Perspective

Multimodality treatment in limited small cell lung cancer (L-SCLC): different perspectives about the optimal approach

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Abstract: Small cell lung cancer (SCLC) is characterized by an aggressive behaviour, but limited-stage disease could be treated with curative intent. In order to improve prognosis in terms of local control and survival in this setting, several studies evaluated the benefit of a multimodality strategy including surgery, chemotherapy and radiotherapy. Recently Yang *et al.* confirmed the benefit of adjuvant chemotherapy alone or with cranial irradiation in a population-based cohort of patients with early-stage SCLC who underwent complete surgical resection. Results of this study are consistent with previous retrospective analysis or small prospective trials without adding anything to the current knowledge and clinical practice. In this perspective, we discuss the role and evidence supporting different locoregional approaches, in a two-hand debate, underlining the importance of a prospective randomized trial defining the best treatment strategy in limited SCLC.

Keywords: Small cell lung cancer (SCLC); limited, surgery; chemotherapy; radiotherapy

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Introduction

Small cell lung cancer (SCLC) represents 15% of all lung cancers and is characterized by a rapid growth and early development of widespread metastases. Approximately 30% of patients with SCLC presents with limited disease treated with curative intent (1). The body of literature investigating the role of surgery as an integral part of treatment of limited SCLC (L-SCLC) in addition to intensive radio- and chemotherapy is consistent, but the subgroup of patients who might benefit from such approach and the best treatment sequence have not clearly defined yet.

The article by Yang *et al.* to which this perspective refers, presents the benefit of adjuvant therapy with or without prophylactic cranial irradiation (PCI) after complete resection for stage T1-2N0M0 SCLC using the National Cancer Data Base on 954 patients; according to their findings there is an improved survival, also at the multivariate analysis, for patients who underwent adjuvant chemotherapy alone and adjuvant chemotherapy with PCI compared to those who underwent surgery alone without adjuvant treatment (P<0.01) (2).

Study results and conclusions present some major limitations as discussed by the authors themselves. Despite the large population-based cohort of SCLC patients analyzed, the study is based on a retrospective analysis. The lack of randomization might represent a selection bias because patients who did not receive adjuvant treatment may have been unfit for adjuvant therapies due to other comorbidities or because of poor performance status (PS); however the authors attempted to minimize this risk by considering the Charlson/Deyo comorbidity condition score as a covariate in the multivariate analysis.

In addition, they considered adequate even a 5-month interval between surgery and the beginning of the adjuvant chemotherapy and an 8-month interval before radiotherapy;

thus it is not clear the real intent of treatment administration (curative versus palliative for disease relapse), since there are no data about the onset and timing of recurrences.

Moreover, the study does not contain any information about the specific chemotherapy regimen and radiotherapy schedule administered, and it is not clear whether some patients received adjuvant radiotherapy both to brain and to lung.

Finally, there are no data about the site of disease relapse (local versus distant recurrence), post-study treatment, and the causes of death (related to study disease versus other causes).

What is the relevance of this study? What should the reader infer about L-SCLC management from this article?

These results are consistent with previous randomized studies and guidelines which underline that surgery alone in L-SCLC is inadequate because of propensity for early and systemic dissemination of SCLC (3-6). Thus, the study may not be considered practice-changing because it does not add anything additional to the current knowledge.

L-SCLC includes a heterogeneous spectrum of disease which might differently benefit from locoregional treatments and with variable prognosis; particularly, large tumor size and the involvement of mediastinal lymphnodes might significantly impact on the clinical course of the disease where the benefits of surgery are still uncertain (7,8).

This is the main reason why the management of L-SCLC in the clinical practice is extremely variable; indeed, the benefit of surgery is clearly shown in T1-2N0M0 stages, while chemoradiotherapy rather than surgery might be considered as the optimal treatment option in L-SCLC with positive lymphnodes (5,6).

To date no prospective clinical studies comparing chemoradiotherapy with surgery plus chemotherapy and/or radiotherapy in L-SCLC has been published; to our opinion, this is the main unsolved question in this setting, because without randomized trials stratified according to the presence or absence of involved mediastinal lymphnodes, the best loco-regional approach cannot be defined.

In the current perspective, we discuss the role and evidence supporting different locoregional approaches to L-SCLC, in a two-hand debate.

Different perspectives about the optimal multimodality management of limited SCLC

Chemoradiotherapy

Patients with tumor stage which might mostly benefit from surgery (stage I) represent only a minority of L-SCLC, while comorbidities occuring in previous or current strong smokers also raise the risk for perioperative complications (5).

The proportion of L-SCLC patients with radiologically negative although pathological evidence of mediastinal lymphnodes involvement is not negligible, thus invasive mediastinal staging is currently recommended before considering surgery for clinical stage I disease (6).

In the paper by Yang *et al.*, mediastinal staging or surgical lymphoadenectomy was performed in the majority but not in all patients under evaluation, thus it is not possible to definitely extend the benefit of surgery with or without adjuvant treatment to all the patient subgroups, where chemoradiotherapy might find an alternative place (2).

Most L-SCLC patients, included those cases with mediastinal lymphnodes involvement, seem to benefit from the combined chemo-radiotherapy approach, with a survival advantage of about 5% at 2–3 years (9,10). Though, there are some critical issues in this approach which should be addressed in order to gain the right perspective.

Several studies and meta-analyses during the past years answered some of these questions. Particularly, it is currently known that a concomitant compared with sequential chemoradiotherapy may offer higher benefits (11-14), in order to avoid tumor cell repopulation. The accepted standard in good PS patients is the early administration of radiotherapy with the first cycles of a platinum-based doublet chemotherapy (6). Dose intensification acquires a particular relevance in the context of a concomitant chemoradiotherapy approach, where the time between the start and completion of radiotherapy plays a role in patients' outcome (15). Radiotherapy schedule and the optimal target volume remain unanswered questions in this setting.

The optimal target volume is strictly correlated to the timing of treatment; obviously, the issue of pre- or post-induction target volume has been discussed in the context of a delay radiotherapy, which is not the current standard in clinical practice. The real matter of debate is in fact the elective nodal irradiation. Few studies in a small sample size addressed this issue, investigating the incidence of nodal recurrence when a CT or PET-guided selective compared with elective mediastinal irradiation was performed, without any definitive conclusion (16-18).

Another open matter of debate is the optimal dosage and schedule of irradiation. In order to improve treatment efficacy, the standard schedule of 45 Gray (Gy) in 25 fractions (F) of 1.8 Gy once a day for 5 weeks, was compared with an intensified schedule of 45 Gy in 30 F of 1.5 Gy twice a day (BD) for 3 weeks (19). Radiotherapy was early administered with the first cycle of chemotherapy in both arms; although the survival benefit of the experimental arm, this intensified

dose was not used in the clinical practice probably because of esophageal toxicity and logistic issues. Higher doses of radiotherapy up to 70 Gy with daily administration (QD) delayed at the third cycle of chemotherapy were explored, and the phase II CALGB39808 study showed this approach to be feasibile with acceptable safety profile (20). Higher doses of radiotherapy concomitant with the first cycle of platinum-etoposide (EP) chemotherapy were also explored in a phase I and a subsequent phase II study (RTOG 9712 and RTOG 0239), where the dose of 61.2 Gy in daily fractions of 1.8 Gy in 5 weeks with a concomitant boost (CB) of BD fractions during the last 9 days of treatment was shown to be feasible and safe (21). The promise of higher effective doses and improved survival lead to the ongoing phase III CALGB 30610 trial comparing three different concomitant chemoradiotherapy regimens (45 Gy BID/EP ×4 versus 70 Gy QD/EP ×4 versus 61.2 Gy CB/EP ×4) with the primary endpoint of overall survival (NCT00632853).

Recently, at the 2016 ASCO meeting in Chicago, Faivre-Finn and colleagues presented the results of a phase III trial comparing two concomitant schedules of chemotherapy and 3D or intensity-modulated radiotherapy, 45 Gy in 30 BD fractions over 3 weeks or 66 Gy in 33 QD fractions over 6.5 weeks starting on day 22 of cycle 1 chemotherapy, with the primary endpoint of 2-year survival (22). No significant differences in survival (2-year survival of approximately 50% in both arms) and toxicity were reported, placing these two schedules as possible standard in good PS L-SCLC patients.

Considering the low incidence of very L-SCLC who might benefit from surgery, the design and conduction of prospective clinical trials addressing the ideal chemo-radiotherapy schedule and the selection criteria for different locoregional approaches, should be prioritized in thoracic oncology.

Moreover, also in resectable stage I SCLC we should consider the "phenotype" of a typical SCLC patient: elderly, with notable smoking history leading to concomitant illnesses contraindicating surgical interventions, but who might safely receive radiotherapy planned with modern techniques or in a sequential approach with chemotherapy.

Surgery plus chemotherapy and/or radiotherapy

Systemic chemotherapy with radiotherapy has been accepted has the cornerstone of treatment in SCLC for several years; the role of surgery in management of SCLC was revaluated only after the introduction of the TNM staging system leading to a better prognostic classification of patients beyond limited and extended disease.

From a number of case-series reports and prospective phase II trials (23-30), the rationale of surgery has three main rationales: (I) surgical resection for L-SCLC could improve local control and overall survival, especially considering that the first site of recurrence after chemoradiotherapy alone for L-SCLC is the primary tumor site followed by mediastinal lymph nodes as showed by autopsy findings; (II) histologically mixed tumors with both SCLC and non-small cell lung cancer (NSCLC) components may benefit from surgery because of less chemosensitivity by the NSCLC component; (III) in the era of immunotherapy and targeted therapies, surgery allows to obtain adequate tumor tissue for molecular and biomarker analysis compared to small diagnostic biopsies.

Several groups demonstrated the benefit of adding surgery to chemoradiation approach with results similar to those obtained in NSCLC; recent detailed reviews present the results of these studies (31-33), while the aim of our perspective is to discuss the strengths and critical issues of this approach. Studies about trimodality approach are heterogeneous in patient selection for surgery, chemotherapy regimen, and radiotherapy administration, making it difficult to draw overall conclusions. However, all these studies supported the role of surgery showing encouraging 5-year survival rates up to ≈70% in stage I disease (T1 and T2 without nodal involvement) and ≈40% in stage II disease, with a local control close to 100% different from local failure rates of 36–50% with chemoradiation strategy (19).

Considering surgery alone inadequate in the treatment of L-SCLC because of known propensity to early dissemination, most reports included the administration of chemotherapy in multimodality treatment, first with non-platinum regimen and most recently with platinum-based protocols (23,24,26,27,29). As in the study by Yang *et al.* (2), the benefit of chemotherapy has been largely confirmed but, to date, whether chemotherapy should be offered as adjuvant treatment after surgery or as induction therapy remains controversial with similar positive results in terms of survival and local control in both settings from retrospective analysis and small phase II prospective trials (23-30). In the context of trimodality approach, patient selection for surgery and the role of chest radiotherapy are main issues to be solved.

When surgery is planned, patients should undergo extensive radiologic staging with chest and abdominal computed tomography scan, magnetic resonance imaging of the brain, bone scintigraphy, positron emission tomographic scanning and/or mediastinoscopy to exclude patients with more advanced tumors. Indeed, survival

findings about primary surgery followed by adjuvant treatment for L-SCLC beyond T1-T2 N0 stage are less persuasive; on the same way, when induction chemotherapy is administered, only patients with initial N2 achieving a N0 staging after systemic treatment have significant survival benefit after surgery. Thus, in this specific setting, repeated mediastinoscopy should be performed before surgery.

Moreover, while chemotherapy is a cornerstone in the management of L-SCLC, chest radiotherapy is more heterogenously administered. Even in presence of N0 at clinical staging, surgery should include hilar and mediastinal lymph node dissection to obtain pathological staging. The studies without adjuvant chest radiotherapy planned suggested that patients with pathologically nodal involvement (also only N1 disease) seem to benefit from thoracic radiotherapy with an improved thoracic recurrence-free survival (27,29).

Another issue to be discussed in this context is the mixed tumor histology; surgical series revealed that about 15% of resected SCLC presents mixed histology including a NSCLC component; this high pathological percentage could be related to the large amount of tumor tissue for analysis from surgery and to the typically peripheral presentation of these tumors which make them more easily resectable. However, these findings and the lower chemosensitivity of NSCLC components justify this trimodality approach (34,35).

Recently, at the 2016 ASCO meeting in Chicago, the same authors, using a propensity-score matched analysis, present the comparison between surgery and adjuvant treatment with or without radiation therapy and concurrent chemoradiation in T1-2 N0 SCLC patients of the National Cancer Data Base. According to their results surgery is used rarely but it is associated with a significant higher overall survival compared to concurrent chemoradiation, also limiting the propensity-matched analysis to patients without comorbidities. However, the study is affected by the same criticisms of the article to which this perspective refers, because all clinical relevant data are collected from the same database (36).

Role of prophylactic cranic irradiation in outcome improvement

Independently from the locoregional treatment approach to L-SCLC, PCI is currently considered a standard of care because of the high incidence of brain recurrence impairing patients prognosis in this setting (37). An individual-data metanalysis of seven randomized trials comparing PCI with no PCI, showed a 16% of death risk reduction with a 3-year survival benefit of 5.4% and a reduction of 54% of brain metastases recurrence in L-SCLC patients in complete remission after loco-regional treatment (38). Currently adopted standard of care is the administration of 25 Gy in 10 F, shortly after chemo-radiotherapy, which achieves also a quality of life improvement, especially in case of limited or no neurotoxicity (39). Higher doses of PCI have been investigated up to 36 Gy, even though burdened with higher chronic neurotoxicity (40).

Mild deterioration of memory, cognitive functions might occur also at the standard dose of 25 Gy/10 F, thus a large place for clinical trials aiming at the reduction of neurocognitive effects may be found in this setting. Recent data in cancer patients with brain metastases showed a promising role of memantine (41) or hippocampal avoidance during whole-brain radiotherapy (42) on preservation of neurological functions, and a phase II-III trial in SCLC patients comparing whole-brain radiotherapy with or without hippocampal sparing is currently ongoing (NCT02635009).

Conclusions

Growing body of evidence encourages a trimodality therapy regimen including chemotherapy, surgery, and radiotherapy in selected patients with very L-SCLC (i.e., without nodal involvement). This approach leads to a longer duration of local remission and overall survival. Though, several unanswered questions about both locoregional approaches are currently under discussion, and the study by Yang *et al.* (2) did not solve the critical issues remained in this topic, which might find a solution in a randomized clinical trial comparing modern chemoradiotherapy protocols to surgery plus chemoradiotherapy in L-SCLC.

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Footnote

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