Editorial

Stereotactic ablative radiotherapy (SABR) for lung cancer: What does the future hold?

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While radiation therapy has long been one of the pillars of therapy for potentially curable stages of lung cancer, outcomes have largely remained disappointing overall. The best outcomes in lung cancer have been achieved with surgery and only in early stage disease, because in early stages complete tumor ablation by surgery is possible in most patients who can tolerate the appropriate resection (lobectomy). Even so, many patients with anatomically resectable early lung cancer are not treated with surgery: in the United States, up to over one third of such patients do not have surgery for reasons including older age and multiple comorbidities (1). Conventional radiation therapy, while modestly effective, does not approach surgical cure rates because it has not been possible or practical to achieve ablative radiation dose intensities tolerably using such techniques (2).

In under two decades, the development of stereotactic body radiation therapy (SBRT) (3), more appropriately called stereotactic ablative radiotherapy (SABR) (4), has revolutionized radiation therapy for early stage lung cancer. Advances in imaging and highly conformal and accurate radiation delivery have made possible the safe administration of truly ablative radiation doses, achieving tumor control rates similar to historical results from surgery. Furthermore, progress in SABR has served as a model of evidence-based medicine, driven by clinical research starting from single institution experiences, to retrospective analyses of multi-institutional data, to prospective clinical trials, many of which are ongoing. In this issue of *Journal of Thoracic Disease*, Dr. Senan and colleagues, investigators who have contributed substantially to the body of knowledge on SABR, provide a timely update of clinical outcomes and current controversies (5).

As summarized in their review, prospective clinical trials have demonstrated high (>90%) rates of primary tumor control within the irradiated target volume, and characteristic normal tissue toxicities have been described along with emerging data on their risk based on dosimetric parameters. Nevertheless, numerous questions remain about how to optimize this therapy. One complicating factor identified by the authors is that apparently similar nominal radiation dose prescriptions reported across series can represent widely varying dose intensities in reality. Future publications on SABR should use standardized dose reporting, specifying how targets were defined, the dose to both the periphery and center of the target, dose conformity, and the type of dose calculation algorithm. Particularly in the lung, algorithms that do not accurately model

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radiation interactions in tissues of heterogeneous density should be phased out because of their unpredictable and potentially large misrepresentation of actual dose delivered (6). Similarly, standardization of how local progression is assessed and distinguished from treatment-related pulmonary changes will be important. With respect to treatment without a pathologic diagnosis, several studies now strongly suggest that this can be justified when indicated by inability to safely obtain a tissue diagnosis and judicious interpretation of clinical and radiographic characteristics and demographic context. However, in the era of molecular and genetic prognostic/predictive biomarkers and therapeutics, which will undoubtedly be integrated with SABR in the future, every attempt should be made to enroll patients on prospective trials and obtain histological and molecular characterization of their tumors, which will ultimately inform personalized therapy. The authors note furthermore that quality assurance of this technically complex and challenging treatment modality is critical to its success outside of premier academic institutions. Encouragingly, the landmark Radiation Therapy Oncology Group (RTOG) 0236 trial (7) achieved excellent results with the participation of many community centers by mandating an extensive credentialing process, effectively teaching many centers proper SABR techniques prior to their participation and highlighting the importance of credentialing and expert oversight.

In the immediate future, prospective clinical trials will help answer some of the current questions on how best to administer SABR. With respect to optimal dosing regimens, the recently completed RTOG 0915 trial compared a single dose of 34 Gy to 48 Gy in 4 fractions in medically inoperable patients with peripheral tumors, and the less toxic regimen will then be compared to the intensive 54 Gy/3 fractions regimen standardized by RTOG 0236. For central tumors, the ongoing RTOG 0813 phase I trial for centrally located tumors is designed to determine the maximum tolerated dose in 5 fractions to refine the development of risk-adapted dosing strategies (8). Most studies of SABR to date have focused on the medically inoperable population, but given the promising outcomes in those patients as well as suggested by retrospective analysis of series including potentially operable patients (9), SABR for operable patients is obviously of interest. The Japan Clinical Oncology Group (JCOG) 0403 phase II trial of SABR for peripheral operable stage IA lung cancer preliminarily found 3-year primary tumor control of 86% and overall survival of 76% in patients with a median age of 79 years (10), quite comparable to historical surgical outcomes, with final results pending. RTOG 0618, a phase II trial of SABR for peripheral operable stage I lung cancer successfully completed accrual in 2010 and results are pending.

Despite encouraging results of SABR, conducting randomized trials between lobectomy and SABR in standard risk operable patients is challenging partly because of the perception by many physicians, particularly surgeons, of lack of equipoise between the treatments, and partly because acceptance of randomization by patients is poor when the treatments seem so different in nature. Although low accrual unfortunately led to the premature closure of a randomized trial in the Netherlands (the ROSEL trial), an international randomized trial of lobectomy vs. SABR using the CyberKnife platform (the Lung Cancer STARS trial) remains open. Recognizing these difficulties, the American College of Surgeons Oncology Group (ACOSOG) and RTOG have recently opened, with strong thoracic surgery and radiation oncology support, the phase III trial ACOSOG Z4099/RTOG 1021 for high risk operable patients with peripheral stage I lung cancer who can tolerate limited surgery but not lobectomy, randomizing between less invasive sublobar resection and SABR, which might be perceived to be less dissimilar in nature and efficacy. Given the high primary tumor control rates of SABR, the main pattern of relapse is distant, with an approximately 20% rate of metastatic dissemination across multiple series (11). The Cancer and Leukemia Group B (CALGB) and RTOG have thus proposed a randomized trial of SABR for larger (2-5 cm) tumors with or without adjuvant chemotherapy to evaluate whether systemic therapy can improve progression-free survival as it does after surgery (12). Finally, combination of SABR with agents directed at radiobiological mechanisms underlying resistance to SABR such as tumor hypoxia will be an important research direction (13).

In the longer term, two important trends promise to have major implications for SABR in lung cancer: "age shift" and "stage shift." First, over at least the next two decades, the aging of the population worldwide will lead to a substantially higher absolute burden of cancer, including lung cancer. Despite the declining age-adjusted incidence of lung cancer in countries such as the United States, the number of patients diagnosed with lung cancer is expected to increase by about 50% by 2030 because of this demographic shift (14), and the problem will be compounded further in developing countries whose age-adjusted lung cancer incidence is still climbing because of past smoking trends. As a result, both the number of patients with lung cancer and the proportion that will not be surgical candidates because of advanced age and associated comorbidities will increase worldwide. Second, only a small proportion of lung cancer is diagnosed in localized stages, 15% in the United States (15), the main reason for the dismal 15% five-year survival for lung cancer overall in the U.S. and even lower globally. Promising results of CT screening for lung cancer from the International Early Lung Cancer Action Project (I-ELCAP) (16) and other non-randomized studies, and now evidence of lung cancer and all-cause mortality reduction from CT screening in the randomized National Lung Screening Trial (NLST) (17), indicate that mortality from lung cancer can indeed be reduced by shifting the

stage at diagnosis to more curable stages through early detection, as is the case with other common cancers. Ultimately this will likely be accomplished with a combination of CT imaging and other biomarkers such as detected in blood and bodily fluids, exhaled breath, etc. Together, these trends will result in many more patients with lung cancer being appropriate candidates for SABR, and most likely in a higher overall cure rate of lung cancer attributable at least partly to treatment with SABR.

In the words of pioneering computer scientist Alan Kay, "The best way to predict the future is to invent it." We must persist in developing early detection strategies and innovative therapies such as SABR, and methodically conduct clinical investigations to demonstrate their efficacy and optimize their application. Thanks to such efforts, we can glimpse what the future holds – despite the long history of grim outcomes the future of lung cancer therapy is finally looking brighter.

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