



Stereotactic body radiation therapy for metastatic non-small cell lung cancer: a versatile treatment, repurposed

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In their recent paper entitled “Trends and costs of stereotactic body radiation therapy in metastatic non-small cell lung cancer”, Lester-Coll and colleagues utilize the SEER-Medicare database to analyze treatment and outcomes data for elderly patients who received stereotactic body radiation therapy (SBRT) as first-line therapy for metastatic non-small cell lung carcinoma (NSCLC). In comparison with patients who received standard-of-care upfront chemotherapy, patients treated with first-line SBRT had improved overall survival and fewer hospitalizations, with similar costs per month of survival (1).

The authors’ findings are timely and relevant. Already, there has been widespread adoption of SBRT over the last two decades (2). Furthermore, applications of SBRT use are expanding, including in the metastatic setting (3-5). From the cancer biology standpoint, there is now increasing recognition of the complex heterogeneity underlying advanced and metastatic malignancies (6,7). These factors collectively have presented opportunities to investigate how SBRT may be utilized in selected metastatic cases, its potential benefits and costs in this cohort, and whether at a health policy level these considerations would favor the use of SBRT for similar cases in the future.

The use of SBRT in the metastatic setting is a relatively recent development. It is part of a paradigm shift in viewing metastatic cases not through the lens of a uniformly dismal prognosis, where the priority for treatment is disease stabilization and symptom management, but rather as heterogeneous cases where a favorable subset could

be selected for aggressive management with curative potential. Often, the extent of metastatic involvement and total disease burden are central considerations to this selection process. Patients with limited metastatic burden, termed oligometastatic (or if applicable in some cases, oligorecurrent), are seen as the most likely to benefit from aggressive management (8,9). Several clinical series and multi-institutional phase II trials have already demonstrated that local control as well as progression-free and overall survival benefits may be attained when utilizing SBRT to metastatic sites in this setting (3-5). It should be emphasized that SBRT in these settings is typically to complement systemic therapy rather than to replace it. The benefits conferred by aggressive local management are not expected to supplant those of systemic therapy in eligible patients. Currently, there are several phase III trials underway to investigate clinical endpoints for SBRT across selected metastatic cohorts (10,11).

There are several limitations to this study that should be acknowledged, many of which Lester-Coll and his colleagues do carefully consider in their discussion. First, the authors’ SEER dataset spanned the years of 2004–2013, when SBRT technology was available, but not as widely implemented and only rarely in the metastatic setting (1,12). Indeed, only a very small fraction of the total metastatic NSCLC patients included in their analysis received upfront SBRT; despite the trend in favor of increasing utilization over time, SBRT was chosen for initial therapy in only 0.5–3% of patients. The current proportion of

similar patients who are managed with SBRT is likely to be significantly higher. It is possible that a recent update to the SEER database, including data up to 2016, could mitigate this limitation to some extent. Second, given the limited granularity of the SEER-Medicare data, it is not clear what proportion of patients have what would be considered oligometastatic involvement, as the data does not distinguish between the extent of metastases. It is possible that the patients who received SBRT were the ones who had limited-burden metastatic involvement, so the survival benefit may reflect the difference in survival based on extent of metastases, independent of the treatment strategy utilized. Third, it is not clear if the SEER-Medicare findings could be extrapolated to practice patterns beyond Medicare-eligible patients, including those who are younger and/or have other demographic differences (12). Fourth, the increasingly widespread molecular profiling of metastatic NSCLC cases for predictive markers that guide initial management may effectively identify an increasing proportion of patients who are driver mutation-positive (e.g., *EGFR* driver mutations, *ALK* gene rearrangement, *ROS1* gene rearrangement, *MET* amplification, or *HER2* mutations). These patients would not fit neatly in the SEER-Medicare treatment decision schema for first-line chemotherapy *vs.* SBRT, as they would be indicated for first-line therapy that is neither chemotherapy nor SBRT. As this population is not explicitly accounted for in the current study, the role for first-line SBRT in these patients remains unclear.

The rapid adoption of immune checkpoint inhibitors in clinical oncology has also altered the treatment landscape of metastatic NSCLC significantly. Immunotherapy has been shown to have an additive or synergistic effect with chemotherapy (13), and in some cases has been demonstrated to be superior by efficacy and/or toxicity profile (14-16) compared to chemotherapy. Across multiple studies, immunotherapy with checkpoint inhibitors has been shown to have a prominent role in the management of locally advanced and metastatic NSCLC (17,18). Unfortunately, given that the SEER-Medicare database does not have any information on the utilization of immunotherapy in the patients included in Lester-Coll's analysis (12), this limits our ability to apply the findings to current clinical practice, where patients may have a reasonable alternative in immunotherapy.

Of note, the use of SBRT and immunotherapy to enhance systemic tumor immunity has been shown to be a promising strategy in metastatic disease (17,19), and

is the subject of several ongoing trials (NCT04214262 and NCT03867175). The overlap between SBRT and immunotherapy use for patients in the era analyzed by Lester-Coll and colleagues (2004-2014) is likely to be very limited. As such, their findings may not account for all the potential benefits of SBRT in the treatment of metastatic NSCLC.

Lastly, Lester-Coll and colleagues show that SBRT use in metastatic NSCLC patients leads to fewer hospitalizations. Although cost of care for patients increases with SBRT use, it is offset by the gain in overall survival such that the incremental cost, normalized by the additional months of life gained, is statistically indistinguishable from the cost in patients who receive standard-of-care upfront chemotherapy. This is an important point, as SBRT has been perceived as an expensive modality where utilization in patients with a poor prognosis and limited life expectancy may be seen as an unjustifiable expenditure of limited healthcare dollars. At a population level, the SBRT-first cohort appears to have achieved prolonged survival, so this is a meaningful endpoint achieved. Any potential gains in quality of life (QOL) would also be important to note, although Lester-Coll did not report QOL endpoints in their paper. Even if there were only modest gains in survival, tumor control, and/or QOL endpoints, it should be noted that modern oncology in the era of immunotherapy has seen a limited number of patients who are exceptional responders, and it is easy to overlook these cases when we review healthcare policy at the population level. Patient selection will be critical, and this may take precedence over population-wide guidelines in management of specific cases.

In conclusion, the analysis by Lester-Coll serves as an important platform to raise awareness of the expanding therapeutic options for metastatic NSCLC patients. However, it is not the only recent development and unfortunately does not account for the significant number of similar cases that would be managed with upfront immunotherapy now. Ultimately, when the therapeutic repertoire for patients expands, it is to the advantage of the patients and their caretakers. However, it is prudent to implement a thoughtful and systematic approach to select the optimal initial strategy for each case.

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