Editorial

# Stereotactic body radiation therapy versus metastasectomy for oligometastases

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*Comment on:* Lee YH, Kang KM, Choi HS, *et al.* Comparison of stereotactic body radiotherapy versus metastasectomy outcomes in patients with pulmonary metastases. Thorac Cancer 2018;9:1671-9.

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Over the past few decades, oncologists are increasingly recognizing the existence of an intermediate state between localized and metastatic cancer, known as the "oligometastatic" state (literally meaning the presence of a few metastases) (1). Radical treatment of these limited sites of metastases, initially in the form of surgical resection or "metastasectomy" has been performed for many years with encouraging outcomes in selected patient populations (2). Recent developments of more active systemic treatments and less invasive local treatment such as stereotactic body radiation therapy (SBRT) has allowed an increasing number of patients to undergo radical treatment of these oligometastases with the hope of improved oncologic outcomes or quality of life.

Results from a number of recently completed randomized Phase II trials from Palma *et al.* (3), Iyengar *et al.* (4) and Gomez *et al.* (5) show that such radical treatment of oligometastases can indeed improve oncologic outcomes. However, it remains unknown what modality of local therapy attains the best therapeutic ratio of achieving local control without significant toxicity. Two of the most common techniques are metastasectomy and SBRT. Proponents of surgery point to its long-established track record, and the certainty that comes from complete resection verified by pathologic examination. On the other hand, proponents of SBRT argue for its non-invasive nature and therefore likely reduced toxicity. Given the increasing population of patients who may benefit from radical treatment of oligometastases, identifying the best modality for such treatment has become of utmost importance.

A recent study by Lee *et al.* from Gyeongsang National University titled "Comparison of stereotactic body radiotherapy versus metastasectomy outcomes in patients with pulmonary metastases" (6) offers some preliminary guidance on this important question. Before analyzing the article, it is useful to consider some inherent difficulties in trying to answer this question. First, while randomized trials would provide the best quality of evidence, there are significant difficulties in designing such a trial given the heterogeneity of patients with oligometastatic disease in terms of disease burden, primary histology and performance status. Second, patients or physicians would likely have strong preferences about choosing surgery versus radiation therapy given the great difference between the two modalities. Third, some patients may not be candidates for resection due to comorbidities and/or the extent and location of the metastases. Therefore, it is likely that non-randomized studies, including cases series or database studies, will contribute to the bulk of evidence in the near future.

The study by Lee *et al.* is a retrospective analysis of an institutional database which identified 51 patients with up to three pulmonary metastases treated between 2010 and 2016 with ablative intent surgery or radiotherapy. Thirty patients who underwent surgical resection were compared with 21 patients who underwent SBRT. Given the

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potential for selection bias, it is important to point out key differences between the two groups. Patients undergoing SBRT compared with surgery had a larger average tumor size of 2.5 *vs.* 1.25 cm (P=0.015), were more likely to have synchronous metastases (57% *vs.* 20%, P=0.006) and were less likely to have received chemotherapy (5% *vs.* 30%, P=0.034). One difference not explicitly stated is that some SBRT patients had more than 1 lesion treated (exact number is not specified) while all of the surgery patients had only 1 lesion treated. One key data point not reported was the total number of radiographically apparent pulmonary metastases and the number treated. Patients were followed for a median of 13.7 months.

Without adjustment for baseline factors, the local control rates were numerically higher in the surgery group at 1 and 2 years, although the differences were not statistically significant. Progression free survival was significantly longer in the surgical group at 1 and 2 years (51% and 46%) versus SBRT (24% and 12%). The overall survival rates were numerically higher in the surgical group, but not significantly different. It's unclear if the small differences in outcomes could have been significant if a larger number of patients had been enrolled.

Results derived from post hoc analyses need to be considered cautiously given the potential for false positive findings caused by multiple testing of the same data. In this study, multivariate analyses showed that larger tumor size and presence of synchronous metastases were significantly associated with greater risk for progression, and that tumor size alone was associated with higher risk for overall survival. Subgroup analyses were further performed for patients with or without synchronous metastases treated with surgery or SBRT. In patients with and without synchronous metastases, there was no difference in PFS or OS in patients treated with SBRT versus surgery. Given the small number of patients in each category, this analysis needs to be interpreted cautiously. Lastly, no formal comparison of toxicity was performed, however one patient developed grade 3 pneumonitis after SBRT and two patients in the surgery group developed what can be classified as grade 4 complications that required surgical intervention (n=1) or intensive medical care (n=1); another developed grade 3 nausea.

Although limited by small patient numbers and its retrospective nature, the study by Lee *et al.* makes two important conclusions which are supported not only by their own data but also by the available published literature. The first is that baseline characteristics such as the presence and extent of other synchronous metastases beyond the ablated lesion play a large role in determining overall prognosis. The importance of selecting the right patients for resection of oligometastatic disease has been well studied and documented in the surgical literature (7). Studies of patients with oligometastases treated with SBRT also show that factors such the histology of the primary, lesion size, response to chemotherapy and presence of synchronous metastases are important determinants of outcome (8,9). There is seeming validity in the notion that patients with good performance status, limited disease burden and favorable disease biology are the ones who would benefit the most from intensification of treatment.

The second conclusion is that both surgery and SBRT result in high rates of local control and that the modality used to ablate oligometastatic disease is not likely to significantly alter the overall oncologic outcome. A similar debate between proponents of surgery versus SBRT also exist in the treatment of stage 1 non-small cell lung cancer. Several systematic reviews, meta-analyses and pooled analyses offer conflicting results. Again, we are hampered by the lack of high-quality randomized trials. What limited randomized data exists, for example from the pooled results of the STARS and ROSEL trials, show excellent and similar rates of local control and overall survival between surgery and SBRT (10). Given the difficulty in showing improved survival for one modality over the other in the treatment of stage 1 non-small cell lung cancer, it is not surprising that no difference can be found in the treatment of oligometastatic disease (11,12) where disease progression at distant sites plays a much larger role than local recurrence in determining overall outcome (9).

This is not to say that surgery and radiation are the same and can be used interchangeably. Certain situations would likely favor choosing one modality over the other. Treatment of metastatic disease is still in large part about improving quality of life, and patient preference must be given an important role. Secondly, given that surgery is generally more intensive than radiation, it should be reserved for patients who have good performance status and physiologic reserve. Thirdly the anatomic location of the metastatic lesions may favor one modality or the other. For example, radiation may be more appropriate for a lesion involving the hilum for which surgery would require a pneumonectomy. On the other hand, multiple lesions scattered in the same lobe may be more readily addressed by a lobectomy rather than attempting to target many lesions individually with radiation. Until more solid data becomes available defining not only

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which patients would benefit from radical local therapy, but what type of treatment modality is best, physicians will need to continue to use their clinical judgment in selecting the best care for their patients.

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## Footnote

*Conflicts of Interest:* MT Milano: royalties from UpToDate. The other authors have no conflicts of interest to declare.

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