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## Surgery in Small-Cell Lung Cancer: Past, Present and Future

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### 1. Introduction

Small-Cell Lung Carcinoma (SCLC) represents about 15% of all lung cancers diagnosed worldwide. Although its incidence is diminished in the last decades, SCLC continues to represent an almost fatal disease due to its propensity to local relapse and distant metastasis, despite initial responsiveness to therapies. Biological behaviour of SCLC has therefore lead to consider it as a systemic disease *per se* not amenable of surgical resection: the Veterans Administration Lung Study Group (VALSG) two-stage classification was in fact based on field irradiation criteria and has been applied to SCLC for long-time.

The introduction of TNM staging system, the common recurrences of local disease despite initial complete response after chemo-radiation therapy, the lack of a valid maintenance therapy after remission or a second-line therapy after relapse renewed interest in surgery in a multimodal treatment setting. However, the second prospective randomized trial in 1994, did not confirm any significant advantage of surgery compared to chemo-radiation therapy and several retrospective studies published in the same years failed to provide strong evidences of surgery's benefits. Lack of homogeneity in design of clinical trials, which are mostly dated, patients selection and other confounding factors made results of meta-analysis too much inconsistent to be added to guidelines; for these reasons, nowadays, surgery is recommended only in small peripheral nodules without nodal involvement (proven by invasive preoperative staging).

Advances in comprehension of biological pathways underlying carcinogenesis in SCLC are the next steps that could deeply modify the approach to disease (patients selection and prognostic stratification, chemosensitivity and treatment modality) beyond the mere histology. Molecular profile should lead to identify subsets of tumours with more favourable prognosis, especially in terms of systemic control of disease, which is actually a major issue in SCLC; these subsets could be overlapped to NSCLC regarding to natural history of disease, making their treatment similar, including indication to surgery.

The aim of this review is to analyze literature to deduce which has been, is actually and could be the role of surgery on overall survival and pattern of recurrence of patients affected by SCLC.

## 2. Clinical background

### 2.1 Epidemiology

Small-cell Lung Carcinoma (SCLC) accounts for approximately for 13-15% of all newly diagnosed cases of lung cancer worldwide (in United States, more than 220.000 new cases lung carcinoma were diagnosed in 2010, with about 160.000 cancer-related deaths [American Cancer Society, 2010]).

More than 90% of patients with SCLC are elderly, current or past heavy smokers, and risk rises with increasing duration and intensity of smoking [Devesa et al., 2005]; rare cases have been reported in people who never smoked [Antony et al., 2010].

Incidence of SCLC is decreasing compared to that of adenocarcinoma [Govindan, 2006]; this reflects the decreased prevalence of smoking in industrialised countries. However, the burden of disease is shifting to developing countries (Asia and Eastern Europe), where, on the contrary, an increase of incidence is expected in next years. Further investment in research against SCLC is therefore warranted.

A revision in the WHO classification of lung cancers might also have contributed to incidence falling of SCLC, as some borderline cases previously described as mixed subtypes are now classified as NSCLC [Travis et al., 2004].

Median survival of untreated patients ranges from 2 to 4 months from diagnosis: historical data of untreated patients come from an old study of VALSG (Veterans Association of Lung Study Group) comparing cyclophosphamide to placebo. In IASLC (International Association for Study of Lung Cancer) database for staging project (the largest series of SCLCs reported), 5-year survival rates were 38/21% for clinical stages IA/IB and 38/18% for clinical stages IIA/IIB, respectively. Considering only resected, fully staged patients, 5-years survival rates were 53/44% for p-stages IA/IB and 43/35% in p-stages IIA/IIB, respectively.

### 2.2 Clinical presentation

Two thirds of SCLCs present as peribronchial lesions with infiltration of bronchial submucosa. Extensive mediastinal lymph node metastases are a common finding at diagnosis; sometimes mediastinal involvement presents as “bulky” disease, causing superior vena cava syndrome. Only in 4-12% of cases SCLC presents as a peripheral “coin lesion” [Quoix et al., 1990].

Clinical presentation of SCLC is strictly related to stage and presence of paraneoplastic syndrome. Common symptoms are cough, wheeze, dyspnoea, haemoptysis for hilar localization. Symptoms may reflect direct involvement of chest wall, superior vena cava, oesophagus, recurrent nerve (pain, mediastinal syndrome, dysphagia, dysphonia) or the site of metastasis (brain, liver, adrenal glands, bone and bone marrow). SCLC is more frequently associated to paraneoplastic syndromes than NSCLC [Gandhi et al., 2006]. The most common are syndrome of inappropriate antidiuresis (15-40% of SCLC patients) and Cushing's syndrome (2-5% of SCLC patients), that can be responsible of infective complications during chemotherapy. Sometimes SCLC presents with dermatological abnormalities as acquired tylosis, trip palms, erythema gyratum repens [Master et al., 2010]. Occasionally SCLC is associated to dermatomyositis, hyperglycemia or hypoglycemia, hypercalcemia and gynecomastia. Neurological syndromes, that may precede diagnosis of SCLC by several months, are caused by cross-reaction of auto-antibodies and T-lymphocytes specific for common tumour epitopes and nervous components [Darnell et al., 2003]. Antibodies directed against the P/Q- type voltage-gated calcium channel in the presynaptic

nerve terminal (expressed by 3% of SCLC) are responsible of Lambert-Eaton syndrome [Payne et al., 2010], that should be differentiated from miastenia gravis, rarely associated to SCLC. Similarly, paraneoplastic encephalomyelitis and paraneoplastic sensory neuropathy have been associated with antibodies directed against Hu proteins, a family of DNA-binding proteins (<1% of SCLC patients) [Gultekin et al., 2000]; neurological symptoms are not always reversible with therapy.

### 2.3 Diagnosis

Although diagnosis of SCLC could be suspected on the basis of clinical and radiological findings, histo-pathological diagnosis is required prior to establish the proper treatment.

SCLC represents the extreme of spectrum of neuro-endocrine lung carcinomas and is defined as pure SCLC or combined SCLC if the non small-cell component accounts for at least 10% of burden disease.

While pre-invasive and in situ lesions are frequently found in NSCLC, they are uncommon in SCLC [Kumar et al., 2005].

Samples can be obtained by bronchoscopy biopsy or fine-needle aspiration from primary tumour, lymph nodes or other metastatic sites. Since tumour shows propensity to spread through tunica submucosa, superficial bronchoscopic biopsy or brush may be falsely negatives. Colliquative necrosis can sometimes hamper diagnosis, especially for cytological samples; however there is a good interobserver agreement among pathologists for differential diagnosis with NSCLC. Immunohistochemistry is used in difficult cases: less than 10% of SCLC tumours are negative for all neuroendocrine markers (chromogranin, synaptophysin, and CD56. Positivity for TTF-1 and cytokeratins helps to distinguish them from lymphomas and other small-cell tumours [van Meerbeek et al., 2011]

### 2.4 Staging

Historically, SCLC had been classified according to the Veterans Administration Lung Study Group (VALSG). In 1957 the VALSG created a dichotomous staging system that took into account the aggressive behaviour of SCLC and the standard of care at that time. This classification underlined the highest importance of radiation therapy and allowed a better selection of patients for this kind of treatment.

The Limited Disease (LD) was characterized by a tumour volume encompassed in one radiation portal (30% of cases): all that was not comprised in one radiation portal was classified as extensive stage (ED), including malignant pleural effusion and haematogenous metastases. [Zelen et al., 1973]. In 1989 the International Association for the Study of Lung Cancer modified the VALSG staging including all non-metastatic patients in the limited stage [Stahel et al., 1991] (Tab.1).

More recently, in 2007, the IASLC based on a retrospective analysis of survival of 8088 patients with SCLC recommended the TNM classification system also for SCLC [Shepherd et al., 2007]. This suggestion comes from the evidence of significantly worse survival of patients with limited-stage disease and N2-N3 lymph node involvement, than for those with N0-N1 lymph node involvement. Patients with pleural effusion without extrathoracic metastasis showed a survival intermediate between stage III and stage IV. In the TNM classification patients with cytology-negative pleural effusion are classified as having stage III disease. This classification is used less frequently in clinical practice because it relies on surgical confirmation for its accuracy and patients with SCLC seldom present at a stage for

which surgery is appropriate (in IASLC database only 349 patients out of 12.620 affected by SCLC were resected, representing only 2,8%).

VALSG staging	TNM staging
<b>Limited Disease:</b> disease encompassed within a tolerable radiation therapy portal <ul style="list-style-type: none"> <li>• Tumour confined to one hemithorax</li> <li>• Involvement of ipsilateral and contralateral mediastinal nodes</li> <li>• Involvement of ipsilateral supraclavicular nodes</li> <li>• Ipsilateral pleural effusion</li> </ul>	From IA to IIIB
<b>Extensive Disease:</b> any other	IV

Table 1. Comparison between VALSG and TNM staging

Considering the therapeutic options (chemotherapy and radiotherapy) representing, to date, the standard of care, it could be argued that the more precise staging of SCLC using the TNM system does not provide extra benefits to select the treatment modality. However TNM has been shown to be prognostic of outcome [Micke et al., 2002], and a more precise definition of nodal involvement may be relevant for radiation treatment. Moreover, surgery for limited disease (T1-2, N0, M0) is nowadays considered a valid therapeutic option [Varlotto et al., 2011]. For these reasons clinicians and cancer registrars recommend to classify SCLC with the TNM staging system [Shepherd et al., 2007]. This recommendation is particularly strong for those trials in LD addressing thoracic and prophylactic cranial irradiation questions and those that include a surgical treatment arm [Vallieres et al., 2009]. In the future a better definition of N stage is needed and prognostic difference in patients with or without cytology-positive pleural and/or pericardial effusions must be addressed.

To assess the extent of disease, which remains the main prognostic factor, several staging tests are available; their execution sequence should be guided by the patient's signs and symptoms at presentation and the availability of the diagnostic tests. Staging should be accurate and fast, considering the rapid growth of SCLC. Staging work-up should include full medical history, physical examination, chest X-ray, hematology and chemistry panels including differential blood count, liver and renal function tests, lactate dehydrogenase (LDH) and sodium levels (hyponatremia, due to ectopic production of antidiuretic hormone or atrial natriuretic peptide, is observed in up to 15% of patients), pulmonary function tests, and contrast-enhanced CT of the chest and upper abdomen. SCLC displays the propensity for early distant metastases to liver, bones, adrenal glands, and above all brain. Therefore, in patients with suspect for distant metastases, additional tests may include bone scintigraphy, CT scan with intravenous contrast or MRI of the brain, and bone marrow aspiration and biopsy. Bone marrow is involved in 15 to 30 percent of patients at presentation, but it represents rarely a solitary site of metastatic disease (2 to 6%). Bone-marrow infiltration should be suspected in presence of an isolated rise in lactate dehydrogenase (LDH) concentration or blood counts indicating otherwise unexplained anemia or a leucoerythroblastic response or if bone scan is positive [Campling et al., 1986]. CT or MRI of the brain are recommended if chemo-radiation with curative intent is under consideration. In one report, the prevalence of brain metastases was 10% with CT and 24% with MRI. In

this series all CT-detected brain metastases were symptomatic, whereas 11% of those detected by MRI were asymptomatic [Seute et al., 2008]. Chest CT scan, abdominal CT scan, brain MRI and bone scintigraphy are mandatory in the evaluation of patients amenable to surgery [Koletsis et al., 2009]. Fluorodeoxyglucose (FDG) uptake is usually high in SCLC, leading to a sensitivity of nearly 100% but its routine use in SCLC remains controversial [Thomson et al., 2011]. PET is, anyway, useful to plan radiotherapy in some countries [Van Loon et al., 2010]. Pathological confirmation is still required for PET-detected lesions that could result in upstaging, in particular if radical resection could be offered. The role of combined fluorodeoxyglucose PET (FDG-PET) and CT scanning is yet to be completely defined but, if available, it may be useful to improve the accuracy of staging by the detection of mediastinal nodal and occult distant metastatic spread. In patients who present with pleural effusion, in the absence of extrathoracic disease, cytopathologic confirmation of tumour involvement is needed.

With improvements in staging through the use of PET/CT and magnetic resonance imaging (MRI), more patients are found to have ES-SCLC: the ratio of LS-SCLC to ES-SCLC was formerly 1:1 and is now 1:3 as more subtle lesions, such as silent adrenal and brain metastases, are identified.

If extensive disease is detected by one test, further staging can be omitted, although bone scintigraphy may be used to identify symptomatic lesions amenable of palliation radiotherapy and brain CT/MRI could be performed or repeated in patients who respond to treatment in order to plan a brain irradiation of symptomatic lesions or to plan PCI in absence of metastasis (since PCI has been extended to ED-SCLC responsive to primary treatments)

## 2.5 Prognosis

Stage is the major prognostic factor of survival but some other prognostic factors have been identified: performance status, weight loss, sex and some laboratory tests (CEA, LDH, NSE, hypoalbuminemia, elevated alkaline phosphatase). No histological or molecular features have been validated yet. Several algorithms have been elaborated for predicting survival but the reliability for individual patients remains poor. Paraneoplastic syndromes are more frequently found in patients with limited-stage SCLC and they are considered positive prognostic factors.

## 3. Historical background of SCLC

SCLC was firstly recognized by Barnard in 1926, who noted that "oat-cell sarcomas of the mediastinum" were metastatic carcinomas of the lung instead.

In the 85 years of SCLC life, some milestones should be reminded:

**1959:** Pathologists recognized SCLC as a separate entity among carcinomas of the lung and Azzopardi defined six features of cells at light microscopic examination [Azzopardi, 1959]

**1963:** VALSG introduced the 2-stage system for SCLC

**1969:** British Medical Research Council reported better survival of radiotherapy arm versus surgical arm in the first clinical randomized trial on SCLC [Miller et al., 1969]. Cyclophosphamide showed to be effective against lung cancer [Green et al., 1969]

**1979:** Medical Research Council showed advantage in survival with combination of chemotherapy (cyclophosphamide) and radiation therapy compared with radiation alone in LD-SCLC [Medical Research Council Lung Cancer Working Party, 1979]

**1982:** Shields re-evaluated surgery as initial treatment in SCLC after introduction of TNM staging system [Shields, 1982]

**1987:** Adding RT to chemotherapy improved survival in LD-SCLC [Perry et al., 1987]

**1989:** The International Association for Study of Lung Cancer (IASLC) was revised for the first time by its introduction the Veterans Administration Lung Study Group staging system [Stahel, 1989]

**1994:** Lung Cancer Study Group published results of the first (and unique, so far) perspective randomized trial in LD-SCLC comparing surgery to RT after induction chemotherapy: Authors concluded that surgery offered no advantage in terms of either survival or local control of disease.

**1995-1999:** Prophylactic Cranial Irradiation (PCI) showed to improve overall and disease-free survival in selected patients (responders to first-line treatments) [Aupérin et al., 1999]

**1999:** studies of dose fractionation of RT demonstrated that twice-daily administration was superior compared to once-daily in terms of local control and overall survival [Turrisi et al., 1999]

Combining this dates we can schematically recognize three periods.

### **3.1 The “Surgical Era” (early 1900-1960s)**

The dramatic increase of tobacco consumption in early 900's produced a sharp increase of incidence of SCLC; on the other hand, prevalence of pulmonary tuberculosis and chest wounds during World Wars promoted advances in thoracic surgery and lung resections. Surgery was considered the standard of care for Small-Cell as well as Non small-cell lung cancer. However high rates of recurrence (both local and distant), even after apparently complete resection, were observed. Results published by British Medical Council Group in first clinical prospective trial randomizing patients affected by SCLC to either surgery or thoracic radiation therapy reported the slight advantage in survival of RT arm. This was enough to abandon surgery at least for primary therapy for SCLC. Dichotomous staging by Veterans Administration Lung Cancer Study Group (1968) reflected and anticipated the centrality of RT as primary treatment for local control of disease

### **3.2 The “advent of Chemotherapy” (1960s-1980s)**

Few years later report of British Medical Council, the pathology study conducted by Matthews in autopsies of patients deceased within 30 days of attempted curative resection showed that SCLC had, in almost all patients, microscopic but widely metastatic disease [Matthews et al., 1973]. This enforced the importance of accurate staging of disease and promoted the need of systemic control of disease. The chemosensitivity of SCLC was first recognized in 1940s when nitrogen mustard (methyl-bis-B-Chloro-ethyl amine hydrochloride) demonstrated capability of inducing tumour regression in more than 50% of patients. Despite a large amount of active drugs towards SCLC, it was perceived quite early that single-agent regimens were associated to frail remissions and high rates of precocious recurrences. In 1970s combination chemotherapy, mainly based on cyclophosphamide showed dramatic responses, even in very incapacitated patients, although long term disease-free survival remained disappointing and natural history of disease did not seem to change. Chemotherapy became the standard of care also in limited disease when Medical Research Council demonstrated the advantage of a combination of cyclophosphamide and radiation compared with radiation alone. During the 1970s thoracic radiation was relegated to an adjuvant, “consolidative” role in LD-SCLC.

### 3.3 Evolution of combined modality treatment (1980s-today)

The last period could be considered as “quiescent”: no tools against disease proved to be revolutionary and efforts were made towards integration of multimodal approach. Paradigms and flow charts of treatment did not reflect the chronological sequence of most important studies but rather controlled studies and consensus expressed by expertise panels of Authors. Etoposide and platinum became from 1980s the first-line treatment. An important study from National Cancer Institute (NCI) in 1976 firstly tested a very aggressive protocol involving simultaneous irradiation of brain, primary tumour and mediastinum and concomitant CAV chemotherapy (cyclophosphamide/doxorubicine/vincristine). Despite unacceptable toxicity (radiation pneumonitis in 38%, mielodepression with fatal sepsis in 24%), this regimen showed the best results, never reached before (nearly 100% complete remissions, 80% of long term survival) [Greco et al., 1979]. This work firstly recognized the importance of tumour repopulation by clones of cells whose resistance was allowed by sequentiality of treatments. Efforts were made in order to minimize tissue interaction without compromising delivery of both radiation and chemo-therapy: timing of radiation therapy [Perry et al., 1987] and dose fractioning [Turrisi et al. 1999] were largely studied by various Authors.

In this period surgery revived with first report from Shields and coll. who concluded that primary surgery and adjuvant chemotherapy could be offered to patients with SCLC in early stages (i.e. T1N0). A large number of subsequent studies (discussed in the chapter) reported favourable long-term survival after surgery with improved local control of disease: one of the most remarkable experience was that of Toronto Group [Shepherd, 1983].

Undoubtedly, advances in both imaging and invasive staging tools (spiral CT, PET/CT, FNA-EBUS) lead to a more precise stratification of disease, allowing selection of patients in really “limited” disease amenable for radical resection. Application of TNM staging as used for NSCLC eliminated one of the barriers that divided SCLC and NSCLC and contributed to better define prognosis of patients previously classified as having Limited Disease (an heterogeneous stage ranging from isolated coin lesion to extensive hilar mass with supraclavicular node metastasis).

Times were mature for another clinical perspective randomized trial involving surgery: it was started by Lung Cancer Study Group in 1983 and ended in 1994. Results again excluded a benefit of surgery even on a multimodal approach, but did not prevent further Authors to report their retrospective experiences on surgically resected SCLC, criticizing at the same time this study.

Main changes of treatment modalities in SCLC are summarized in Fig. 1

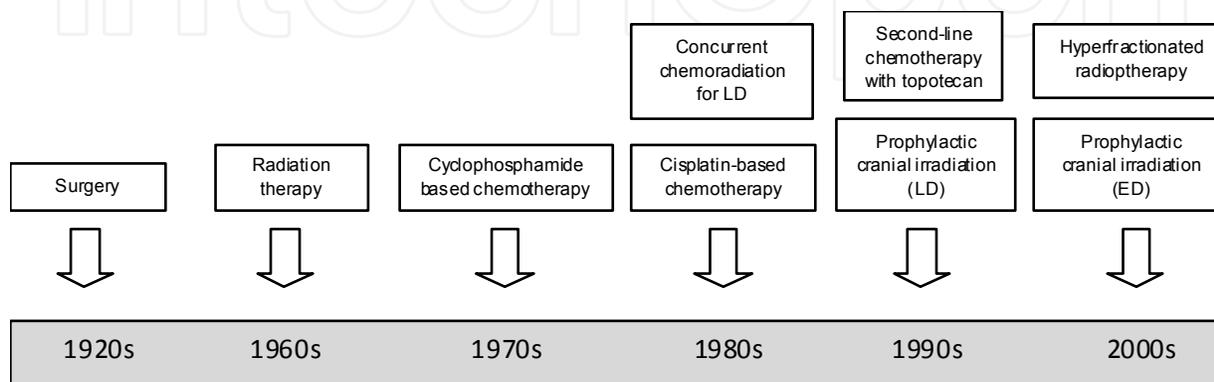


Fig. 1. Evolution of treatment modalities through decades

#### 4. Current guidelines for treatment (NCCN/ACCP)

It should be noted that guidelines for the treatment of SCLC are based on review of a literature that lacks of big randomized prospective trials and is heterogeneous regarding to kind of treatment, timing, endpoints and selection of patients.

The National Comprehensive Cancer Network (NCCN) has recently developed a review of its guidelines, declaring that every recommendation for SCLC has to be considered category 2A, because they are “based upon lower-level evidence” but “uniform NCCN consensus that the intervention is appropriate” (see Table 2). [NCCN Clinical Practice Guidelines in Oncology]

Category 1	The recommendation is based on high-level evidence (e.g., randomized trials) and there is uniform NCCN consensus
Category 2A	The recommendation is based on lower-level evidence and there is uniform NCCN consensus
Category 2B	The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).
Category 3	The recommendation is based on any level of evidence but reflects major disagreement

Table 2. NCCN category of recommendation.

The American College of Chest Physicians (ACCP) in 2007 produced a systematic literature review resulting in evidence-based guidelines, graded upon the “ACCP grading system for guideline recommendations”

Both documents debate on diagnostic and therapeutic options for SCLC and are quite similar in recommendations, except for the use of PET (not yet standardized in 2007 ACCP guidelines) and for the choice of staging system (NCCN recommending the use of the new TNM instead of Veterans Administration Lung Study Group classification).

Guidelines for treatment have a key point in the use of platinum-based chemotherapy plus radiotherapy for all fit patients (Performance Status 0-2) with limited stage disease, followed by Prophylactic Cranial Irradiation (PCI); topics of discussion are timing of radiotherapy (concurrent versus sequential, early versus late), volume, dose and fractionation of radiations, treatment of unfit-elderly patients, maintenance and second line chemotherapy and surgery.

Cisplatin has to be preferred to Carboplatin in combination with Etoposide in first line treatment; in phase III randomized trials, Irinotecan was substituted for Etoposide in combination with Carboplatin in advanced disease with mild improve in survival and thus being added to guidelines as an option for patients with extensive-stage disease. In these patients, where the treatment of choice is chemotherapy alone with initial response of about 60-70% but median survival of 9-11 months due to early relapse, maintenance or consolidation chemotherapy beyond 4 to 6 cycles is currently not recommended outside clinical trials (grade of recommendation IB); likewise, the introduction of a third agent (alkylating agent with or without anthracycline) showed minor advantage in duration of response without improving survival and carried greater cumulative toxicity. The use of cytochine or anti-angiogenetic agents (i.e. Bevacizumab) is not currently recommended in first line treatment, even though randomized phase III trials are currently running.

Second line treatment is generally a single agent therapy, administered with an interval of at least 3 month since initial therapy (otherwise disease has to be considered refractory or resistant) and should be given until 2 cycles beyond best response, progression of disease, development of major toxicity.

The addition of thoracic radiotherapy has improved survival in patients with limited stage disease (grade of recommendation 1A); staging of SCLC actually involves relationship between extension of disease and radiation port field. As far as timing is concerned, early (within 30 days to 9 weeks since the beginning of chemotherapy) concurrent chemo-radiotherapy is recommended for patients with limited-stage disease (grade of recommendation 1A). Hyper-fractionation of radiation dose has not yet been correctly compared to once-daily administration in available trials, according to NCCN review of literature.

PCI given after completion of chemotherapy in a low dose per fraction causes less neurological toxicity and prevent the emergence of brain metastasis, both in limited and extensive stage disease; it is recommended for fit patients who achieve a complete or partial response to initial treatment (Grade of recommendation 1B).

Radiotherapy is also recommended in relapse for palliation of symptoms.

The European Society of Medical Oncology (ESMO) in the 1st consensus conference in lung cancer stated guidelines for diagnosis, treatment and follow up of SCLC, underlying the absence of randomized trials comparing surgery with concurrent chemo-radiotherapy. Nevertheless, with grade of recommendation III D, surgical resection may be considered for very limited disease (T1-2, N0), only after histological confirmation of N parameters by mediastinoscopy, followed by PCI.

ACCP guidelines stress the importance of invasive mediastinal staging, with grade of recommendation 1A. NCCN guidelines specify that lobectomy has to be preferred if resection is performed and that adjuvant chemotherapy alone is recommended for patients without nodal metastasis, while mediastinal RT has to be added in case of nodal involvement (Fig. 2)

## 5. Studies regarding surgery in SCLC

Except from those by British Medical Council and Lung Cancer Study Group, all studies focused on surgery in SCLC are retrospective or prospective non-randomized, so conclusions should be interpreted cautiously.

However, also those phase III trials have been criticised on several points.

The British Medical Council study, dated 1963, did not include patients with peripheral lung lesions, since preoperative evaluation and diagnosis were made using rigid bronchoscopy available at that time; secondly, rate of complete (R0) resection was low (approximately 50%) compared to resections for NSCLC; finally, staging was performed without modern tools, like contrast CT-scan or PET, nor histological confirmation by mediastinoscopy was obtained. So it is likely that a remarkable number of patients with occult intrathoracic and extrathoracic disease was included in the study and randomized to surgery, compromising the long term survival results.

Twenty years later, after advent of chemotherapy as standard primary treatment, times were mature for another randomized trials, set up by Lung Cancer Study Group in 1983. Eligibility criteria include LD stage, according to VALSG staging: this means that also patients with clinical evident mediastinal adenopathies were included in the study. Conversely, patients with peripheral nodules and normal bronchoscopy were specifically excluded from the study. Induction therapy was quite heterogeneous (anthracycline based regimen) and only 144 of 340 patients (42%) accrued in the trial were randomized (68 to surgery arm and 76 to radiotherapy arm). Six patients randomized to surgery refused

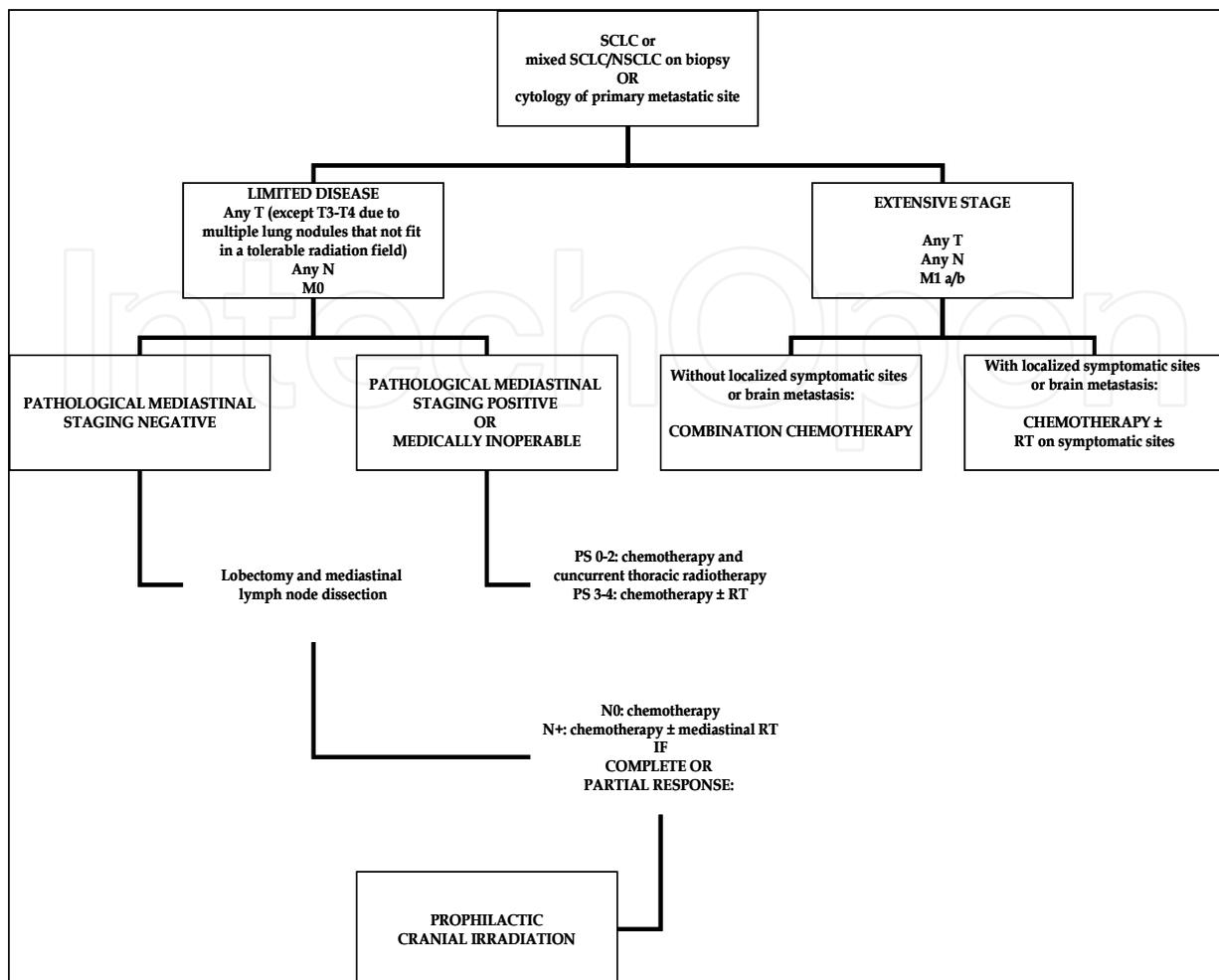


Fig. 2. NCCN clinical practice guidelines

thoracotomy and, on the contrary, eight patients requested surgical intervention and received off-randomization surgery, representing a significant cross-over (10%) between the two arms. Moreover, few other data should be pointed out: only 65% of patients responded to induction chemotherapy, in 17% of patients assigned to surgery only exploratory thoracotomy was performed and, above all, the high proportion of patients included with bulky N2 or N3 nodal metastasis (who unlikely achieved a complete mediastinal downstaging). Interestingly N status and post-treatment clinical stage did not influence resectability (a result correlated with clinical understaging).

The conclusion of the study was that surgery did not add any benefit neither in terms of survival nor of pattern of recurrence.

The same results were anticipated in a retrospective study of 1985 based on 33 operated patients compared to 46 patients who fulfilled criteria of operability and resectability but were treated with non-surgical management. However microscopic or macroscopic residual disease was left in half of patients, suggesting that clinical staging was not so accurate in predicting resectability of disease [Østerlind, 1985]

Considering these weak points, rejection of surgery did not discourage several Authors, which continued to report good results with surgery combined to either induction or adjuvant chemotherapy and radiotherapy in some cases.

Rostad et al. analyzed 2442 patients with SCLC in a national survey in Norway, 38 of which were surgically resected (25 received adjuvant therapies). For stage I addition of surgery to conventional treatments (chemo-radiation) improved 5-year survival rate from 11.3% to 44.9%, so Authors concluded that patients with resectable disease in stage I should be referred to surgery [Rostad, 2004].

The same conclusion is reported by Leo and Pastorino in their review [Leo & Pastorino, 2003] for T1-2N0M0 patients which can be treated by surgery and adjuvant chemotherapy, while patients in stage II-III should undergo surgery only in the context of clinical trials.

Rea et al. reported a 32% overall survival in 104 patients with SCLC surgically resected, despite a remarkable percentage of stage III (43.3%), which resulted as a major negative prognostic factors [Rea, 1998]

Brock et al reviewed their institutional experience of 1415 SCLC among whom 82 (6%) underwent surgery with curative intent from 1976 to 2002 [Brock, 2005]. Surgery was accompanied by induction or adjuvant chemotherapy in 77% of patients. Authors found a 5-year survival of 85.7% for stage I SCLC (similar to that historically expected for completely resected stage I NSCLC without adjuvant chemotherapy). Favourable prognostic factors were early stage, lobectomy as surgical procedure, female gender and date of intervention after 1987 (a surrogate marker for availability of platinum based chemotherapy). Pattern of recurrence was not reported in this study, however Authors concluded that lobectomy plus platinum based chemotherapy is a feasible option yielding excellent results in T1-T2N0-M0 SCLC.

High 5 years survival rate was reported also by Tsuchiya in a retrospective series of patients treated with a similar protocol [Tsuchiya, 2005]. Interestingly, Authors reported only 10% of local failure after surgery, which is lower than commonly reported after chemo-radiation therapies alone.

Badzio and coll. in a retrospective series of patients treated with surgery or non-surgical management reported a significant improvement in survival in surgical resected patients (22 months Vs 11,  $P < 0.001$ ) [Badzio, 2004]. The control group of patients treated with chemo-radiotherapy was built using pair-matched case-control according to main prognostic factors, stage and resectability; moreover diagnosis of surgical treated patients was established only postoperatively, thus minimizing some bias related to selection of patients.

In 2006 the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S) presented a multicenter study on 47 patients with SCLC out a total of 2994 lung cancers resected [Gomez de Antonio, 2006]. Thirty-three % of patients had incomplete resection suggesting that the criteria for surgery were not predictable enough for resectability. The routine use of mediastinoscopy (performed only in 19% of cases) might have identified some of the patients whose clinical staging was underestimated and which added to low rate of respectability. Moreover a low proportion of patients received adjuvant treatments. These factors accounts for an overall survival which does not exceed that reported in literature for patients with possibly more advanced stage managed with chemo-radiotherapy.

Recently, Schreiber and coll. analyzed patients included in the Surveillance, Epidemiology and End Results registry (SEER), which is the cancer registry representative of United States [Schreiber, 2010]. Among 14,179 patients affected by SCLC coded as localized (T1-2Nx-0) or regional disease (T3-4Nx-0), 863 (6%) had undergone surgical resection, making them one of the larger population based cohort ever reported in literature. Overall 5-year survival rates were 26.3 Vs 9.3% ( $P = 0.01$ ) in favour of surgery with median survival of 22 Vs 12 months,

respectively. Advantage of surgery to survival was much more substantial in N0 patients (median survival 40 Vs 15 months), which on the other hand did show benefit from addition of PORT (Post-Operative Radiation Therapy). These data seem to suggest that radical surgery alone could be adequate for local control of disease and, conversely PORT may be detrimental for survival. Another retrospective analysis of SEER database conducted in 2010 and focused only on stage I confirmed reasonable outcome in patients who underwent lobectomy without PORT [Yu et al., 2010]. Unfortunately both studies, although based on large population, lack of data concerning chemotherapy, margins of resection, pathologic confirmation of diagnosis and performance status (not recorded in SEER database).

Study	Number of patients	Treatment Modality	Local recurrence	5-year survival
Fujimori, 1997	22	PE x 2/4 → S	5%	Cumulative: 66.7% (3-year) Stage I-II: 73.3% (3-year) Stage IIIA: 42.9%
Lucchi, 1997	127	S (15) S → CT (RT) (92) CT → S → CT (15)	4.1% (10.6% local+distal)	Cumulative: 22.6% 47% in stage I 0% in N2 patients 0% with surgery alone
Eberhardt, 2003	46	Stage I-IIA: PE x 4 → S Stage IIB-IIIA: PE x 3 → CTRx (HfRTx) → S	0%	Cumulative: 39%
Badzio, 2004	134	S → CT (67) CTRx (67)	5% 15%	Cumulative: 27% (4% CTRx) Stage IA: 59%
Rostad, 2004	38	S S → adjuvant	n/a	Stage I: 44.9%
Brock, 2005	82	(CT) → S → (CT)		Stage I: 58% Stage II: 18% Stage III: 23% Stage IV: 0%
Tsuchiya, 2005	62	S → PE x 4	10%	Stage IA/IB: 73/67% Stage II: 38% Stage III: 39%
Granetzny, 2006	95	S → CTRx (Stage I) CT → S → CTRx (Stage III)	n/a	Median survival (months) 31.3 (Stage I) 31.7 (Stage III – downstaged) 12.4 (Stage III – not downstaged)
Gomez De Antonio, 2006	47	CT → S (3) S → CT (30) S (14)	n/a	Cumulative: 26% R0 resection: 31% Stage I: 36%
Schreiber, 2009	863	S S → RT CT data n/a		Cumulative: 34.6% Stage I: 44.8% Stage II-III: 26.3%

S: surgery, CT: chemotherapy, CTRx: chemoradiation therapy, PE: Platinum-Etoposide, HfRTx: Hyperfractionated Radiation therapy

Table 3. Some of the recent trials supporting the role of surgery

A current year report on a small series of patients (28) underlines the low rate of local failure (3/28) after surgery compared to distant (especially brain) metastasis, which confirms the role of PCI [Ogawa et al. 2011]

### 5.1 Rationale of surgery in SCLC

As pointed out by Anraku and Waddell [Anraku, 2006] in their review, rationale of surgery can be summarized in the following clinical presentations.

- **Small peripheral coin lesions:** typical or atypical carcinoids may be misdiagnosed as SCLC since their diagnosis is often made on cytological samples obtained by either trans-thoracic fine needle biopsy or trans-bronchial biopsy by bronchoscopy
- **Combined histology tumours:** definitive histology of tumours initially diagnosed as pure SCLC reveals a Non Small-Cell component in 11-25% [Asamura, 2006]. Percentages are higher in surgical reports possibly due to the fact that combined SCLC tends to arise peripherally and resection is feasible more frequently and because a larger amount of tissue for individuation of both components is available with surgical specimen [Mangum, 1989]. Although prognosis is mainly determined by the aggressiveness of Small-Cell component, the Non Small-Cell one may fail to chemoradiation protocols commonly used against SCLC being responsible of weak responses or early relapses.
- **Early stages (T1-2N0M0)** benefit of surgical resection in terms of improved local control of disease: first site of recurrence (which occurs in approximately 50% of cases after concurrent chemo-radiation protocols [Turrisi, 1999]) is the tumour bed site followed by hilar/mediastinal lymph nodes, even in patients who achieve complete pathological remission [Elliott, 1987]. Adjuvant radical resection (i.e. with R0 margins) after induction chemoradiotherapy has shown local control of disease in almost all cases and this is reflected in a slight advantage in long-term survival [Eberhardt, 2003]. Table with local recurrences and survival
- If general criteria for operability and resectability are met, **adjuvant “salvage” surgery** is preferable in cases of a chemotherapy resistant tumour or early local relapse (usually: 3 months) after an initial response, compared to second-line therapies which are often ineffective against SCLC. In their report, the Toronto Group identified a small subset of patients without node metastasis that benefit from salvage surgery). A second biopsy, if feasible, is worthy to be considered before surgery [Shepherd, 1991] to demonstrate a NSCLC component.
- **New metachronous tumours** appearing two years after a SCLC successfully treated patients could be second primary NSCLC and after a complete re-staging should be surgically resected even if histology can not be obtained preoperatively [Anraku, 2006]

### 5.2 Patient selection criteria and choice of surgical procedure

If a diagnosis is obtained preoperatively, pathologists should exclude any possible coexisting NSCLC component. Even more than in NSCLC, accurate staging is crucial before planning surgery in fit patients, as discussed before. Toronto Group demonstrated better 5-year survival (18% vs 6%) in patients without mediastinal nodes involvement preoperatively [Shepherd, 1991]; in a recent phase II trial on surgery after induction chemotherapy only patients who achieved complete nodal downstaging had a fair survival. Mediastinoscopy and eventually re-mediastinoscopy after primary treatment is therefore

recommended to detect nodal involvement which is microscopic and subclinical in a considerable percentage of patients. This matter accounts for discordance between clinical and pathological staging in SCLC.

If a SCLC is diagnosed in operative theatre at frozen section of specimens, radical resection (preferably lobectomy) is recommended if intraoperative histological examination of mediastinal lymph nodes does not reveal metastasis; however, surgery can be proposed to patients with mediastinal nodes micrometastasis if they can easily tolerate the procedure. Sublobar resections are recommended in less fit patients or in presence of nodal involvement.

## 6. Targeting the complex biology of SCLC

First cytogenetic studies, dated 1982, found that a deletion on chromosome 3p was present in 95% of SCLC [Whang, 1982]. This chromosomal region contains tumour-suppressor genes relevant to the pathogenesis of the tumour e.g. RAR $\beta$  [Naylor 1987, Kok 1987] and F1H1 [Franklin, 2010]. The 3p loss alone is not specific of SCLC, since it is frequently encountered also in other tumours. Thanks to the high-throughput technology as comparative genomic hybridization (CGH) and gene expression arrays, researchers discovered that in 90% of SCLC samples, the most frequent sites of chromosome loss are 3p, 5q and 13q, the last determining the loss of retinoblastoma gene (RB1) [Ried, 1994]. Mutation studies on biology of SCLC showed that this type of tumour has frequent mutation in the gene encoding for p53 protein (TP53) [Hanahan, 200] but rarely presents mutation in the tyrosine-kinase signalling gene including KRAS and EGFR [Franklin, 2010], which are actually the most known pathways with larger number of active drugs (mainly tested in lung adenocarcinomas).

Targeted cancer therapies are drugs or antibodies that block the growth and the spread of cancer by interfering with specific molecules involved in tumour growth and progression. These therapies are being studied for use alone, in combination with other targeted therapies, and in combination with other cancer treatments, such as chemotherapy. By blocking signals that make cancer cell grow and replicate, targeted cancer therapies can help to stop cancer progression and may induce cancer cell death through apoptosis.

To give an example the PI3K/AKT/mTOR intracellular pathway is chronically activated in SCLC through inactivating mutations in PTEN gene and this activation pathway correlates with sensitivity to Everolimus in vitro [Marinov, 2009]. Furthermore, the amplification of BCL-2 genes seems to be correlated with the sensitivity to the highly potent small-molecule called ABT-737 suggesting that patients with bcl-2 protein over expression, may have some benefits from bcl-2 inhibitors [Olejniczak, 2007]. In SCLC cell lines, microRNA and gene-expression signatures of chemo-resistance have been described [Guo, 2010] and several inhibitors of growth factor pathways implicated in SCLC are in clinical development (NCT00896752); the compound PD173074 induces apoptosis in vitro and in vivo in SCLC by inhibition of FGF2 signalling [Pardo, 2009].

The targeting of specific molecules has been already studied in several trials, even though with limited success. One of the emerging need in clinical research dealing with SCLC is inadequacy of preclinical models of disease used to date. Cancer-cell-line-based xenograft models employed as standard testing ground especially for drugs have revealed as a surrogate of disease. In vitro activity level is then weakly predictable of clinical efficacy thus explaining the high rates of failure of new drugs tested in clinical studies. Human cancers

cells, compared to cancer-cell cultures, grow up in hypoxic and nutrient-poor complex environments which promotes continue selection of more aggressive cell-clones. This explains the reason why cell-line-based SCLC xenografts tend to grow as relatively indolent tumours, while corresponding human disease is characterized by aggressive clinical and biological behaviour.

Moreover, as for standard chemotherapy, the use of a single molecular target drug in such complex malignancy as SCLC, is wrong. The inhibition of multiple targets or the combination with standard chemotherapeutic agents are likely to have greater potential. The customizing of therapy with novel agent to individual patient's characteristics is becoming the most beneficial approach to treatment of SCLC. In addition to new agents, biomarkers of chemosensitivity need be identified to efficaciously assess single agents for relapse after first-line therapy or as a maintenance therapy in placebo-controlled, randomised designs. Several studies have identified genes or proteins in lung cancer whose expression levels are associated with response to antitumor drugs. The breast cancer resistant protein (BCRP), is one of the ABC transporters reported to be associated with resistance to anticancer drugs like doxorubicin, irinotecan, mitoxantrone, and its expression was found to be associated with a poor clinical outcome in SCLC patients undergoing chemotherapy [Kim, 2009]. Chiappori et al. reported that RRM1 and Topo2 alpha proteins expression are biomarkers of chemotherapeutic efficacy in SCLC [Chiappori, 2010] and, recently, Usuda et al. demonstrated that the expression levels of Klotho protein was correlated with the prognosis following resection in SCLC patients [Usuda, 2011]. These results are encouraging; however, this findings need to be incorporated into common signatures for individual therapies and further tested in prospective clinical trials. Of course, biostatistical concerns still exist for predicting response to drugs as for predicting patient prognosis.

## 7. Conclusions

Although the incidence of SCLC has been steadily decreasing over time, it continues to represent a relevant problem of public health due to its aggressive clinical behaviour and the lack of effective therapies; it is considered one of the most elusive cancers. Twenty-five years ago it was considered to be the next malignancy added to the list of curable cancers, because of the effectiveness of several chemotherapeutic agents and radiation therapy, and the discover of central nervous system sanctuary, which would require distinct treatment. Conversely, despite active and ongoing research involving novel approaches to treat SCLC, few discovers had a successful translation in clinical practice over the past 25 years, with cumulative improvement of only 15% in survival which remains dismal and moreover seems to have now reached a plateau.

### 7.1 Current evidences

Over the last 25 years, few landmarks in therapy have been provided by clinical trials focused on LS-SCLC. Minimal progress was noted in ES-SCLC.

Main strategies that demonstrated able to add small but significant improvements in survival can be summarized in the followings:

- **Advantage of addition of radiotherapy to chemotherapy:** The defining report, Cancer and Leukemia Group B (CALGB) 8083 [14], published in the *New England Journal of Medicine*, showed, for patients with LS-SCLC, a local control, failure-free survival, and

overall survival benefit with the addition of thoracic radiation to chemotherapy using a cyclophosphamide and doxorubicin-based regimen. At 2 years, only 13% of patients who received chemotherapy alone maintained local control, compared with 54% of patients receiving chest radiotherapy. Although the likelihood of relapse in the chest may be reduced by up to 50% when thoracic irradiation is administered after chemotherapy, 20–36% of patients will have local recurrence even after combined modality treatment [12,13]. An analysis of the site of first relapse demonstrated that, even for patients who have achieved clinical complete response, the primary tumour bed and hilar or mediastinal lymph node areas are the most frequent single sites of failure [Elliott, 1987]. Failure to achieve control at the primary site remains the most important obstacle to cure in patients with limited SCLC [Shepherd, 1991].

- **superiority of twice-daily radiation therapy over daily fractionation:** hyperfractionating radiation therapy was defined and experimented in order to respond to the need of improve local control of disease, which remains a serious issue in non-surgical managed patients
- **advantage of prophylactic central nervous system radiation (PCI)** in all responding patients (also with ES-SCLC)

## 7.2 Take home messages

There are other recommendations without strong evidence, but for which there is general agreement:

- **Resection is a reasonable option as initial treatments for early stages T1-2N0-M0 patients:** if preoperative diagnosis of SCLC has been obtained, nodal or distant metastasis must be excluded using by either non invasive or invasive staging, avoiding futile thoracotomies. Induction chemo-radiotherapy did not demonstrated superior to adjuvant setting. In any other stage of presentation, surgery is contemplated only in clinical trials.
- **Clinical understaging is frequent in SCLC** (concordance with pathological stage is only 58% in IASLC database) and common criteria of resectability often fails to predict complete resections in SCLC, due to propensity to spread through peribronchial lymphatic vessels to regional lymph-nodes. Introduction and more liberal use of EUS in flexible bronchoscopy or mediastinoscopy may help to rule out patients with micrometastasis not amenable of surgical resection
- **Surgery improves local control of disease** if radical resection is achieved. Local failure rates vary in literature from 0 to 15%, which is considerably lesser than 35-50% reported for chemo-therapy with twice-daily radiation therapy (the standard of care, to date) [Pijls-Johannesma et al., 2007; Turrisi et al., 1999]. In resected specimens after concurrent CT with HfRTx, Eberhardt found persistence of vital disease at the primary site [Eberhardt & Korfee, 2003]. However, there is no evidence, to date, that this translates in an improvement of overall and disease-free survival, which could eventually derive from progresses in systemic treatments.

## 7.3 Challenge to systemic disease

Since the overwhelming majority of patients with LD-SCLC have subclinical metastatic foci at the time of diagnosis, chemotherapy is an essential part of multimodal treatment to control systemic disease.

Cytotoxic drugs active in SCLC discovered in the early 1980s remains a standard of care at present. Advances in supportive care and technical advances in radiation therapy have allowed the application of therapies with less toxicity and well tolerated by most patients. Fall in treatment-related deaths implies an improvement on survival (compared to history of 20-yrs ago) which is actually difficult to be discriminated by the true prolongation of survival due to change in natural history of disease.

At now, most of ongoing clinical trials deal with various combination of active cytotoxic agents, but it has become evident that only small improvements in survival should be expected by such protocols. The issue is not spectrum of active drugs, as is the case in melanoma, for example but rather the rapid development of drug resistance and the failure of second-line therapy, especially in case of no response to primary treatment or early relapse of disease (< 3 months). Therefore clinical research on SCLC is shifting towards target-therapy, although most efforts have been and are still spent on lung adenocarcinoma, because its arise in incidence makes it more attractive in terms of cost/effectiveness of research.

Another issue in SCLC-related researches is paradoxically the introduction of fine-needle aspiration techniques rather than biopsy for histologic diagnosis: this has dramatically diminished the material available for studying compared with other lung cancers and other epithelial tumors.

#### **7.4 Current perspectives: “Time to fish or cut bait”**

“Immortalization” of old randomized trials which refused surgery in multimodal treatment of SCLC in others era is no more acceptable today. A different staging system, lack or routine diagnostic tools and some evident weak points make these milestones anachronistic at now.

However, due to small number of cases and bias in selection of patients, retrospective series starts to carry a small usefulness in adding greater evidence in any type of treatment not contemplated in current guidelines. Meta-analyses too seem not to be reliable on studies that encompass sometimes two or three decades: lack of homogeneity between cohorts characteristics, staging system, diagnostic tools and type of treatments administered are a major issue to significance of results reported.

As brilliantly stated from Shepherd in comment to another retrospective trial on SEER database [Yu, 2010] “it is time to fish or cut bait”: thoracic oncologists have to seriously face the question of role of surgery in multimodal approach to SCLC; if they decide to fish, a large multi-center, international prospective randomized trial seem the only feasible option to achieve powerful statistical results [Shepherd, 2010]. Trial should accrue a large number of patients in a limited period of time with strict eligibility criteria in order to ensure as more homogeneity as possible among centres regarding patients selection, staging criteria and treatment modalities. In the forthcoming seventh edition of the TNM staging system, the IASLC has recommended to apply TNM stratification to SCLC in future clinical trials on LD-SCLC. At least one of the arm should be treated with chemo-radiation therapy followed by PCI, which represents actually the standard of care.

The small number of patients eligible for surgical trials makes accrual extremely slow, so that 3 trials started before 2003 have not been published yet (Essen Thoracic Oncology Group, West Japan Thoracic Oncology group, German Multicenter Randomised Trial).

Meanwhile advances in comprehension of molecular biology of SCLC will perhaps improve systemic control of disease, supporting and not excluding the role of surgery as the most

powerful tool of cytoreduction local strategy even in more locally advanced disease in order to eliminate potential residual clones of resistant cells. It seems in fact still REMOTE the possibility discover of definitive systemic therapy capable of achieve complete local and distant, permanent remission of disease

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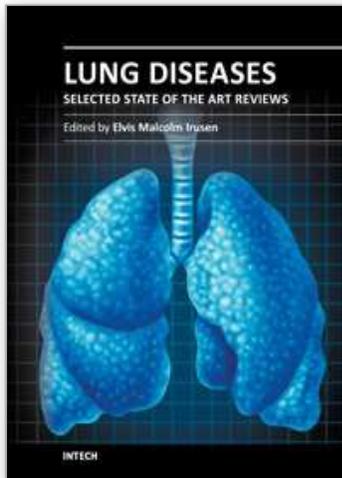
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## **Lung Diseases - Selected State of the Art Reviews**

Edited by Dr. Elvisegran Malcolm Irusen

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The developments in molecular medicine are transforming respiratory medicine. Leading clinicians and scientists in the world have brought their knowledge and experience in their contributions to this book. Clinicians and researchers will learn about the most recent advances in a variety of lung diseases that will better enable them to understand respiratory disorders. This treatise presents state of the art essays on airways disease, neoplastic diseases, and pediatric respiratory conditions. Additionally, aspects of immune regulation, respiratory infections, acute lung injury/ARDS, pulmonary edema, functional evaluation in respiratory disorders, and a variety of other conditions are also discussed. The book will be invaluable to clinicians who keep up with the current concepts, improve their diagnostic skills, and understand potential new therapeutic applications in lung diseases, while scientists can contemplate a plethora of new research avenues for exploration.

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