Commentary

Oligometastases to the liver: predicting outcomes based upon radiation sensitivity

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Liver metastases from solid tumors such as colon, rectum, pancreas, lung and breast are a major cause of mortality and morbidity in patients with cancer. Systemic therapy is the mainstay of treatment for patients with liver metastases however local therapies can play an important role in extending survival in those patients with limited extrahepatic disease burden. Although there is growing interest in local therapy for these so called "oligometastatic" cancers, the concept of local therapy for metastatic disease is not new (1). Surgical resection for liver metastases has been performed with curative intent for many years (2).

Although surgery remains the gold standard for definitive management of limited liver metastases, many patients opt against resection or are not surgical candidates due to the location and/or extent of disease, or medical comorbidities (3). For these patients, other options include liver directed therapies such as chemoembolization, radioembolization, radiofrequency ablation, microwave ablation and stereotactic body radiotherapy (SBRT). SBRT is an attractive option for the treatment of oligometastatic disease as it is a non-invasive method delivering ablative doses of external beam radiotherapy to the target tumor while minimizing dose to the surrounding normal tissues (4).

SBRT has been shown in numerous prospective and retrospective studies to result in high rates of local control with minimal toxicity (5-7). Recently, a randomized study of SBRT for oligometastatic lung cancer showed improved progression survival compared with systemic therapy alone (8).

Initial trials of SBRT for oligometastases included tumors of varying histologies (5,7,9-12). Primary tumor type appeared to impact local control rates after SBRT. For example, Milano *et al.* found that 6-year local control rates after SBRT for oligometastatic breast and non-breast cancers after SBRT were 87% versus 65% respectively (5). Takeda *et al.* observed that 1-year local control after SBRT for oligometastatic lung lesions varied from 80% for colorectal primaries to 94% for non-colorectal primaries (7). In one of the largest series to date, Onishi *et al.* reviewed 380 patients with pulmonary metastases treated with SBRT and found that on multivariate analysis, colorectal histology was the only predictor of local progression (13). These findings suggest a difference in the degree of radiosensitivity based upon histology. However, a more precise causal link has not been established, and a biologic basis for the oligometastatic disease state as well as the oligometastatic tumor response to SBRT is not well-understood (14).

The recent paper titled "Radiosensitivity Differences between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes after Stereotactic Body Radiation Therapy" published by Ahmed *et al.* in the *International Journal of Radiation Oncology Biology and Physics* (15) aims to bridge the gap between empirical evidence and biological mechanism. The authors previously developed a radiosensitivity index (RSI) based upon an RNA assay of the expression of ten genes; this assay had been validated in multiple independent clinical cohorts of varying histologies. In the first part of the study, the authors derived the gene expression profile from a database of 372 surgically resected metastatic liver lesions of varying histologies, with the vast majority (84%) being colorectal adenocarcinoma.

The authors found that metastatic tumors of colorectal adenocarcinoma origin had higher RSI (i.e., more radioresistant) than those of breast, lung, pancreas

adenocarcinoma or anal squamous primary cancers. Interestingly, the authors also found that the when multiple metastatic tumors were removed from the same patient, the intra-patient RSI difference was much smaller than the inter-patient difference, i.e., RSI from tumors removed from the same patient were not as variable.

In the second part of the study, the authors retrospectively identified 33 patients with 38 liver metastases of varying histologies treated with SBRT at their institution. The 27 metastatic lesions of colorectal primary and the 11 lesions of non-colorectal primary were similar in terms of maximum diameter, prescribed SBRT dose and previous lines of chemotherapy. However, the 11 non-colorectal metastases had primary histologies with lower median RSI such as breast, lung adenocarcinoma and anal squamous carcinoma. There was a dramatic difference in the local control. The 12- and 24-month local control for colorectal liver metastases were 79% and 59% *vs.* 100% and 100% for non-colorectal liver metastases. Colorectal histology remained a significant predictor of local control on multivariate analysis. Interestingly, other factors such as tumor size, number of lines of chemotherapy, age and gender were not predictive of local control. There was a trend towards improved local control with higher prescribed dose (60 *vs.* 50 Gy).

Taken together these two datasets indicate that liver metastases from colorectal primaries are more radioresistant and have lower rates of local control after SBRT. Differences in gene expression profile contributing to the RSI index offers a plausible biological explanation for the origin of this radioresistance. A natural next step alluded to by the authors would be studying whether dose escalation can overcome differences in radioresistance and improve local control.

One major limitation of this study, acknowledged by the authors, is that the RSI index and clinical response to SBRT came from two independent datasets. This is understandable given that lesions treated with SBRT are not often biopsied prior to treatment. However, this does raise the question of how similar the two populations were in terms of clinical characteristics. Secondly, it precludes a one to one correlation between the RSI of a lesion and clinical outcome. This is important given the intra-histology variation in RSI (shown in Figure 1 in the paper) for colorectal carcinoma is quite wide (median of 0.43 with a range of ~0.07–0.62 and interquartile range of ~0.29–0.49). Therefore, it is unclear if colorectal lesions with higher RSI are more prone to local failure and therefore whether treatment intensification can be restricted to these specific lesions versus utilizing a more dose-intense regimen for all colorectal metastases. Secondly, it is still unclear whether improvements in local control can translate into improvements in survival. This study reported that although non-colorectal histologies have better local control, their 12 and 24 months overall survival remained similar to those with colorectal histology. Other outcome measures such as distant progression-free survival could lend further insight into comprehending this.

Despite these shortcomings, this is an important study which adds to our understanding of the biological behavior of oligometastatic lesions treated with SBRT. It is hoped that with continued research, a more personalized approach to treatment can be developed for each individual patient based upon the precise biology of his or her own tumor.

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Footnote

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Comment on: Ahmed KA, Caudell JJ, El-Haddad G, *et al.* Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys 2016;95:1399-404.

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