



Stereotactic body radiotherapy as an alternative to metastasectomy for pulmonary oligometastasis

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The lung is a common site of metastasis from malignant tumors. The reported incidence of pulmonary metastasis is 20–54% in patients who died of an extrathoracic malignancy (1). Selected patients undergo pulmonary metastasectomy (PM) for lung metastasis. The number of PMs significantly increased from 2000 to 2011, with average annual increases of 9.4%, 3.6%, and 4.7% for colorectal cancer, breast cancer, and melanoma, respectively, according to the report by Bartlett *et al.* (2).

In a landmark study, the International Registry of Lung Metastases retrospectively examined 5,206 patients who received PM for lung metastasis from various types of cancer (3). The actuarial survival rate after complete metastasectomy was 36% at 5 years, whereas the corresponding rate for incomplete resection was 13%. Resectability, disease-free interval, and number of metastases were identified as significant prognostic factors. The recently compiled “Expert Consensus Document on Pulmonary Metastasectomy” by Handy *et al.* for the Society of Thoracic Surgeons consists of 9 general statements and 9 statements detailing cancer type-specific management of pulmonary metastasis (4). It begins with the following recommendation: “*When caring for patients with cancer and pulmonary oligometastases, PM should be considered within a multidisciplinary team and carefully individualized.*” However, whether PM has better survival benefits than systemic chemotherapy or observation is unclear owing to a lack of solid evidence.

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is becoming a standard treatment for patients at a high risk for surgery and medically inoperable patients with early stage non-small cell lung cancer (NSCLC). Using data derived from several retrospective studies of NSCLC patients and propensity score matching, Chen *et al.* found that overall survival (OS) rates were higher for surgery than for SBRT, whereas cause-specific survival rates were similar (5). However, there are no randomized trial data directly comparing these procedures.

SBRT has been used to treat metastatic lung tumors since the 1990s (6). The Expert Consensus Document on Pulmonary Metastasectomy notes that “*Thermal ablation or SABR is reasonable therapy for patients with pulmonary oligometastases particularly for patients considered high-risk for resection or refuse resection.*” However, to our knowledge, only 3 studies have compared the outcomes of SBRT and PM in patients with metastatic lesions: Widder *et al.* and Lodeweges *et al.* at the University of Groningen (7,8), Filippi *et al.* at the University of Torino (9), and Lee *et al.* at Gyeongsang National University (10). The Lee *et al.* study is the most recent and focuses on SBRT and PM for local treatment of pulmonary oligometastasis (10). This editorial introduces this study.

Lee *et al.* compared outcomes in patients with up to 3 pulmonary metastases treated via SBRT (21 patients) or PM (30 patients). Synchronous metastases were observed in

20% and 57% of the PM and SBRT patients, respectively. For SBRT, the prescription dose was 60 Gy in 3 fractions or 48 Gy in 4 fractions; for PM, wedge resection or lobectomy was performed. Local tumor control did not differ significantly between the two modalities (75.2% and 91.5% at 2 years for SBRT and PM, respectively; $P=0.163$), nor did OS (68.2% and 81.8% at 2 years; $P=0.534$). The 2-year progression-free survival (PFS) rate was significantly higher in the PM group than in the SBRT group (46% and 11.9%, respectively; $P=0.02$); this difference mainly reflected the greater incidence of synchronous metastases in the SBRT group. No severe treatment-related toxicities were observed in either group. Multivariate analysis revealed that synchronous metastases significantly predicted poor prognosis in both SBRT and PM patients (hazard ratio, 3.46 for PFS). The authors suggest that SBRT is a viable alternative to PM.

The paper by Lee *et al.* is valuable because it addresses a topic—the effectiveness of SBRT versus PM in patients with lung oligometastasis—for which there is limited evidence. Unfortunately, the cohort size was small (21 SBRT and 30 PM patients) and the follow-up period was short (median, 13.7 months). Moreover, the high prevalence of synchronous metastases (20% and 57.1% in the PM and SBRT groups, respectively) clouds the interpretation of the survival results. Lastly, no information on the treatment of the synchronous metastases was provided.

The definition of oligometastasis is currently muddled. It was originally considered a tumor state “*intermediate between purely localized lesions and those widely metastatic*” by Hellman and Weichselbaum, who noted that “*Patients with oligometastases, either de novo or following systemic treatment, should be cured by ablation of these lesions*” (11). Two oligometastasis-related terms have been proposed: oligo-recurrence and oligoprogression. As stipulated by Niibe and Hayakawa, oligo-recurrence refers to a few distant metastases after control of the primary tumor by the initial treatment (12). In other words, oligo-recurrence is oligometastasis with a disease-free interval after the previous treatment. As specified by Cheung, oligoprogression is a “*clinical scenario where a few metastases progress, whereas all other metastases are stable or responding to a systemic therapy strategy*” (13). During oligoprogression, the “rogue” tumors cannot be directly cured by local treatment alone; systemic treatment is also required. The synchronous metastases in the paper by Lee *et al.* presumably were in an oligoprogression state.

SBRT can be applied not only to lung metastases, but

also to metastases in other organs (14). The Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET) phase 2 trial assessed the impact of SBRT on OS, PFS, toxicity, and quality of life (QOL) in patients with a controlled primary tumor and up to 5 oligometastatic lesions (15). It included patients with metastases in the lung, liver, bone, and other organs. SBRT was delivered to all metastases in the study arm, whereas palliative radiotherapy was delivered to the metastases, if necessary, in the control arm. The results of this randomized trial were presented by Palma *et al.* at the 2018 annual meeting of the American Society for Radiation Oncology (16). SBRT extended the median OS time from 28 to 41 months ($P=0.09$) and significantly doubled the median PFS time from 6.0 to 12 months ($P=0.001$). Toxicities of grade 2 or worse were common in the SBRT arm, while QOL was did not differ significantly between the two arms. The SABR-COMET study shows that SBRT is a reasonable treatment option for patients with oligometastases in various organs.

In conclusion, SBRT is a potential alternative to metastasectomy in patients with pulmonary oligometastasis, as indicated by the findings of Lee *et al.* SBRT can be applied to metastases in other organs as well and may increase survival times in patients with oligometastasis. Future studies are needed to determine which patients will benefit from local treatment including SBRT and metastasectomy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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