

Is there a benefit to locally consolidative therapy for oligometastatic non-small cell lung cancer?

Lauren Boreta, Sue S. Yom

Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

Correspondence to: Sue S. Yom, MD, PhD, MAS. UCSF Radiation Oncology, 1600 Divisadero St. H1031, San Francisco, CA, USA.

Email: sue.yom@ucsf.edu.

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Metastatic non-small cell lung cancer (NSCLC) is known to have a particularly poor prognosis, with a median overall survival of 8 months and a 10% survival rate at 2 years (1). Historically, treatment for metastatic NSCLC has been palliative chemotherapy (2) which has been shown to modestly prolong 1-year survival in comparison with best supportive care (3). Nowadays, with the advent of more sensitive imaging modalities, improvement in the specificity of radiation therapy delivery, and targeted systemic therapies, many patients with limited metastatic disease are being detected and treated more aggressively, in the absence of randomized, prospective data to support these practices. In patients with metastatic lung cancer, where obstructive or functionally limiting manifestations of disease can reduce performance status and diminish quality of life, there may be a uniquely important role for early enactment of locally directed therapy.

Several retrospective and single arm prospective studies have demonstrated the utility of local consolidative therapy, using either surgery or radiation (4), to ≤ 3 or ≤ 5 metastatic sites in NSCLC—what is termed the oligometastatic state. Local control rates are generally equivalent between surgery and stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic disease, nearing 80–95% at 2 years (5). But time to progression, disease-free survival and overall survival appear to be dependent on favorable patient factors, such as a longer disease-free interval prior

to development of metastases, adenocarcinoma histology, absence of nodal metastases, lower overall tumor burden, and local control of primary tumor (6–8). A review by Tree *et al.* published in *Lancet Oncology* concluded that outcomes in these retrospective studies were in large part dependent on patient selection, and that randomized prospective evidence was needed to elucidate treatment outcomes (6,9).

A multi-institutional phase II trial published in *Lancet Oncology* by Gomez *et al.* is the first prospective randomized study to demonstrate markedly improved progression-free survival (PFS) with local consolidative therapy as compared to systemic maintenance therapy or observation in oligometastatic NSCLC (10). This study was stopped early, at a point when investigators had enrolled 49 patients with stage IV NSCLC who had received standard first line therapy and had three or fewer metastases at the completion of primary treatment. Study subjects were randomized to immediate local therapy versus maintenance treatment with either systemic therapy or observation. The local therapies offered were hypofractionated radiation or SBRT, surgery with or without radiation, chemoradiation, and surgery to all sites of disease. Treatment type, dosing, and fractionation were not standardized and were at the discretion of the treating clinicians. Maintenance treatments included pemetrexed, EGFR-directed targeted therapy, bevacizumab or observation, again decided by the physician. Progression was determined by PET/CT or CT of the chest, abdomen,

and pelvis.

The study was closed early due to significant PFS benefit in the experimental arm at the time of planned interim analysis. Patients who received local therapy had PFS time of 11.9 months in the local consolidative treatment group compared to 3.9 months in the standard maintenance therapy group (HR 0.35, $P=0.0054$). The one-year PFS was 48% in the local therapy arm, compared with 20% in the maintenance therapy arm. Furthermore, the time to development of a new lesion was longer in the local therapy arm: 11.9 *vs.* 5.7 months in the maintenance therapy group. Post-hoc analysis showed that aside from treatment group, the presence of EGFR or ALK mutations was associated with improved PFS.

The rates of adverse events were similar between the two groups, with no grade 4 toxicities observed. The grade 3 radiation-related toxicities were esophagitis, pneumothorax, and rib fracture, compared to grade 3 fatigue and anemia in the maintenance therapy group. Quality-of-life measures were assessed by MDASI questionnaire but were not completed by a majority of patients and were not analyzed.

Notably, patients with both synchronous and metachronous metastatic disease were included in the study, although the majority had synchronous disease, thought to represent a more aggressive phenotype. Also, only patients who did not have progression of disease after initial systemic treatment were included. As only patients with good response to upfront chemotherapy were randomized, investigators selected a subset of patients with more biologically favorable disease. Finally, this trial was based on a PFS endpoint, which arguably was overly congruent with the intervention, rather than OS which might have been more reflective of clinical import.

Other trials have attempted to assess the value of treating oligometastatic disease in NSCLC patients. In a single-arm phase II study from De Ruyscher and colleagues, 39 patients with stage IV disease and less than four sites of disease received fractionated or stereotactic radiation with or without chemotherapy to the primary tumor, and surgery or radiation to the sites of metastases. The authors reported a median PFS of 12.1 months and OS of 13.5 months, although there were six patients who remained free from progression at 2 years (11). Two other smaller-size phase II trials of SBRT in combination with either chemotherapy or erlotinib showed PFS durations of 11.2 and 14.7 months, respectively, with OS durations of 23 and 20.4 months, respectively (12,13).

These trial data are supported by several case series and

retrospective studies confirming that 20–25% of patients with limited metastatic disease who receive aggressive local therapy have a durable overall response, and the question remains how to best identify these patients, as radical local treatment alters prognosis in these select few. Meanwhile, results are eagerly awaited from ongoing clinical trials either exclusively aimed at NSCLC, such as SARON (NCT02417662) and ROLE (NCT01796288), or inclusive of multiple oligometastatic tumor types, such as CORE (NCT02759783) and SABR-COMET (NCT01446744).

While much of the older literature examined surgery as the local therapy of choice for oligometastatic disease, more recent studies have examined the use of SBRT and stereotactic radiosurgery (SRS), which are recognized as less invasive alternatives with comparable local control rates for many tumor subtypes (14). Short-term local control for early-stage lung cancer treated with SBRT alone is phenomenally high at 98% (15). Milano reported local control rates of 65% at 6 years for non-breast cancer metastases treated with SBRT, and 87% for breast cancer metastases treated with SBRT (16). However, while there is little doubt of the efficacy of SBRT as a convenient, patient-friendly, and non-invasive way of securing local control, with the rapidly increasing availability of this previously exotic technology, selection criteria are badly needed to prevent its injudicious use for all forms of metastases.

In addition to the surgical literature, investigations of intracranial metastatic disease comprise a significant portion of the evidence for treatment of patients with oligometastatic lung cancer. Prognosis in patients with intracranial NSCLC metastases is related to extra-cranial disease burden as well as number of intracranial metastases, age, performance status, and molecular alterations in either EGFR or ALK (17). SRS is often utilized as an alternative to resection in those with multiple lesions or surgically inaccessible tumors. One retrospective series demonstrated that in patients with metastatic tyrosine kinase-naïve EGFR mutant lung cancer, those treated with SRS upfront fared better than those treated initially with TKI alone (median overall survival of 58.4 *vs.* 19.4 months, $P=0.01$), despite similar clinical characteristics (18). In contrast to the current trial that selected patients for local intervention after a good response after chemotherapy, these data suggest that CNS metastases from NSCLC may respond better with upfront local rather than systemic treatments. Furthermore, this study reinforces the idea that durable local control, especially in the CNS, is important not just for palliation but also for survival.

The trend to treat oligometastatic disease with focally directed radiation technologies is coming at a time when imaging technologies are detecting more areas of asymptomatic disease, and systemic or targeted therapies are allowing patients to continue treatment longer than ever before, tempting clinicians to treat limited metastatic disease more aggressively despite the relative lack of high-level evidence. In prostate cancer, Ga-PSMA PET scans are detecting areas of distant, low volume disease before biochemical failure after primary radiation or surgery and are radically changing patterns of clinical decision-making (19). In breast cancer, advances in systemic therapies have significantly improved survival for those with metastatic disease. For example, in one retrospective series, Rahman *et al.* reported a median OS of 41.8 months in patients with complete response to doxorubicin-based chemotherapeutic regimens (20). Comparatively, metastatic lung cancer has a far worse prognosis than that of either prostate or breast cancer, and thus any potential for modest improvements in survival or quality of life results in considerable interest.

There are thought to be subsets of oligometastatic disease with differential outcomes. Patients with long latency periods after treatment to the primary tumor are thought to have an improved prognosis compared to patients with synchronous metastatic disease (5,8). Milano *et al.* reported that in patients with metastatic breast cancer, those with progression after systemic therapy who then were treated with SBRT to limited metastases had a 2-year OS rate of 15%, compared to 55% in those who had stable or regressing disease after primary treatment, again indicating that proper clinically based selection of patients for treatment may be as important as the type of treatment offered (16). With rapid advances in genomic and molecular assays, investigators are now working to identify oligometastatic signatures that could be used clinically to guide management decisions. Lussier *et al.* analyzed tissue from resected lung metastases and identified microRNA expression patterns that correlated with low or high rates of metastatic spread that were also predictive of both clinical phenotype (oligometastatic type or rapidly progressive type) and survival when applied to an independent data set (21). Continued research into the biologic basis of cancer progression and consequent subtyping of oligometastatic disease will undoubtedly refine clinical decision making in the future, allowing for better patient selection for radical local treatments.

The risks of aggressive treatment of oligometastatic

disease by systemic therapy, radiation or surgery are, of course, additional toxicities potentially causing diminished quality of life without providing meaningful benefit. For this reason, the clinical indications for early local therapy need to be determined and studied carefully, balanced against the effects on patients' well-being and physical, functional, and emotional status. In this study, Gomez *et al.* attempted to collect quality of life data, but very unfortunately many surveys were not completed and the data could not be analyzed. In future studies, the impact of treatment choices from the patient's perspective, otherwise known as patient-reported outcomes, should be considered equally as important as objective clinical outcomes, and efforts should be made to collect these types of data.

The natural history of oligometastatic disease can vary greatly, but in select patients, radical local therapy can provide durable control and may improve survival in the metastatic setting. This pivotal phase II study is reflective of an evolution in the treatment paradigm for metastatic lung cancer, enabled by novel improvements in systemic therapy and radiation therapy. It has provided valuable randomized evidence in support of aggressive treatment for oligometastatic NSCLC in highly selected patients. Similar trials in this and other disease sites incorporating clinical, genomic and quality of life data are expected to ensue.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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