, which is a byproduct of uranium decay (Keller, Adak, Wagner, Herskovic, Komaki, Brooks & Johnson, 2000).

SCLC is distinguished from NSCLC by its rapid growth characteristics and the early development of widespread metastases. SCLC is highly responsive to chemotherapy, while there is a substantial historical experience documenting the futility of local-regional modalities alone. Prior to the introduction of systemic chemotherapy, median survivals for patients with limited disease (LD) and extensive disease (ED) were approximately 12 weeks and 5 weeks, respectively (Zelen, 1973).

Many studies have demonstrated that chemotherapy significantly improves survival when compared with surgery or radiation therapy (RT) alone, and combination chemotherapy is the mainstay of therapy for both LD and ED SCLC.

Although the combination of chemotherapy plus radiation improves survival in patients with limited stage disease, local recurrence rates in patients undergoing chemo radiotherapy are between 35 and 50 percent. This

high local failure rate has led to reconsideration of the role of surgery as an improved way to achieve local control.

Surgery for early stage small cell lung cancer (SCLC) is rarely used. However, results from a population-based database support an increased role for its use: surgery with adjuvant chemotherapy with or without radiation for node-negative SCLC was associated with better survival compared with concurrent chemo radiation, study findings reported at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting has shown (Yang, Chan & Yerokun, 2016).

Similarly in a recent review on the role of surgery in SCLC Leo and Pastorino (Leo & Pastorino, 2003) concluded that surgery can be proposed in T1, T2/N0 disease followed by adjuvant chemotherapy. Surgery in stages II and III (*see figure 2*) must be planned in a multidisciplinary basis, in the context of controlled trials. Likewise, Waddell and Shepherd (Waddell & Shepherd, 2004) support the option of surgery in stage I although whether is offered as the initial treatment or after induction therapy remains controversial.

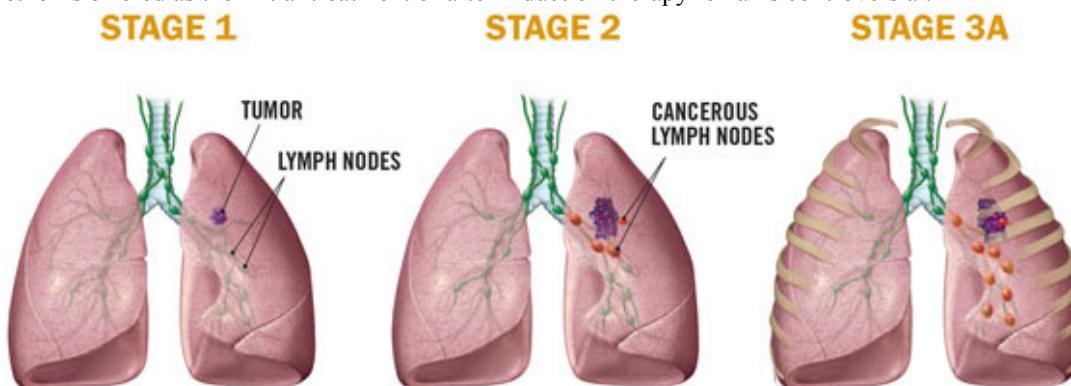


Figure (2): Small cell of lung cancer (stage 1, 2 and 3)

### 1.2 Problem Statement

Today the question whether surgery should be the first step followed by chemotherapy or preoperative chemotherapy followed by adjuvant surgery is the subject of several cooperative trials. It seems reasonable to expect that with a longer period of observation the results of these ongoing trials would lead to a conclusion, which sequence would be preferable. Most probably it would turn out that for stage I, II surgery would be the first step followed by chemo- and radiotherapy and for stage III disease debulking chemotherapy to distinguish responding patients who thereafter may receive adjuvant surgery would be preferable (Lim, Belcher, Yap, Nicholson & Goldstraw, 2008).

Therefore, the problem of this study lies in its attempt to explore the multimodality therapy and the role of surgery for small cell lung cancer in all its stages.

### 1.3 Surgery Revived

The role of surgery was reevaluated after the introduction of the TNM staging system. The clinical trials that appeared in the literature to argue surgical resection were mostly no randomized and retrospective. Shields et al (Shields, Higgins, Matthews & Keehn, 1982) reviewing the Veterans Administration Surgical Oncology Group experience, postulated that surgery is indicated in LD-SCLC, particularly stage T1, N0 while the issue of limited local recurrence following surgery was pointed out by Shepherd et al from the Toronto group (Shepherd, Ginsberg, Evans, Feld, Cooper, Ilves, Todd, Pearson, Waters & Baker, 1983).

Similarly the Brompton experience showed 5 year survival rate of 57.1% for stage I (Shah, Thompson & Goldstraw, 1992).

Eventually, these reports revived the interest in the role of surgery in LD-SCLC. Meanwhile adjuvant chemotherapy was evaluated in a more recent report by the Toronto Group and demonstrated an improved survival (Shepherd, Evans, Feld, Young, Patterson, Ginsberg & Johansen, 1988).

There was the need for a prospective randomized trial and indeed this was conducted by the Lung Cancer Study Group. In this trial surgery after induction chemotherapy failed to show a survival improvement or less local recurrence rate compared to radiotherapy (Lad, Piantadosi, Thomas, Payne, Ruckdeschel & Giaccone, 1994).

This study has been criticized mainly because patients with T1, N0 disease were excluded from thoracotomy and therefore they were denied of the benefit that radical resection can offer in long term survival. Therefore the role of surgery in the integrated management of small cell lung cancer remained under investigation with retrospective studies demonstrating 5 year survival of approximately 50% for stage I disease (Lucchi, Mussi, Chella, Janni, Ribechini, Menconi & Angeletti, 1997).

#### 1.4 Justification for surgery in early stage SCLC

Anraku and Waddell (2006) in a recent excellent review summarized the rational for surgery in SCLC:

- 1- Small peripheral lung nodules that are in fact typical or atypical carcinoids tumors may be misdiagnosed as SCLC.
- 2- Histologically mixed tumors with both SCLC and NSCLC components may fail to chemo radiation protocols since there is less sensitivity of the NSCLC component to chemotherapy. Indeed it has been shown that final histology for tumors initially reported as SCLC revealed a NSCLC component in 11–25%. Furthermore studies on neuroendocrine tumors showed that 26.5% of resected SCLC are actually included in the combined small cell lung carcinomas according to WHO more recent classification. Thus it seems more logical to offer surgery in mixed or combined small cell tumors.
- 3- Surgical resection for T1-2, N0, M0 SCLC could offer better local control of the disease compared to chemotherapy alone. Indeed current chemo radiotherapy protocols have demonstrated local failure rates approximating 50%. Additionally R0 surgical resection after induction chemo radiotherapy has shown a control of local relapse in almost 100% of the patients. Likewise, 5 and 10 year survival rates were 39% and 35% for all included patients, resected or not and 44% and 41% respectively for patients with stage IIB to IIIA treated with a trimodality approach including adjuvant surgery.
- 4- Salvage surgery could be preferable compared to second line chemotherapy in cases where after an initial response to chemo radiotherapy a chemotherapy resistant tumor or a local recurrence of the disease has occurred. Similarly patients with mixed histology, as noted above, who present with residual or non-responsive tumor after chemo radiotherapy should better be treated with salvage surgery.
- 5- Second primary, histologically proved NSCLC, tumor after curative chemo radiotherapy for initial SCLC should be surgically resected. Ankaru and Waddell brilliantly emphasized this indication since any new tumor appearing two years after an initial SCLC successfully treated could be a NSCLC.

#### 1.5 Recent evidence supporting the role of surgery

So far there have not been any data from prospective randomized control trials comparing chemotherapy or chemo radiotherapy with induction chemo radiotherapy followed by adjuvant surgery. However accumulated data from non-randomized clinical trials have shown that surgery, as part of multimodality treatment protocols, can contribute to both prognosis and local recurrence control. Granetzny et al (2006) in a recent retrospective trial studied the effect of surgery in a trimodality treatment in SCLC. The study included 95 patients, the majority being in stages I and II. Patients were divided in two groups. Group I received surgery followed by adjuvant, mainly platin doublets and anthracycline based, modern chemotherapy protocols. Group II had definitive surgery following neoadjuvant chemotherapy which continued postoperatively in addition to thoracic and cranial radiotherapy. They concluded that patients with stage I and II SCLC can be treated with promising results using a combination of primary surgery and adjuvant chemotherapy as well as thoracic and cranial irradiation. Patients in group II appeared to benefit from lung resection after induction chemotherapy only if complete clearance of mediastinal nodal disease has been achieved, as proven by repeated mediastinoscopy prior to surgical intervention.

#### 1.6 Conclusion

Despite the lack of scientific evidences based on randomized trials that surgery in limited disease may be superior to chemo radiotherapy, we believe that time has come to accept that it has to play an important role either as a primary treatment or as adjuvant therapy, always in the field of multimodality treatment approaches. It is justified to offer primary surgery followed by chemo radiotherapy in stage T1, N0 and possibly in stage T2, N0. In stage II induction concurrent chemotherapy and radiotherapy should be given and radical resection should follow with intent to curative therapy only if there has been a definite initial response to the induction treatment. Prophylactic cranial irradiation should be part of the treatment program only for those patients obtaining a complete remission. In stage IIIA, if adjuvant surgery is planned, a mediastinoscopy should always precede the surgical treatment. If mediastinal clearance has not been achieved then we doubt whether surgery will contribute to survival or local recurrence. Finally surgery should be considered in mixed tumors, as a salvage treatment or in the rare cases of a second NSCLC tumor.

Since a control randomized trial between chemo radiotherapy and primary surgery is difficult to be obtained among patients with limited SCLC, the question how to best integrate surgery into a multimodality approach treatment will remain unclear. We still need to further define and clarify our treatment strategy.

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