Editorial Commentary

Stereotactic ablative radiotherapy versus metastasectomy for pulmonary metastases: guiding treatment in the oligometastatic era

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Provenance: This is an invited article commissioned by the Section Editor Shuangjiang Li (Department of Thoracic Surgery and West China Medical Center, West China Hospital, Sichuan University, Chengdu, China).

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.

Submitted Feb 18, 2019. Accepted for publication Mar 26, 2019.
doi: 10.21037/jtd.2019.04.16
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.16

Across the spectrum of stage IV cancers, there is increasing evidence of an oligometastatic state as a distinct clinical entity, whereby tumour burden is limited to 5 or fewer lesions confined to a few sites (1,2). In this clinical scenario, there is an increasing utilization of local treatments, including surgical resection (metastasectomy) and stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR). Systematic reviews, consensus statements, and clinical practice guidelines support the appropriateness of pulmonary metastasectomy (PME) for patients with lung metastases from a broad range of primary cancers in carefully-selected patients (3-5). PME has been associated with improvements in disease-free survival (DFS) and overall survival (OS); however, most of the current evidence is based on retrospective and non-randomized data (6-8). PME data has the strength of large patient numbers with long follow-up. The surgical approach provides large samples of tissue to guide systemic treatment. SABR is increasingly being utilized as a local "curative" modality for pulmonary oligometastases, and its advantages include convenience, low toxicity profile, and the ability to treat central lesions, with similar outcomes to PME (9).

It is in the age of this evolving paradigm that Lee *et al.* from Gyeongsang National University retrospectively report the outcomes of PME *vs.* SABR for patients with pulmonary oligometastases at their institution (10). They included patients with 1–3 pulmonary metastases and who had not received prior thoracic radiotherapy, which yielded 30 patients with 30 metastases who underwent surgery and 21 patients with 29 metastases that were treated with SABR. Wedge resection (n=28, 93.3%) and lobectomy (n=2, 6.7%) were the PME approaches. SABR was delivered to peripheral metastases using 60 Gy in 3 fractions and central lesions received 48 Gy in 4 fractions.

The authors found that, while there was no difference in OS between the two groups, progression-free survival (PFS) was significantly longer with PME compared to SABR (2-year PFS 46.0% *vs.* 11.9%, HR 0.457; 95% CI: 0.232–0.90, P=0.02) on univariate analysis. The improvement in PFS is, however, with several caveats: the median tumour size in the SABR group was double that in the PME group (2.5 *vs.* 1.25 cm, respectively; P=0.015); patients with synchronous metastases, a known negative prognostic factor, were more likely to be treated with SABR (P=0.006); and the PME group was more likely to receive adjuvant systemic treatment (P=0.034). Ultimately, the local control (LC) rate was not significantly different between the two groups (P=0.722): after a median follow-up of 13.7 months, 1- and 2-year LC rates were 83.5% and 75.2% with SABR and 96.6% and 91.5% with PME, respectively. These data suggest that PME and SABR are both excellent local treatment modalities for pulmonary oligometastases.

Similar to other studies, tumour size and synchronous metastases were associated with poorer PFS (HR 1.216; 95% CI: 1.082–1.367, P=0.001; HR 3.461; 95% CI:

1.72–6.964, P=0.001, respectively) and OS (HR 1.386; 95% CI: 1.107–1.735, P=0.004; HR 3.894; 95% CI: 1.065–14.236, P=0.040, respectively) on univariate analysis. On multivariate analysis, tumour size was the factor most prognostic for OS (HR 1.386; 95% CI: 1.107–1.735, P=0.004). Both treatments were well-tolerated, with one grade 3 toxicity in the SABR group (pneumonitis), and three patients requiring inpatient care due to complications of PME (one patient with acute bleeding requiring surgery, one patient with acute respiratory distress syndrome requiring ICU, and one patient with nausea requiring fluid resuscitation).

Despite the encouraging, "better-than-expected" survival in some oligometastatic patients, the potential risks of local metastasis-directed treatment must be weighed with the potential control or survival benefit. When deciding on the optimal local treatment, patient selection appears to play a crucial role. Surgery has been shown to provide better locoregional control in larger central tumours with lymphadenopathy (11,12), has an acceptable post-operative mortality rate of 1–2% (13,14), and has an otherwise low toxicity profile (15). Surgery also has the benefit of providing tissue for pathologic evaluation of response and resistance characteristics, which predict response to systemic treatments, such as immunotherapy or targeted therapy has the advantage of being an outpatient treatment and its toxicity profile is purported to be even lower than that of surgery. SABR also appears to limit further metastatic progression, either due to minimized tumour seeding or via the abscopal effect (16).

Ultimately, while the study by Lee *et al.* adds to the existing, largely retrospective data on local treatments for lung metastases (17), further prospective data are needed to demonstrate efficacy over standard systemic modalities (18). Indeed, while LC rates with surgery and SABR are excellent, distant failure is the predominant pattern of progression, and can occur in relatively short order. Two recent randomized control trials support local consolidation treatments in metachronous multi-histology and synchronous oligometastatic NSCLC. The SABR-COMET randomized phase II trial was recently published by Palma *et al.* (19), demonstrating increase in median OS from 28 months (95% CI, 19–33 months) with standard-of-care systemic treatment to 41 months with standard of care plus SABR (95% CI, 26 months to an upper limit that has not yet been reached; P=0.09). In another trial led by MD Anderson, the use of local consolidative treatment in synchronous oligometastatic NSCLC provided a PFS benefit over standard-of-care systemic therapy (11.9 *vs.* 3.9 months, P=0.0054) (20); a subsequent abstract has reported an OS benefit (21). There are several randomized trials currently underway designed to estimate OS rates achieved with SABR. The SARON phase III trial in the UK (NCT02417662) is evaluating SABR for oligometastatic NSCLC with 1–3 synchronous metastases, comparing standard-of-care platinum-doublet chemotherapy with and without radical radiotherapy/SABR to the primary and stereotactic radiation to metastases. The CORE trial (NCT02759783) is randomizing patients with extracranial oligometastatic breast cancer, prostate cancer, and NSCLC to standard treatment or standard treatment plus SABR.

With the growing acknowledgement that local treatments may improve outcomes in oligometastatic cancer, we are treating patients in a time of paradigm shift (18). Beyond the need for randomized trials to determine the appropriate patient population for this approach, the integration and potential synergy and toxicity with targeted and immune therapies are urgent priorities, and the decision to offer surgery or SABR should be a result of multidisciplinary discussion.

Acknowledgements

None.

Footnote

Conflicts of Interest: AV Louie declares having received honoraria from Varian Medical Systems Inc. and AstraZeneca. The other authors have no conflicts of interest to declare.

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Cite this article as: Malik NH, Keilty DM, Louie AV. Stereotactic ablative radiotherapy versus metastasectomy for pulmonary metastases: guiding treatment in the oligometastatic era. J Thorac Dis 2019;11(Suppl 9):S1333-S1335. doi: 10.21037/jtd.2019.04.16

