Local treatment of synchronous oligometastatic non-small cell lung cancer (NSCLC)—current consensus and future perspectives

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The integration of effective systemic therapies such as immunotherapy with immune checkpoint blockade (ICB) and targeted therapies improves survival outcomes significantly for patients with advanced non-small cell lung cancer (NSCLC). Mounting clinical evidence suggests that the application of radical locoregional therapies (LRT), including surgery and stereotactic body radiotherapy (SBRT) to synchronous oligometastatic NSCLC (SOM-NSCLC) improves outcomes beyond those achieved using systemic therapies alone (1,2). However, more precise definitions of SOM-NSCLC are needed to facilitate the care of patients and interpretation of prospective clinical trial results.

Although metastatic NSCLC historically had dismal survival rates, research has explored heterogeneity within this group to determine which patients may benefit from LRT to selected sites of oligometastases. The biological concept of oligometastatic cancer was initially introduced in 1995 by Drs. Hellman and Weichselbaum as an intermediate state of limited tumor foci in one or limited organs that differs from the classic microscopic or "leukemia-like" dissemination (3). They explained differing virulence patterns between SOM and metachronous OM disease; for SOM, limited disease sites are diagnosed simultaneously with the primary uncontrolled, and metachronous oligometastatic or "oligo-recurrences" that appear after initial control of the primary with a measurable disease-free interval (DFI) (4). SOM is expected to have better outcomes if controlled initially compared to metachronous oligometastatic disease that succeeded in escaping previous systemic therapy and evading the immune system. Dr. Weichselbaum and Hellman illustrated that temporal evolution of SOM disease will vary according to several factors e.g., (initial disease site and extent, histology, molecular profile, type of first line systemic therapy and its response) with disease free interval >36 months carrying the best prognosis (5).

In the *Journal of Thoracic Oncology* in December 2019, Dingemans *et al.* and the Lung Cancer Group of the European Organization of Research and Treatment of Cancer (EORTC) published a multidisciplinary consensus report for the definition of SOM-NSCLC based on a systematic review and results from expert surveys that were designed for this consensus statement (6). Data were collected from 21 studies published between 1996 to 2017 that included 1,215 patients (7). Based on the systematic review, the definition of SOM applied when five or fewer metastatic lesions were identified in up to three different organs. The consensus group defined SOM-NSCLC stage based on the technical feasibility of radical treatment with acceptable toxicity. There was extensive experts discussion about the value of treating a larger number of lesions (e.g., >5) if still technically feasible. Survey questions including ten "real-life" cases were addressed to thirty thoracic oncology experts to unify the definition of SOM-NSCLC, given the variety of management paradigms. Following the

8th TNM staging system (8), contralateral pulmonary lesions were counted as one metastatic site, while nodules within the same lobe of the lung (T3) and ipsilateral lung nodules (T4) did not count as metastases. Also, mediastinal nodes were considered in the N descriptor and not as metastatic. According to this consensus statement, all organs could be considered for LRT except where radical treatment was not feasible (serosal membranes, meninges and bone marrow). The impact of site-specific metastases on outcome was controversial and the consensus did not endorse any specific sites (i.e., brain or adrenals) to change the concept of oligometastatic disease. One limitation is that histological and genomic classifications were not considered in this consensus statement.

Advanced diagnostic imaging is the current cornerstone to discriminate SOM-NSCLC from the poly-metastatic stage. To avoid toxicities of unnecessary local treatments, in Dingemans *et al.* there was complete expert agreement on the value of 18-fluorodeoxyglucose-positron emission tomography with computed tomography (18F-FDG PET/CT) and brain magnetic resonance imaging (MRI) for staging. Pathological confirmation of at least one metastasis was emphasized especially in the setting of solitary lesions. Dedicated imaging and biopsies were recommended if believed to change the treatment course (6).

With the promising survival results for SOM-NSCLC, the EORTC consensus statement on definition of this disease stage is a step toward clearer inclusion criteria for future randomized controlled trials. Also, this consensus raised debatable questions and research points to be discussed further. For example, with the definition of SOM-NSCLC based mainly on the feasibility of the LRT comes the possibility of long-term toxicities, which need to be considered in routine clinical practice and discussed with patients and multi-disciplinary teams. Although the toxicity profiles of LRT are well tolerated, LRT combination with ICB and targeted therapies requires additional study.

Furthermore, mediastinal lymph nodes are not considered metastatic sites for SOM-NSCLC in the EORTC consensus; however, high nodal burden carries negative impact on prognosis and specifically requires aggressive interventions (9,10). Definitive thoracic therapy for primary and mediastinal nodes should be attempted using surgery or radiotherapy to improve outcomes with ablating oligometastatic sites (11). Invasive mediastinal staging would be mandated to solidify the treatment plan. It will also add an important prognostic point about

extent of mediastinal invasion (12). Hypofractionation and SBRT fractionation schemes have been reported to improve locoregional control of the primary thoracic disease in SOM-NSCLC (13,14). Conventional concurrent chemoradiation therapy could also serve as an effective local control strategy for SOM-NSCLC with high mediastinal nodal burden (15).

Since the influence of specific oligometastatic sites on survival is controversial, relapse patterns of certain sites may affect LRT long term outcomes. For example, brain lesions *per se* should not exclude patients from LRT trials, and SOM-NSCLC patients have higher rates of cranial failure after systemic therapy and extracranial LRT (11,16). For patients presenting with brain lesions, nearly half of the failures reported after local therapy occurred in the brain outside the irradiated field. Frequent monitoring of the neuraxis may be a reasonable strategy for SOM-NSCLC when LRT is adopted (15). There are some clinically useful nomograms that could be used to classify patients of higher risk of relapse included in randomized clinical trials of LRT (17). Brain metastases appear to significantly impact overall prognosis for SOM-NSCLC.

A meta-analysis by Ashworth *et al.* included 49 studies with a total of 757 OM-NSCLC patients and showed that 5-year overall survival was 29.4% for patients in favorable risk group (good performance status, lower intrathoracic disease burden and limited metastatic lesions i.e., </=5 lesions). Prognostic factors for improved response to LRT were synchronous lesions and nodal stage. Statistically significant poorer outcomes were observed with non-surgical management of the primary lung cancer and the presence of brain metastases (18). Other prognostic markers to identify tumors with limited metastatic capacity included: number, size of metastatic lesions and number of involved organs (5). Ashworth *et al.* defined "four aces" or prognostics factors including young age, patient fitness, slow-growing disease (i.e., metachronous metastases or a long DFI between the original cancer and the metastatic recurrence), and low disease burden (i.e., a smaller number of metastases) (9). Patients who had good response to first line chemotherapy tended to benefit when aggressive local treatment is applied to primary thoracic and oligometastatic sites (19).

From the meta-analysis by Giaj-Levra *et al.* (7), most of the evidence for the additive value of LRT emanated from multiple retrospective and non-randomized studies. However, better-than-expected survival outcomes were

Table 1 Summary of the two-randomized phase II trials of SOM-NSCLC

Variable/outcomes	Gomez *et al.*	Iyengar *et al.*
No. of patients	49	29
Systemic therapy	Platinum-based doublet or EGFR/ALK targeted TKI	Platinum-based doublet-EGFR mutations and ALK gene rearrangement were excluded
No. of metastatic lesions	≤3	≤5
Type of LRT	Radiation therapy/surgery	Radiation therapy
RT fractionation	• Intermediate hypofractionation • SBRT • Conventional	• SBRT (21–30 Gy)
Primary disease management	• Intermediate hypofractionation • Conventional with chemotherapy • Surgery • SBRT	• SBRT • Hypofractionation (45 Gy)
Median PFS (months)	14.2	9.7
Median OS (months)	41.2	Not powered

LRT, locoregional therapy; PFS, progression-free survival; OS, overall survival; SBRT, stereotactic body radiotherapy; SOM-NSCLC, synchronous oligometastatic non-small lung cell cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors.

observed using LRT for SOM-NSCLC from two important prospective clinical trials summarized in *Table 1*.

In the first study by Gomez *et al.*, 49 patients with good performance status i.e., Eastern Cooperative Oncology Group performance status score of ≤2 and ≤3 metastases received first line systemic therapy (platinum-based doublet) for 4-6 cycles. For patients with tumor driven mutations, 3-month of tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangement were used. Randomization to maintenance systemic therapy with or without LRT (surgery or radiation) was offered to patients with no disease progression after the first line. The median progression-free survival (PFS) in the LRT group was 11.9 *vs.* 3.9 months in the maintenance treatment group [hazard ratio 0.35 (90% CI, 0.18–0.66), log-rank P=0.0054]. Updates of survival data at 3-year showed a durable improvement of PFS and OS in LRT arm compared to the control arm (14.2 *vs.* 4.4 months, P=0.022) and (41.2 *vs.* 17.0 months, P=0.017), respectively (1). A continuous OS benefit was reported after disease progression for patients treated by ablative LRT (median 37.6 *vs.* 9.4 months, P=0.034). In the same study, salvage LRT was still a feasible option for 41% of patients who progressed. In multivariate analysis, LCT trended to correlate with better OS when used initially or as salvage.

Twenty percent of patients experienced ≥grade 3 toxicity in the LRT arm compared to 8.3% in the control group in this trial (1).

In another phase II randomized clinical trial, by Iyengar *et al.*, 29 patients with oligometastatic NSCLC (≤5 lesions) were randomized to consolidative SBRT to all lesions or continuation of conventional maintenance systemic therapy. The primary thoracic disease was treated by SBRT or hypofractionated radiation. SBRT single-fraction doses included 21 to 27 Gy. Three-fraction SBRT doses included 26.5 to 33.0 Gy. Five-fraction cumulative doses included 30.0 to 37.5 Gy. If SBRT fractionation schemes for primary disease did not allow normal tissue constraints to be met, an alternative hypofractionation protocol was 45 Gy in 15 fractions. Median PFS for the SBRT and chemotherapy arm was 9.7 months compared to 3.5 months in chemotherapy only arm (P=0.01) with comparable toxicity rates between both groups (2).

Although LRT in SOM disease achieves durable local control, distant failures are still of high concern. In Tree *et al.*, 80% of distant progression of SOM disease after SBRT treatments occurred within 2–4 years (20). Median time to progression from the two NSCLC trials ranged from (9–11 months) (1,2). For patients presenting with oligometastatic recurrent lesions after initial LRT, salvage LRT could still be offered as a salvage treatment option,

although there is no clear data about time sequencing of LRT and systemic therapies.

We are observing a major shift towards incorporating immunotherapy as early as possible in the course of management of NSCLC patients. The PD-L1 inhibitor, durvalumab has become the standard of care as consolidative therapy for Stage III NSCLC after completion of definitive concurrent chemoradiotherapy (21). For stage IV NSCLC, ICB has demonstrated improved median OS and PFS in the first-line as well as second-line settings in both squamous and non-squamous NSCLC (22-24). Synergy is expected when oligometastatic lesions are treated with LRT, especially SBRT, in combination with ICB. In a Phase II prospective clinical trial, pembrolizumab was used after 4 to 12 weeks of completing LRT to 51 OM-NSCLC patients who had ≤4 metastatic sites. LRT arm was associated with a median PFS of 19.1 months, significantly greater than the historical median of 6.6 months (P=0.005). Median PFS was 18.7 months (95% CI, 10.1–27.1 months) when maintenance pembrolizumab was added (25). Phase III trials are ongoing to further investigate the synergistic role of ICB in SOM-NSCLC. For example, the LONESTAR trial (NCT03391869) is a Phase III trial currently recruiting metastatic NSCLC patients to evaluate LRT value after ICB compared to ICB alone. This trial offers nivolumab and ipilimumab in combination with local consolidative therapy with either surgery or radiation (26).

Different phenotypes and genotypes carry a predictive value to LRT in SOM. Oncogene-driven tumors tended to benefit from LRT with relevant TKIs in first and 2nd line (16,27), which will be elucidated further by the ongoing clinical trial (NCT03410043) that is treating EGFR-mutated patients with Osimertinib and LRT. The results of the meta-analysis by Li *et al.*, showed that having an EGFR mutation is an important predictive factor linked to improved OS for NSCLC patients with brain metastases (28). In a retrospective study by Weickhardt *et al.*, patients who had oligoprogression on their first TKI erlotinib or crizotinib showed improved median progression free survival when LRT was combined with the same line of targeted therapy supporting the value of SBRT as an effective modality controlling these sites that may have lost its oncogenic addictive response and delaying the switch to second line TKI's (16). Similar improvement was reported when LRT for oligometastatic and primary sites was added to first line EGFR-TKI in SOM-NSCLC retrospective analysis by Xu *et al.* (27).

In a prospective single arm analysis of 24 patients with extra cranial oligoprogression, erlotinib was combined with SBRT to treat oligometastatic sites progressed after 1st line chemotherapy. Median PFS was 14.7 months, and median OS was 20.4 months with SBRT with only 6 % of failure at the irradiated sites (29). Results of 2nd generation of EGFR TKI osimertinib are promising with clinically meaningful efficacy against CNS metastases with a high disease control rate and durable response regardless of radiation therapy (30). Randomizing SOM-NSCLC patients to more effective TKIs as osimertinib with LRT is expected to answer two questions; first if that local ablative treatments may add toxicity in a good prognostic group, or if local treatment will enhance these improved outcomes when combined to the TKI therapy. Ongoing trials such as NORTHSTAR (NCT03410043) attempts to address these points (31).

The intrinsic molecular subtypes of colorectal cancer with liver oligometastatic lesions were able to differentiate three robust risk groups based on gene expression profiling. This molecular analysis helps predict survival outcomes with LRT and identify patients with curable liver oligometastasis (32). Similar profiles for SOM NSCLC are awaited to further clarify tumors with limited metastatic capability where LRT is of maximum value. Circulating tumor DNA (ctDNA) mutational burden was reported as a quantitative biomarker that correlated with NSCLC evolution and proposed to identify an early relapsing or metastatic stage (33). In a correlative study (34), ctDNA metrics, cytokine levels, and T-cell receptor biology were studied in association to LRT in oligometastatic NSCLC treated within phase II trial (1). These biological markers are expected to guide patient selection for future definitive LRT trials.

Although the EORTC consensus on SOM-NSCLC was a step to define this evolving disease stage, additional evidence is still needed. Ongoing prospective randomized clinical trials summarized in *Table 2* are recruiting to consolidate the role of LRT in SOM-NSLC stage with integration of immunotherapy and targeted therapies. Finally, it is emphasized that consensus on appropriate treatment of SOM-NSCLC patients in our current clinical practice should be obtained within dedicated thoracic multidisciplinary discussions addressing risks and benefits in view of the current evidence.

Table 2 Ongoing studies on LRT of SOM-NSCLC patients

Clinicaltrials.gov identification number	Phase	Number of patients	Primary end point	Country
NCT03137771 (NRG trial-LU002)	II/III	300	PFS/OS	USA
NCT02417662 (SARON)	III	340	OS/PFS	UK
NCT03119519	II	148	PFS	China
NCT03827577 (OMEGA)	III	195	OS	Italy
NCT03391869 (MDACC)	III	270	OS	USA
NCT03965468 (CHESS)	II	47	PFS	Europe, multicenter
NCT02893332 (sindas)	III	200	PFS	China
NCT03808337 (promise-005)*	II	142	PFS	USA

*, recruiting both breast and NSCLC oligometastatic patients. PFS, progression-free survival; OS, overall survival; LRT, locoregional therapy; SOM-NSCLC, synchronous oligometastatic non-small lung cell cancer.

Footnote

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