



Adjuvant therapy for resected early-stage small-cell lung cancer: is now time to rethink about that?

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Small-cell lung cancer (SCLC) has historically been considered a highly chemo-radiosensitive malignancy, rarely susceptible of surgical resection due to advanced stage presentation with bulky nodal disease and frequent systemic involvement. Actually, surgical series documented SCLC in just 2–3% of patients (1) and, although several randomized trials contributed to define the management of extensive and limited stage SCLC, very few data are available for the early stage, possibly resectable, disease. The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology guidelines (2,3) recommend surgery followed by adjuvant chemotherapy and prophylactic cranial irradiation (PCI) as reasonable treatments for patients with T1-2N0M0 disease. Nevertheless, the evidence supporting the use of adjuvant chemotherapy comes from four, quite dated, phase II single arm studies (4-7) (Table 1), while the recommendation regarding PCI is exclusively based on data from trials evaluating the impact of chemotherapy and radiation in patients with not-resectable limited stage SCLC (13). For this reason, the management of patients with very limited stage SCLC (T1-2N0M0) is still far to be defined.

In the article by Yang *et al.* (14), a large retrospective analysis was performed using the National Cancer Data Base (NCDB) and including 1,574 patients with pathologic T1-2N0M0 SCLC who had undergone surgical resection in the predefined study period from 2003 to 2011. To minimize the possibility that the adjuvant treatment was used to treat recurrence rather than to prevent it, the investigators define adjuvant chemotherapy when administered within 5 months after surgery and adjuvant

radiation when administered within 8 months after surgery. The time intervals reflect the condition in real world medical practice, in which patients often experience delays between surgery and initiation of adjuvant treatments.

Among 1,574 patients with resected T1-2N0M0 SCLC, 954 satisfied the investigator's criteria, 354 patients underwent subsequent adjuvant chemotherapy, 190 patients underwent adjuvant chemo-radiation (87 received radiotherapy directed to the lung, 99 directed to the brain, 4 had unknown location of radiotherapy), 22 patients underwent radiation therapy alone [17 receiving thoracic radiotherapy (TRT) and 5 patients receiving PCI]. Treatment with adjuvant chemotherapy with or without radiation compared with no adjuvant therapy was associated with a significant increase in median overall survival (OS) of 24 months (66 *vs.* 42.1 months) and in 5-year OS of 12.3% (52.7% *vs.* 40.4%; $P < 0.01$). Multivariate analysis showed that the use of adjuvant chemotherapy with or without radiation to the brain was significantly associated with improved survival compared with surgery alone, while there were no significant differences in 5-year survival between patients who received adjuvant chemotherapy with radiation to the lung or postoperative radiation only and patients who underwent only surgery.

The study by Yang *et al.* confirmed the survival benefit of adjuvant chemotherapy in resected pathologic T1-2N0M0 SCLC, with a 5-year OS rate of approximately 50%, that is comparable to the one reported in another retrospective analysis using the NCDB (8) and in four prospective trials, which documented a 5-year OS rate for resected early stage SCLC ranging from 36% to 70% (4-7). Furthermore,

Table 1 Clinical trials and retrospective analyses of adjuvant treatment for resected SCLC

Reference	Type of study	N*	Stage	Adjuvant chemotherapy regimens	Adjuvant PCI or TRT	Survival outcome
(4)	Phase II	73 [186]	pT1-2N0M0	8 cycles of CAV or 6 intermittent cycles of alternating CT, using 3 different drug combinations (CAV or CTX + CCNU + MTX or IFO + VP-16)	Elective PCI given after adjuvant chemotherapy	4-y OS 56%
(5)	Phase II	42 [42]	pT1-3N0M0	6 cycles of CTX (1 g/m ² , d 1), EPI (60 mg/m ² , d 1), and VP-16 (120 mg/m ² , d 1–3–5) every 3 wks	No	5-y OS 36%; mOS 32.7 ms
(6)	Phase II	37 [104]	pT1-2N0M0	4-6 cycles of CAV (CTX 1200 mg/m ² + ADM 50 mg/m ² + VCR 1 mg/m ² d 1) or CDDP (60 mg/m ² d 1) + VP-16 (120 mg/m ² d 1–3–5) or CDDP (60 mg/m ² d 1) + VP16 (120 mg/m ² d 1–2–3) and EPI (50 mg/m ² d 1)	Elective PCI given after adjuvant chemotherapy	5-y OS 52%
(7)	Phase II	35 [62]	p stage IA/B [†]	4 cycles of CDDP (100 mg/m ² , d 1) and VP-16 (100 mg/m ² , d 1–3)	No	5-y OS 73% (stage IA); 5-y OS 67% (stage IB)
(8)	Retrospective	1,287 [2,476]	p stage IA/B [†]	Adjuvant CT (in 45% of the 2,476 pts); no information about the regimens	Adjuvant TRT in combination with CT (in 32% of 2476 pts); not information about PCI	5-y OS 50% (stage IA); 5-y OS 45% (stage IB)
(9)	Retrospective	2,686 [3,566]	p stage I [§]	No data available	TRT in 22% of 3,566 pts	TRT not significantly improves OS in resected pts
(10)	Retrospective	1,560 [1,560]	p stage I [§]	No data available	Adjuvant TRT in 38% of pts	5-y OS (surgery + RT) 57%; 5-y OS surgery without RT =49% (P=0.90)
(11)	Retrospective	45 [82]	p stage I [¶]	Adjuvant CT (not specified the regimens used) in 41 of 82 resected pts	Adjuvant TRT in combination with adjuvant CT in 25 of 82 resected pts; PCI in 19 of 82 pts and in 8 stage I pts	5-y OS for stage I (surgery + platinum adjuvant CT) 86% vs. 41% (surgery + non-platinum adjuvant CT) (P<0.02)
(12)	Retrospective	50 [91]	p stage I [¶]	Adjuvant CT (CTX +VCR or CDDP + VP-16) in 42 of 91 resected pts	Adjuvant TRT in 12 of 91 pts; PCI in 5 of 91 pts	5-y OS 80% (surgery and ≥4 cycles of perioperative CT)

SCLC, small-cell lung cancer; N, number of patients; p stage, pathological stage; d, day; wks, weeks; ms, months; y, year; pts, patients; CTX, cyclophosphamide; EPI, Epirubicin; VP-16, Etoposide; CAV, cyclophosphamide + adriamycin + vincristine; CCNU, Lomustine; MTX, Methotrexate; IFO, Ifosfamide; ADM, Adriamycin; CDDP, Cisplatin; VCR, Vincristine; TRT, thoracic radiotherapy; PCI, prophylactic cranial irradiation; CT, chemotherapy; OS, overall survival; mOS, median overall survival. *, number of patients with the reported stage; in parenthesis the total number of patients considered in the study; †, UICC TNM classification 4th edition [1992]; ‡, TNM classification of malignant tumours 7th edition [2009]; §, International Classification of Diseases for Oncology, 3rd edition. World Health Organization [2000]; ¶, TNM classification of malignant tumours 5th edition [1997].

the investigators suggested a promising role of PCI after surgery and adjuvant chemotherapy, reporting a significant OS benefit of PCI in surgically resected SCLC. In contrast, they did not observe any significant survival benefit for adjuvant radiation alone and adjuvant chemotherapy with postoperative thoracic radiation compared to surgery alone. These last findings were remarkably consistent with the previous analyses of the SEER database (9,10).

Although based on a large national database and clarifying interesting aspects about the management of resected SCLC, the analysis of Yang *et al.* could not avoid some limitations, mainly related to its retrospective nature. For what concerns adjuvant chemotherapy, important information are missing regarding the specific chemotherapy regimens administered in this population based cohort study. Nevertheless, considering that the study period was 2003–2011 and that the combination of platinum-etoposide became the standard of care for SCLC in the 1990's, when this regimen demonstrated to be superior to cyclophosphamide-anthracycline-vincristine (CAV) in limited stage SCLC (15) and equivalent to CAV but with less toxicities in extensive stage SCLC (16), it is strongly plausible that platinum-etoposide was the preferred adjuvant chemotherapeutic regimen used in the analysis by Yang and colleagues. Furthermore, in 2005, the superiority of platinum-based chemotherapy compared to non-platinum regimens, was demonstrated also in the adjuvant setting, in a retrospective analysis including stage I SCLC who underwent surgical resection and postoperative adjuvant chemotherapy (11).

Although platinum-etoposide was probably the most common adjuvant regimen used in the analysis by Yang *et al.*, the investigators did not address in their study the question regarding the use of cisplatin or carboplatin. In fact, despite the equivalence in terms of survival between cisplatin and carboplatin in advanced SCLC, as reported in the COCIS meta-analysis (17), this result should not be translated to the adjuvant setting, considering that only the 30% of patients included in COCIS meta-analysis had limited stage SCLC. Actually, the small percentage of limited stage SCLC in the COCIS meta-analysis and the absence of efficacy of carboplatin-based combination in adjuvant treatment for non-small-cell lung cancer (NSCLC) (18), might suggest a possible differential treatment effect between adjuvant carboplatin and cisplatin also for resected SCLC; however, no definitive conclusion regarding this issue can, ultimately, be drawn.

In the analysis of Yang *et al.*, besides the specific

chemotherapeutic agents used, also the number of administered cycles of chemotherapy cannot be ascertained. In this regard, in a retrospective review of early stage SCLC patients who underwent surgical resection, the administration of four or more cycles of adjuvant chemotherapy compared to one to three cycles was an independent factor to determine postoperative survival (12), suggesting that four or more cycles of adjuvant chemotherapy should be considered the standard treatment for resected SCLC.

Regarding PCI, its role is quite controversial in extensive stage SCLC, where a randomized trial reported a striking improvement in 1-year OS rate of 14% (27% *vs.* 13%, HR 0.68) (19) and a more recent meta-analysis outlined the absence of a significant survival benefit (HR 0.95, P=0.89) (20). For what concerns patients with limited stage SCLC and with complete remission after chemo-radiotherapy treatment, a large meta-analysis showed that PCI significantly improved the 3-years OS of 5.4% (15.3% *vs.* 20.7%, HR 0.84) (13). In the adjuvant setting, the analysis of Yang *et al.* represents the first study supporting PCI after surgery and adjuvant chemotherapy, showing at the multivariate analysis a significant reduction in the risk of death of 48% in favor of PCI (after adjuvant chemotherapy) compared to surgery alone (HR 0.52, P<0.01). Although the authors have performed a comparison of prognostic variables between the two groups, a further adjustment of the results with a propensity score analysis would have increased the value of the analysis, by minimizing the biases related to its retrospective nature.

In their retrospective analysis, the investigators did not find a significant survival benefit with adjuvant radiotherapy or adjuvant chemotherapy followed by thoracic radiation compared to surgery alone. This result seems to be in contrast with the benefit of 5.4% in 3-year OS observed by adding TRT to chemotherapy in limited stage SCLC (21), with the improvement of 10% in 2-year OS (13% *vs.* 3%, P=0.004) reported in patients with extensive stage SCLC included in the CREST trial (22) and with the significant reduction in the risk of death (HR 0.82, P=0.02) demonstrated in a meta-analysis of five trials comparing TRT *vs.* no TRT (20). The study of Yang and colleagues and the retrospective analyses of the SEER database (9,10), outlined that adjuvant TRT might have a less determinant role in controlling micrometastases compared to adjuvant chemotherapy and PCI. Furthermore, these results differ from a recently published retrospective analysis of the NCDB reporting a significant OS benefit for adjuvant chemo-radiotherapy compared to surgery alone (HR 0.41,

$P < 0.0001$) in resected SCLC (8). In the analysis of Yang and colleagues, the doses and the schedules of administration of TRT cannot be ascertained and it is possible that the lack of survival benefit from adjuvant TRT could depend on the use of inappropriate doses and/or old-fashioned schedules of radiotherapy. In fact, in limited stage SCLC, early concurrent TRT with a time of starting any therapy and end of radiotherapy (SER) ≤ 30 days (23) and accelerated TRT (24) were, respectively, associated with a significant 2-year OS benefit of 5% and 5-year OS benefit of 10% if compared to TRT with SER > 30 days and to standard fractionation schemes.

Finally, it is possible that, in Yang's analysis, a selection bias contributed to the much higher survival reported in patients treated with both adjuvant chemotherapy and PCI and to the absence of survival benefit for patients treated with only adjuvant thoracic radiation. In fact, although the authors tried to minimize this bias including the Charles/Deyo Comorbidity Condition (CDCC) score as a covariate in the multivariable model, it is still possible that patients with best performance status received both adjuvant chemotherapy and PCI after surgery, while patients who received only adjuvant TRT had more comorbidities or poorer clinical conditions.

The observations made by Yang and colleagues, supporting the use of a multimodal adjuvant treatment for early stage SCLC including surgery, adjuvant chemotherapy and PCI, are extremely helpful for medical oncologist to manage patients with resected T1-2N0M0 SCLC. Nevertheless, the 5-year survival rate of stage I SCLC still ranges between 40% and 60% (25); for this reason, the development of more powerful and modern adjuvant therapeutic tools and radiation techniques, both integrated in a multimodal treatment strategy, will represent one of the toughest challenge for the future research in this field of thoracic oncology.

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Footnote

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