EDITORIAL

Single-Fraction Carbon Ion Radiotherapy for Early-Stage NSCLC—The Future Is Now

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For patients with early-stage NSCLC, surgical resection has been the preferred treatment intervention. Those who are either nonsurgical candidates or refuse surgery are treated with radiation therapy. Historically, treatment with conventionally fractionated photon radiation has provided less than favorable results, with local control rates in the range of 50% to 70%.[1,2] To improve local control and overall survival in this patient population, protocols have sought to improve the therapeutic ratio by changing the dose per fraction. Advances in radiation techniques led to the development of stereotactic ablative body radiotherapy, allowing for larger doses per fraction to be utilized and thus resulting in improvement in local control rates approaching that of surgery.[3]

Utilizing charged particles for radiotherapy has been of interest for decades. As charged particles move in tissue, they deposit energy (dose), cause ionization of tissue, and create highly reactive free radicals. This has two important consequences. One is that after traversing tissue to a certain depth, charged particles impart all of their initial kinetic energy and stop moving. In other words, charged particles have a finite range in tissue, unlike a photon beam, which can be only exponentially attenuated but not stopped. The second consequence is that these free radicals cause enhanced biological damage that can contribute to a higher relative biological effectiveness (RBE) compared with photons. The most commonly used heavy ion therapy is carbon ion radiotherapy (CIRT).

Researchers at the National Institute of Radiological Sciences have systematically investigated the optimal dose fractionation regimens for the treatment of peripheral early-stage NSCLC. They have previously reported their findings for regimens with a higher number of fractions.[4–6] In this issue of the *Journal of Thoracic Oncology*, Yamamoto et. al. report on their groundbreaking results for single-fraction CIRT.[7] A total of 218 patients with either stage T1 or stage T2 were treated on a dose escalation trial. The overall survival and local control rates at 5 years for all patients were 49.4% and 72.7%, respectively. Yamamoto et. al. found an improvement in local control when patients received more than 36 Gy (RBE) ($p = 0.0001$). At the highest dose level of 48 to 50 Gy (RBE), an impressive 5-year local control rate of 95.0% was observed, with corresponding overall survival and progression-free survival rates of 69.2% and 60.0%, respectively. Overall, the treatment was well tolerated, with no grade 3 or higher pulmonary or skin toxicities and only one patient with a late toxicity of grade 3 chest wall pain.

These results are impressive in that high local control rates were achieved by using CIRT and are an improvement over those of studies investigating single-fraction stereotactic ablative body radiotherapy.[8,9] This study's significance is that long-term results in terms of local control and overall survival for this patient population were reported. Especially of interest is the fact that CIRT appears capable of obtaining improved control rates for stage T2a tumors in the range of 80%. The control rate for larger tumors (T2b) was disappointing; however, it is difficult to make a final determination given the small number of patients treated. Currently at the National Institute of Radiological Sciences, patients with tumors larger than 5 cm are being treated on a dose escalation trial using more fractions.

Given the significant investment costs and infrastructure required to establish and maintain a heavy ion center, more efficient use of its resources is critical for long-term viability and wider utilization. Further incorporation of hypofractionated regimens for particle therapy would allow for a higher capacity to treat patients. Also, potentially being able to deliver a treatment in a single fraction

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improves convenience for the patient tremendously, which in turn makes potential extended travel to a national heavy ion center more attainable.

By demonstrating that patients with early-stage NSCLC can be safely and effectively treated with single-fraction CIRT, Yamamoto et. al.[7] have developed an exciting therapeutic option. CIRT makes it possible to deliver treatment with high accuracy and precision, given the nature of using heavy ions. This is a further advancement that cannot be obtained with photon or proton therapy. CIRT is truly the ideal single-fraction treatment—it is noninvasive, can be delivered on an outpatient basis, and has zero recovery time. Additionally, the currently reported results approach the control rates seen for surgery, especially for the higher-dose cohort. This provides an attractive alternative for patients hesitant to undergo an invasive procedure with its potential morbidities.

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