Therapy for small-cell lung cancer: When the past meets the future

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ABSTRACT

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Despite the incidence of small-cell lung cancer (SCLC) has decreased over the years to approximately 10–14% of all lung cancers [1], this tumor still represents a challenge for most physicians due to its rapidly-progressive behavior. As a rule, the outcome is relatively poor in those cases receiving oncological therapy with a median survival of 16–17 months and a 5-year overall survival (OS) of 10% [2], even worse in SCLC patients not receiving any kind of therapy (5-year OS of 5%) [3].

Contrary to that reported for non-small-cell Lung cancer (NSCLC), the quest for the optimal strategy in the setting of limited-stage SCLC has had a rapid rise from the 60s until the 80s and then had a stalemate until today. In fact, in the past some authors reported acceptable outcomes in selected cases undergoing surgery with radical intent with a 5-year OS of 25% [4]. Given these results, although the decision on whether administering chemo (CT) or surgery depended on the surgeons' or oncologists' experience, most physicians have recommended the use of surgery in those patients without metastases or bulky mediastinal disease. Subsequently, the "gold rush" was interrupted in the 90s when the Lung Cancer Study Group (LCSG) [5] reported the results of a randomized controlled trial comparing surgery with non-surgical treatment in early-stage SCLC. This study comprised of 146 patients who were randomized for surgery or for no further treatment after the administration of CT and chest radiotherapy (RT). The final results revealed comparable

results with a 2-year OS of 20% in both study arms. The main limitations to this study were several, mainly the heterogeneous cohort (composed by patients either with or without nodal involvement) and the chemotherapeutic regimen (different from the current protocol with platinum and etoposide). Despite these biases, this study ratified the "banishment" of surgery for many years and the National Comprehensive Cancer Network (NCCN) and the American College of Chest Physicians (ACCP) have "prohibited" the use of surgery until some years ago, even in case of resectable and node-negative disease.

Although this "prohibition" was widely accepted, in literature some authors have simultaneously explored the role of surgery even in case of locally-advanced SCLC. A recent analysis on 2476 performed on the National Cancer Database (NCDB) [3] revealed acceptable 5-year OS rates with 49%, 32% and 27%, respectively, for p-stage I, II and III. In particular, this study evidenced a significant outcome benefit in surgically-treated N2 SCLC compared to non-surgical IIIA stage (5-year OS 18% vs 12%, respectively). Similarly, Takei et al. analyzed 243 patients reporting a 5-year OS of 52.6 % for all resected SCLC [6]. In addition, the definition of the seventh TNM staging system has been based on the analysis of 349 SCLC patients undergoing surgical resection and suggested the utility of surgery in node-positive cases as well, given the 1-year and 5-year survival rates of resected N1 and N2 disease were 74% and 33%, and 54% and 6%, respectively [7].

Considering these interesting outcomes, early-stage SCLC patients undergoing surgery have been associated with improved outcome compared to non-surgical ones. As a result, the NCCN and ACCP have recently changed direction and would seem to be returned back to the starting point. In fact, the more recent guidelines recommend surgical resection (over non-surgical treatment) followed by platinum-based adjuvant CT only for clinical stage I SCLC [8]. However, when nodal involvement is evidenced at preoperative workup, surgery should be avoided.

Regarding the nodal involvement, two issues are actually debated. Firstly, the prognostic impact of

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nodal involvement in resectable SCLC, that has been rarely explored so far. In this setting, Inoue et al. [9] reported better survival rates in N1 patients compared to N2 tumors, while, according to Miyamoto et al., no survival difference among node-positive patients was demonstrated regardless of pathological N status [10]. Likewise, Badzio et al. showed no prognostic difference when comparing N1 and N2 disease [11]. Based on these data, the kind of nodal involvement (N1 or N2) would not seem to be useful for stratifying the outcome of such patients. Thus, further studies are needed to assess this point.

The second issue that has not properly elucidated up to now is the optimal procedure to evaluate the nodal status. In fact, although the use of both conventional and nuclear imaging may improve clinical staging, some authors reported that N2 metastases are reported in more than 50% of clinical N1 patients [12, 13], reflecting a high underestimated metastatic potential of SCLC. As for NSCLC, mediastinoscopy represented the “gold standard” to assess mediastinum for many years. Concerning SCLC staging, Inoue et al. [13] reported that mediastinoscopy biopsy correlated with final pathology in about 80% of surgically-treated SCLC patients. Recently, a retrospective study on EBUS-TBNA has demonstrated a more accurate nodal staging with 96.4%, 100%, and 97.2% of sensitivity, specificity and accuracy, respectively [14]. Thus, the assessment of the optimal strategy to stage SCLC patients is an ongoing debate that needs to be further evaluated in order to obtain specific guidelines.

In conclusion, contrary to that advocated until few years ago, surgery for SCLC may be recommended as a part of multimodality therapies. Nowadays, it is difficult to apply the biased results of past trials [5] in the setting of SCLC patients who are potentially eligible for surgery, due to the recent improvements in terms of staging (PET, EBUS, etc.) and oncological treatments. Probably, it is time to perform a new randomized trial in Europe exploring the role of surgery in N0 patients as well as in those with nodal involvement and locally-advanced disease.

Keywords: Radiotherapy, Small-cell lung cancer, Therapy, Tumor

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Giovanni Leuzzi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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