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Review

A review of the role of surgery for small cell lung cancer and the potential prognostic value of enumeration of circulating tumor cells

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Abstract

Small cell lung cancer (SCLC) is disseminated in the majority of patients at first presentation and, thus, treated with chemoradiotherapy. Despite initial high response rates, chemoresistance appears rapidly and results in a dismal prognosis. However, patients with limited cancer may exhibit better disease control upon surgical treatment. Correct staging is highly critical in the selection of those patients which are likely to benefit from surgery. Studies of the inclusion of surgery in the multimodal treatment of SCLC vary widely in number of patients, selection, treatment and follow-up. Nevertheless surgical therapy for confined SCLCs achieves favorable long-term survival compared to chemoradiotherapy, depending on a precise assessment of the degree of tumor dissemination. Recently, extremely high counts of circulating tumor cells (CTCs) were reported in patients with SCLC compared to other malignancies. In several studies the number of CTCs was found to constitute a prognostic parameter and a marker of response to therapy. Therefore, the assessment of CTCs as so-called "Liquid Biopsy" seems to constitute a more precise method to detect tumor dissemination earlier when compared to clinical staging. In conclusion, in the era of precision oncology enumeration and identification of CTCs of SCLC patients have the potential to help in the selection of patients most suitable for tumor surgery.

Keywords: Small cell lung cancer; Surgery; Chemotherapy; Circulating tumor cells; Dissemination

Introduction

Small cell lung cancer (SCLC) comprises approximately 15% of all lung cancers but is a leading cause of death due to early dissemination and rapid development of drug resistance.[1,2] Despite high response rates to initial platinum-based treatment, it is an aggressive disease with a median survival of 9–12 months for patients with extended stage disease (ED-SCLC). Most patients are diagnosed with advanced disease except a small subgroup with "limited disease" (LD-SCLC) which holds a better prognosis and may benefit from surgery. However, the standard of care for SCLC patients is chemoradiotherapy, even for patients with early-stage malignancy, mainly fostered by a study reported in 1973 by the British Medical Research Council which favored radiotherapy over surgical intervention.[3,4] Unfortunately, the high response rates of chemoradiotherapy fail to translate into long-term survival.[5]

Therefore, further investigations into the inclusion of surgery into treatment of LD-SCLC within carefully designed prospective clinical trials seemed justified within a more modernized study design.[6] Since SCLC patients with confined disease are rare, trials comparing the efficacy of surgical interventions are difficult to complete. However, improved diagnostic and staging methods with better definition of the extension of the disease led to more substantiated trials. Patients' selection is fundamental, and

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extensive radiologic staging including PET scan and mediastinal lymph-node biopsy were recommended. Many tumors release biomarkers into the blood stream and may shed cells, vesicles called exosomes, and traces of DNA into body fluids as well.[7,8] The isolation and identification of circulating tumor cells (CTCs) represents a sensitive method to detect tumor dissemination at the cellular level.[9,10] In particular, SCLC is distinguished by extremely high numbers of CTCs which represent predominantly epithelial cell adhesion molecule (EpCAM)-positive tumor cells and are, therefore, easily to detect at early stages of tumor spread.[11] Thus, in the era of precision oncology, this form of a "Liquid Biopsy" may constitute a much more sensitive technique to assess tumor progression of SCLC far in advance of clinical imaging.

Overview of surgical treatment of SCLC patients

The disaffirmation of clinicians toward surgery in SCLC was backed by a prospective randomized trial in the 1960s in which 144 patients showed no survival benefit when surgical intervention compared with radical radiotherapy was assessed up to ten years post-treatment (Table 1).[3,12] In an EORTC trial, 328 patients with LD-SCLC were recruited to evaluate surgical treatment for patients responding to chemotherapy.[13] Cyclophosphamide, adriamycin and vincristine (CAV) were administered for five cycles and patients achieving at least partial response randomized to undergo or not pulmonary resection. Of the 146 evaluable patients 70 were randomized to surgery and 76 to no surgery, respectively, resulting in 28% eradication of tumors in operated participants. However, the survival curves for the two arms with a 2-year survival of 20% were not different. This result disfavored the addition of pulmonary resection to neoadjuvant chemotherapy of SCLC. Despite these negative results, positive evidence accumulated for surgical care for LD-SCLC. In an early study by Shah et al., 28 SCLC patients who underwent thoracotomy without adjuvant therapy showed an overall 5-year survival of 43.3%.[14] The actual 5-year survival for patients in stages I and III was 57.1% (n = 14) and 55.5% (n = 11), respectively. However, diagnostic advances subsequent to the negative older trials justified a reevaluation of the issue, given the greater degree of accuracy with the TNM classification.[12] The reassessment of the role of surgery in patients is based on clinical data indicating a much better prognosis in selected patients with LD-SCLC (T1-2, N0, M0), with surgery considered versus chemoradiotherapy.[15,16] In addition to conventional mediastinoscopy, positron emission tomography-computed tomography (PET-CT) and endobronchial ultrasonography-guided transbronchial needle aspiration have become available for node diagnosis.[17]

A meeting of the Lung Cancer Study Group of the International Society of Chemotherapy (ISC-LCSG) in 1989 led to the initiation of a cooperative study of surgery for SCLC in combination with postoperative chemotherapy.[18] Between 1991 and 1995, Ulsperger et al. and Karrer and Ulsperger published a study comprising surgery and adjuvant chemotherapy for SCLC carried out

Table 1
Summarizes a range of studies which investigated surgical therapy for LD-SCLC.

Reference	Patients (n) with surgery	Adjuvant (n)	Neo-adjuvant (n)	Survival			Comment
				Stage pI	Stage pII	Stage pIII	
Shah et al., 1992.[14]	28	–	–	57.1%	0%	55.5%	
Lad et al., 1994.[13]	70	146		28% eradication	–	–	76 Controls no surgery; survival not significantly different
Rostad et al., 2004.[22]	96	–	–	44.9%	–	–	11.4% 5y Survival for conventional treatment
Nakamura et al., 2004.[23]	69		32	48.9	33.3	20.2	Downstaging positive effect
Badzio et al., 2004.[24]	67	67		28 mo	17 mo	17 mo	Controls: 13/12/8 mo survival
Granetzny et al., 2006.[25]	95	64	31	31.3 mo	–	31.7/12.4 mo LN+	Retrospective analysis
Schreiber et al., 2010.[4]	863			52.6%	31.8%		15–42 mo/12–22 mo Surgery improved survival
Weksler et al., 2012.[26]	895			38 mo	25 mo		19/16 mo survival of controls; SEER database
Takei et al., 2014.[27]	243			66.7	42.6	23.4	
Xu et al., 2014.[28]	106	59	47	35%	35%	20%	For pIIIa-N2: neoadjuvant therapy superior
Kawano et al., 2015.[29]	57			43.4%	13.4%	13.4%	Pneumonectomy yields worse outcome
Stish et al., 2015.[30]	54			37%	nd	nd	Segmentectomy yields worse outcome
Takenaka et al., 2015.[31]	88			58%	29%	18%	25/24/18% 5y survival of controls
Coombs et al., 2015.[32]	2476			51%	25%	18%	Added chemotherapy – hazard ratio 0.57