Editorial Commentary



# Radiotherapy target volume for limited-disease small cell lung cancer: good news from the dark side of the moon

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Thoracic oncologists worldwide usually detect and treat small cell lung cancer (SCLC) 5 to 6 time less frequently than its big brother, non-small cell lung cancer (NSCLC). It is, therefore, the number of cases in a busy clinic nowadays which may be seen as a driving wheel for any innovation, since more patients imply more research opportunities. Numerous unanswered questions seem to remain in the domain of both limited disease SCLC (LD SCLC) as well as extensive disease SCLC (ED SCLC). While, however, recent years had witnessed encouraging moves with the introduction of immunotherapy in ED SCLC (1), life of patients harboring LD SCLC still remain déjà vu, being virtually unchanged for the last two decades. Two major (one may say, monumental) aspects of the "change" in LD SCLC were introduction of cisplatin/etoposide (PE) as the backbone of the modern treatment in the 1970s and introduction of the three-dimensional thoracic radiotherapy (3D TRT) in the 1990s. While the first one helped improve treatment results in the CHT-alone domain and decrease side effects, especially when such CHT was combined with TRT, TRT itself passed a long way of trying to identify itself as the indispensable part of the treatment in SCLC. While TRT in ED SCLC was established at the turn of the century (2) and confirmed 15 years later (3), impact of TRT was somewhat easier and faster documented in LD SCLC. Luckily, and in spite of the two times less patients (when compared to those of ED SCLC), different natural history of the LD SCLC disease and its significantly better outcome led researchers to undertake more of the combined TRT and CHT studies which all addressed the issue of optimization of treatment approach in this setting.

In spite of existing differences in studies done in 1970s and 1980s, two meta-analyses (4,5), firmly showed that TRT-CHT was superior to CHT alone. Past 30 years have also witnessed numerous attempts to introduce new CHT drugs, targeted agents and immunotherapy, none of which has, currently, been considered equal to TRT combined with PE. While this "progress block" additionally stimulated researchers to investigate new drugs, the domain of TRT combined with PE has witnessed progress in several aspects. Issues of time-dose/fractionation, prophylactic cranial irradiation (PCI) and the timing of combined TRT and CHT attracted interest of researchers. Based on an important Intergroup study (6), hyperfractionated thoracic RT (Hfx TRT) was shown to be superior to daily (QD) fractionated TRT of the same dose (45 Gy). In spite of the clear message, even nowadays it remains underutilized in a daily practice and, furthermore, specific nihilism led to further loss of almost 20 years until another fractionation study showed that even 66 Gy given QD is not superior to that same Hfx TRT dose (45 Gy, 1.5 Gy bid) (7). We all fared a bit better when the issue of PCI was considered as meta-analysis from 1999 clearly showed necessity of administration in at least complete responders (CR) after

TRT-CHT (8). We also seem to have approached the solution of the problem of timing of TRT and CHT in LD SCLC in spite of the fact that existing meta-analyses and systematic reviews (9-12) may have created confusion 15 years ago due to somewhat differing results. Luckily, again, additional insight into this issue (13) helped clarify some important aspects in this setting, favoring early administration of concurrent RT-CHT over its later administration.

So, here we are, on the bridge towards the issue of the optimal TRT target volumes in a combined modality approach in LD SCLC. And that bridge is somewhat easier to pass if one considers treating LD SCLC when TRT concurrently starts the day 1 of the first CHT cycle. You simply treat what you see, although some may still consider worthwhile using elective (ENI) or selective nodal irradiation (SENI) (14). However, the same bridge is not easily passed if you start TRT during cycle 2 or 3, as is the most widely accepted and current practice, favoring administration during cycles 1–3 over the cycle ≥4. Question, then, appears as: besides deciding about ENI, SENI or no-ENI, how about treating pre-CHT *vs.* post-CHT volumes? Lack of studies and, consequently, in-depth analyses of preferred concurrent cycle 2 versus 3 (including extremely unlikely expectation that such a question would be asked in any trial, anytime, anywhere), puts the timing of TRT-CHT during cycles 2 *vs.* 3 out of focus of any meaningful discussions. Additionally, some LD SCLC patients have large tumor (T) and/or lymph node (LN) component and oncologists frequently succumbed to the fear that starting, e.g., 45 Gy, 1.5 Gy bid concurrently with cycle 1 of the standard dose PE would eventually bring significant acute toxicity, some of which have indeed been observed in the past. Therefore, many clinicians remain on the safe side starting TRT post-cycle 1; it remains irrelevant for this discussion of whether it is during the cycle 2 or 3 or how to treat patients who experience CR after induction CHT. The question to treat pre-CHT or post-CHT volumes remain vital as ever. However, no matter how vital this question is, surprisingly there is no high level evidence supporting any finding, but things may just have changed…

It is frustrating fact that only one prospective randomized clinical trial has only obliquely examined the issue of RT treatment volume in SCLC. This study, performed by the Southwest Oncology Group (SWOG) more than 30 years ago (15) has rather unusual response-based randomization schema. The patients with a partial response (PR) or stable disease (SD) receiving non-CDDP based CHT were randomized to TRT based either on the pre- or the post-CHT volume of disease. No statistical differences in survival or recurrence patterns were noted as a function of volume treated which led SWOG researchers to suggest post-CHT volumes as appropriate for target delineation. However, one should not forget the timing of that publication (reflecting old and outdates diagnostic and treatment technology) including the fact that TRT volumes were determined from a chest X-rays (CXR) (15). In the pre-CHT arm, the X-ray was taken before the induction CHT; in the post-CHT arm, the post-CHT X-ray served for planning, making the significance of these findings at least dubious nowadays. Several retrospective analyses used patterns of local/regional failure to address the same issue. In one study (16), when post-CHT volumes were used the majority of patients who failed in the chest also failed in the lung but outside the TRT field, but not within LNs, suggesting that pre-CHT volumes should be preferred. Contrary to that, other suggested the use of post-CHT volumes (17) due to no difference between pre- and post-CHT TRT volumes. Using a different approach, though aiming the same issue, some (18,19) attempted to correlate patterns of failure and clinical trial violations. In patients in whom "inadequate treatment portals" of TRT were observed, it led to inferior local control and overall survival (OS). When, however, more sophisticated CT-based simulation techniques became available (20,21), significance of the dose delivered rather than the delineated target since tumor recurrences unequivocally predominated within the post-CHT volume. Therefore, temporal trends became obvious in that both out-of-trial and trial setting requested for somewhat limited TRT fields. This implies significantly important discussion about the use of era-defined "contemporary" technology used in this setting, which seems to be especially important nowadays with the use of PET-CT.

Fresh publication from *Cancer* (22) brings all of these issues into the focus, being the very first prospective randomized clinical trial on TRT target volume for LD SCLC. After 2 cycles of PE, Hu *et al.* (22) randomized patients to receive TRT to the post-CHT or pre-CHT tumor volume with involved-field RT being received in both arms. TRT consisted of 45 Gy given via 1.5 Gy bid. Endpoints included local/regional progression free survival (PFS) and OS as well as patterns of failure and side-effects. Due to their effort to systematically contour LN regions 1–10 recording of intentional and incidental radiation doses was possible. Four-dimensional (4D)-CT simulation was recommended, 3D conformal radiotherapy

 

(3DCRT) and intensity-modulated radiotherapy (IMRT) were used, while 2D RT was not permitted. International Commission on Radiation Units and Measurements Report 50 guidelines were used to delineate the gross tumor volume (GTV) which included the primary tumor (GTV-T) and positive pre-CHT LNs (GTV-N) (defined as LNs in the mediastinum with a greatest dimension ≥1 cm, or positive sampled LNs, or an F-18 fluoro-2-deoxyglucose (FDG) standard uptake value ≥2.5 on PET/CT at initial staging). In patients randomized to post-CHT primary tumor extent, the clinical target volume-tumor (CTV-T) included the post-CHT residual GTV-T with a margin of 0.8 cm. Patients randomized to pre-CHT primary tumor extent had their CTV-T including the pre-CHT GTV-T with a margin of 0.8 cm. When LN regions were involved before induction CHT, they were included in the TRT fields as CTV-N for both arms even if the LN disappeared after induction CHT. Either arm did not allow for ENI to the uninvolved LN regions. A margin from 1.0 to 1.5 cm around CTVs was used to create planning target volumes (PTVs).

This single-institutional study was, unfortunately, closed early because of slow accrual: between June 2002 and January 2017, it recruited 315 patients, of which 309 patients were eligible for the analysis. Patient and tumor characteristics were balanced between the two arms, including the use of PET-CT in approximately 20% of all patients. The median follow-up was 19.6 months for all patients. Fifty-two patients (34.2%) in the post-CHT arm and 46 (31.1%) in the pre-CHT arm developed local/regional failure (P=0.77). Of them, 4 patients (2.6%) in the post-CHT arm and 6 patients (4.1%) in the pre-CHT arm developed isolated out-of-field LN failure (P=1.00). The 3-year local/regional progression-free probability was 58.2% versus 65.5%, in the post-CHT versus pre-CHT arm (P=0.44). The median OS in the post-CHT versus pre-CHT arm was 21.9 and 26.6 months, respectively. The estimated 5-year and 7-year OS rates in the pre-CHT versus post-CHT arm were 22.8%, and 21.2% versus 28.1%, and 21.5%, respectively (P=0.26). As expected, acute esophagitis was significantly more frequent in the pre-CHT arm (P=0.01) as well as significantly more grade 2 and 3 pulmonary fibrosis was observed in that arm (P=0.01). All but station 8 (only partially included during TRT) positive LN regions were subjected to prescribed doses. The negative LN regions that received average incidental RT doses >30 Gy were 3P (36.7 Gy), 4L (34.8 Gy), 7 (34.4 Gy), 6 (34.4 Gy), 4R (32.4 Gy), 5 (31.7 Gy), and 2L (31.5 Gy).

How one considers these data alone? How one puts them into the context of existing evidence? What these data indicate for future approaches, if at all? Considered alone, they are pretty straight forward: no need to treat pre-CHT volumes as both PFS and OS were similar to post-CHT volumes as well as toxicity was lower in the latter group. They also indicated that with post-CHT volumes and no ENI, a number of more centrally located LN stations received incidental RT of ≥30 Gy, i.e., 2/3 of the prescribed dose to the visible T/N. When one considers these results in the context of observations, not the evidence, accumulated with the time, i.e., chronologically, they seem to perfectly support it. We moved from 2D to 3D and then 4D TRT as we have also moved Cobalts to Linacs and successfully implemented more powerful softwares in treatment planning and execution of TRT. We have moved from CXRs to CTs, finally and increasingly using PET-CTs. All these technological advances enabled us to be more precise in both what we see (anatomically and/or metabolically) and what we treat and document. Therefore, again, these trends are supported (some may say materialized) by this PRCT (22), seemingly first ever in this setting. Hu *et al.* (22) also open up new aspects in this setting by reporting for the first time the use of GTV-T in LD SCLC, investigation of which showed safety of using it with no increase of any out-of-field or marginal recurrence of the T component. What this study indicates for the future also seems "easy" to anticipate. The vast majority of practicing radiation oncologists and researchers will continue to use post-CHT volumes. This will additionally be supported by the fact that PET-CTs are becoming widely available worldwide for both diagnosis, staging, and treatment planning in these patients.

Question one may ask before closing this chapter is whether there would be a meaningful approach to use PET-CT-based adaptive planning after, e.g., 75% of the total planned TRT dose has been given using limited field TRT? If one believes in CT-based response to CHT (i.e., using post-CHT volumes), should it then believe even more to PET-CT volumes in the process of adaptive planning? If so, would then anticipated shrinking of the RT volumes during the RT course enable dose escalation as data points to excellent outcome if dose of 54 Gy, 1.5 Gy bid is given in both LD SCLC and ED SCLC (2,23).

Like any other trial, this trial is not a perfect one. Take, for example, short follow up or the time period of almost 15 years needed to recruit the patients. To extend this, patients in pre-CHT arm did not have their CT simulation

 

done pre-CHT which may have led to incorrect volume judging in these patients. Similarly, albeit on the other side, CT-simulation before induction CHT probably led, at least in some patients, to mismatch to second CT-simulation after induction CHT due to, if not frequent, then definitely occasional, patient weight loss, different Linac couch positioning and immobilization. Finally, as hotly debated in NSCLC (24,25) it should not be forgotten that incidental RT to several LN stations of ≥30 Gy could have eradicated microscopic deposits there.

Regardless of these, Hu *et al.* (22) should be commended for their elegant and important work that is pivotal in many aspects. They bring to us the issue that represents one of the most agonizing issues in the field of thoracic oncology when several aspects (technology and biology related) are grouped in the moment of the decision making in patients with LD SCLC. They may have shut some doors but opened new ones, challenging thoracic oncologists and clinical researchers to further optimize our treatment endeavors in the years to come.

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