


Stereotactic Body Radiotherapy as an Alternative to Definitive Surgery in Cancers of Various Organs

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Stereotactic radiotherapy is an advanced form of radiation therapy that allows precise delivery of high radiation doses to a small focused target from multiple different directions. It started in the late 1960s with the Leksell Gamma Knife. During the 1980s, stereotactic irradiation using a linear accelerator (linac) became feasible for the treatment of intracranial lesions. In the 1990s, this technology was applied to lung tumors, which was the start of stereotactic body radiotherapy (SBRT). Since then, numerous encouraging clinical data have been accumulated regarding SBRT for lung tumors, including the authors' own,^{1,2} and SBRT has now become an indispensable treatment for patients with inoperable stage I non-small cell lung cancer and solitary lung metastasis and a treatment option for operable patients. Based on these encouraging results, the indication of SBRT was then widened to include liver tumors, tumors of the spine, prostatic cancers, and renal tumors. In this special issue, a number of reviews and a dozen original articles are included regarding SBRT for cancers of various organs. These articles support the wide applicability and excellent clinical results of SBRT, with all potentially contributing to the establishment of SBRT as a definitive treatment for patients with various tumors. Thus, the techniques for SBRT may have mostly been established, but some issues regarding physics and biology remain controversial, and so they need to be addressed. Below, we present our opinions and ideas.

Several methods of SBRT have been developed. A conventional and the most commonly used one is to use multiple (at least 7) noncoplanar and coplanar fixed beams of a linac. CyberKnife is also useful as it can deliver many more beams serially and automatically with a compact linac unit on a robotic arm. More recently, helical tomotherapy and volumetric modulated arc therapy (VMAT) have also been investigated as SBRT modalities, and especially the use of VMAT seems to be increasing. The use of noncoplanar beams in addition to coplanar beams may be better in terms of the dose distribution in the surrounding normal tissues, but helical

tomotherapy and coplanar VMAT may also be useful depending upon the tumor location, provided that the treatment plan achieves a dose distribution comparable to that produced by multiple portal coplanar and noncoplanar irradiation and respiratory motion is explicitly managed. Volumetric modulated arc therapy with a combination of coplanar and noncoplanar beams is of course useful. Hence, if the dose distribution in the planning target volume (PTV) and dose constraints in normal tissues satisfy the criteria that have mostly been established for each organ and tissue, all of these techniques could provide appropriate SBRT.

Management of respiratory movements has been a very important issue in SBRT of the lung, liver, and so on, and it has been studied by many investigators in detail. Gating and chasing methods have been investigated extensively, but many efforts are still required to ensure precise treatment delivery and quality assurance. Recently, ultrahigh-dose-rate irradiation at over 8 Gy/min using flattening filter-free beams has become available and is being increasingly used. With such beams, one portal can be treated within 15 seconds during breath-holding. This method appears to be more practical, precise, and useful than the gating and chasing methods, provided that patients can hold their breath for 15 to 20 seconds. It may become the standard approach. A useful device for breath-holding named "Abches" was developed by Onishi's group³ and it is becoming increasingly used in Japan.

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Some changes in the dose prescription method were made recently. Previously, prescription to the isocenter was commonly used, but recently, volume–dose prescription methods are being increasingly employed. Especially, prescription to the 80% to 95% dose line of the PTV has become popular. With such dose prescription methods, the doses to the PTV can be more firmly guaranteed than with isocenter prescription. When the prescription line is set at a lower percentage, the maximum dose within the PTV becomes higher, but it does not matter and does not jeopardize treatment because the hot spot is located within the target. There has been a complicated issue regarding the method of PTV prescription for SBRT of lung tumors; some differences occur in the dose and its heterogeneity and conformity in the gross tumor volume (GTV) depending on the width of the PTV margin and lung density around the GTV, because the margin area is mostly composed of air. Therefore, although prescription to the 95% or 80% isodose line of the PTV might become standard for tumors in most solid organs in the near future, dose prescription to 95% or 80% of the GTV should be considered for lung tumors. Also, the dose prescription line should be unified to either 95% or 80%, in order to compare the treatment results among different institutions.

Biologically, optimal fractionation schedules may be the most important issue. Empirically, 4-fraction treatment has been commonly employed for lung tumors in Japan. Fewer treatment schedules have also been used, but from the standpoint of radiation biology, larger fraction numbers are better to utilize the very favorable phenomenon of reoxygenation. Shibamoto *et al*⁴ proposed the concept of the “reoxygenation utilization rate,” indicating the percentage of fractions in which the reoxygenation phenomenon is exploitable. This rate is 0% when single-fraction treatment is delivered, and 50% for 2-fraction treatment; that is, the benefit of reoxygenation can be expected with the second fraction. The rate goes up to >80% with 6 or more fraction treatments, and so such fractionated treatments would be better to treat tumors with a large hypoxic fraction, that is, large tumors. For tumors smaller than 2 cm, 4-fraction treatment might be sufficient.


Another biological issue is the evaluation of the SBRT doses. Many investigators have used the biological effective dose (BED) to compare different fractionation schedules. However, BED was originally elaborated for normal tissue responses, and it never takes the reoxygenation phenomenon into account. Therefore, “BED10,” which was erroneously considered to represent the tumor response, especially for non-small cell lung cancer, contains innegligible errors. Also, the α/β ratio for the tumor response is variable with a broad range even in a specific tumor type like lung cancer, and using “10 Gy” as a representative α/β ratio for all tumors is unacceptable. Biological effective dose is based on the linear-quadratic (LQ) model and it is known that this LQ model does not fit well to the high-dose-per-fraction or single- or few-fraction treatment.⁵ Deviation is marked when the LQ model is applied to single high-dose treatment, and the calculated BED overestimates the true effect of single- or few-fraction treatment.⁶


Nevertheless, no other models are appropriate, so when using the LQ model and BED in SBRT, one must be aware of their limitations. Clinicians who use “BED10” in SBRT without hesitation are regarded as those who have no knowledge of radiation biology.

The latest hot topic regarding SBRT is its combination with immunotherapy, in particular, an immune checkpoint inhibitor. Radiotherapy is considered to exert bystander effects on unirradiated tumors and tissues, and one of them is an “abscopal effect,” which is an immunological effect on other metastatic lesions outside the treatment field induced by irradiation of tumor tissue. Until recently, it had been mostly ignored in clinics due to its low incidence and weak power, except for rare case reports. Meanwhile, the abscopal effect of radiotherapy has rapidly attracted attention owing to the recent popularization of SBRT and immune checkpoint inhibitors. Stereotactic body radiotherapy has been reported to induce the abscopal effect⁷ and thereafter amplify the effect of immune checkpoint inhibitors.⁸ There have been many experimental and clinical studies investigating the synergistic effects of the combination of SBRT and immune checkpoint inhibitors. It is very important to enhance the power of treatments locally by radiotherapy and systemically by immunotherapy. The combination therapy of SBRT with immune checkpoint inhibitors might become an ideal and innovative treatment strategy in the future.

It should be noted that most of the abovementioned data are available from cell culture or animal models, and not much data are available regarding human tumors, so there are still a lot of unknown issues. With the accumulation of encouraging clinical data, the abovementioned physical and biological issues in SBRT will be resolved soon, and SBRT will be further developed as a well-established definitive radiotherapy method. In the future, SBRT may further develop using particle beams as stereotactic proton (or carbon) therapy, which will lead to further improvements in the prognosis of patients with cancer.

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