

REVIEW

Increasing the Therapeutic Ratio of Stereotactic Ablative Radiotherapy by Individualized Isotoxic Dose Prescription

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Abstract

To obtain a favorable tradeoff between treatment benefits and morbidity (“therapeutic ratio”), radiotherapy (RT) dose is prescribed according to the tumor volume, with the goal of controlling the disease while respecting normal tissue tolerance levels. We propose a new paradigm for tumor dose prescription in stereotactic ablative radiotherapy (SABR) based on organ-at-risk (OAR) tolerance levels called isotoxic dose prescription (IDP), which is derived from experiences and limitations of conventionally fractionated radiotherapy. With IDP, the radiation dose is prescribed based on the predefined level of normal tissue complication probability of a nearby dose-limiting OAR at a prespecified dose-volume constraint. Simultaneously, the prescribed total tumor dose (TTD) is maximized to the technically highest achievable level in order to increase the local tumor control probability (TCP). IDP is especially relevant for tumors located at eloquent locations or for large tumors in which severe toxicity has been described. IDP will result in a lower RT dose or a treatment scheduled with more fractions if the OAR tolerance level is exceeded, and potential dose escalation occurs when the OAR tolerance level allows it and when it is expected to be beneficial (if TCP < 90%). For patients with small tumors at noneloquent sites, the current SABR dose prescription already results in high rates of local control at low toxicity rates. In this review, the concept of IDP is described in the context of SABR.

Stereotactic ablative radiotherapy (SABR), also referred to as stereotactic radiotherapy (SRT), stereotactic body radiotherapy (SBRT), or radiosurgery (RS), is a form of radiotherapy (RT) in which a high dose per fraction is delivered in a limited number of fractions with the aid of dedicated imaging and patient immobilization devices to minimize the treatment set-up margins of the irradiated tumor. With SABR, there is a steep-dose gradient outside the target volume to minimize the dose to organs at risk (OAR) and hence reduce the normal tissue complication probability (NTCP). SABR is increasingly being used in patients with metastasized cancer.

To obtain a favorable tradeoff between treatment benefit and morbidity (“therapeutic ratio”), the radiation dose is typically prescribed according to the target volume, with the goal of controlling the disease while respecting normal tissue tolerance levels. The therapeutic ratio (1) is explained in Figure 1. In resemblance to conventionally fractionated radiotherapy, we propose a paradigm shift for dose prescription in SABR from target-based to OAR-dependent tolerance levels called isotoxic dose prescription (IDP) (2,3). With IDP, radiation dose is prescribed based on the predefined level of NTCP of a nearby dose-limiting OAR at a prespecified dose-volume constraint (4–6). Simultaneously,

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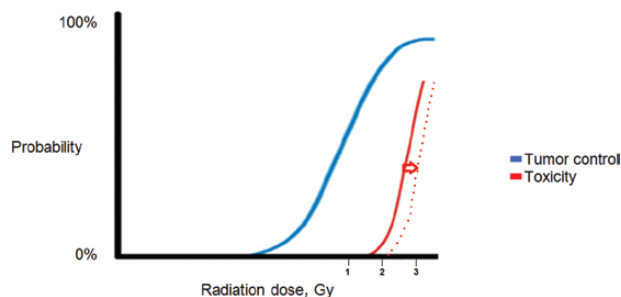


Figure 1. Therapeutic ratio in radiotherapy. The therapeutic ratio denotes the relationship between the probability of tumor control and the likelihood of normal tissue damage. An improved therapeutic ratio represents a more favorable tradeoff between tumor control and toxicity (53). The numbers 1, 2, and 3 represent potential stereotactic ablative body radiotherapy (SABR) dose prescriptions. With the dose prescribed in example 1, there is a relatively low TCP of +/-40% with a normal tissue complication probability (NTCP) of 0%. At the dose prescribed in example 2, the TCP is +/-80% with a low NTCP of +/-5%. The prescribed dose in example 3 results in a TCP of +/-95%, but at the cost of a NTCP 50%, which is often regarded as being an unacceptable risk for NTCP. There are two options for lowering the NTCP: The SABR dose is lowered to example 2, or the SABR dose is delivered in more fractions in which the NTCP curve moves to the right (red dotted line), which results in a larger therapeutic ratio.

the prescribed total tumor dose (TTD) is maximized to the technically highest achievable level in order to increase the local tumor control probability (TCP). The concept of IDP is shown in Figure 2. IDP is especially relevant for tumors located at eloquent locations or for large tumors in which severe toxicity has been described. IDP will result in more fractions to achieve an ablative dose for SABR or to reduce the prescribed dose if the OAR tolerance level is exceeded. IDP will facilitate dose escalation when tolerance dose to critical OAR allows it and when it is expected to be beneficial (if TCP < 90%). For patients with small tumors at noneloquent sites, the current SABR dose prescription already results in high rates of local control at low toxicity rates, and then IDP is less relevant. In this review, the concept of IDP is described in the context of SABR.

Current Status of SABR

Dose prescription with SABR is far beyond the 2 Gy dose level of conventional fractionation, ranging from 7.5 to 100 Gy in one to eight fractions. Typical hypofractionation schedules comprise three to five fractions ranging from 10 to 20 Gy for early-stage non-small cell lung cancer (NSCLC), a single fraction of 24 Gy for a small brain metastasis, a single fraction of 12 Gy for vestibular schwannoma, and a single fraction of 70 Gy for trigeminal neuralgia (7). The difference in SABR fractionation schedules is explained by the difference in disease entities (eg, a benign or malignant, type of tumor) while also taking into account life expectancy; high local control rates of approximately 90% are already achieved in vestibular schwannoma with a relatively low single-fraction dose, whereas for early-stage NSCLC, much higher doses are mandatory. In some countries (eg, the United States and the Netherlands), reimbursement may be, in part, dependent on the number of fractions or the dose per fraction, and this may influence the choice of fraction schedules and thereby the therapeutic ratio. There is evidence that the 2 Gy equi-effective dose (ie, the biologically equivalent total dose delivered using a fraction size of 2 Gy) in the SABR of early-stage NSCLC should be above 100 Gy to achieve local control rates of above 90%. (8) In patients with oligometastatic cancer, lower SABR doses are often used, which results in relatively low local TCP. In a large retrospective

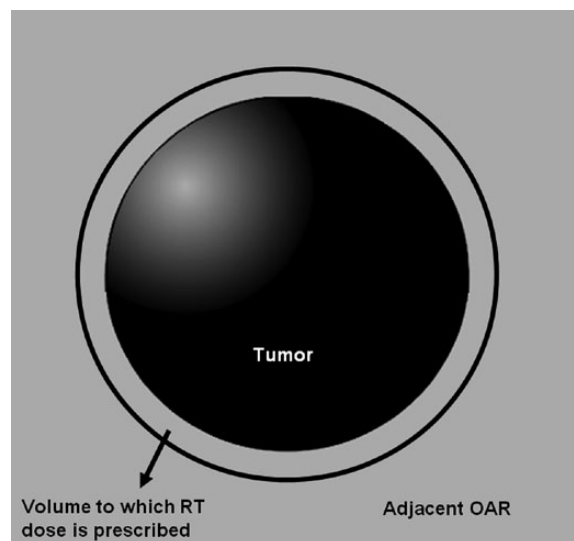


Figure 2. Concept of isotoxic dose prescription. Concept of isotoxic dose prescription (IDP): The radiotherapy dose is prescribed in relation to a volume of a dose-limiting adjacent organ at risk (OAR) based on a predefined level of acceptable normal tissue complication probability (NTCP). The total tumor dose (TTD) is escalated to the technically highest achievable level. An example of IDP for stereotactic ablative body radiotherapy of a brain metastasis is that a maximum volume of 10 cm³ of adjacent brain tissue may receive at least 12 Gy in a single fraction, which corresponds to an NTCP of 10% for symptomatic radionecrosis independent of tumor volume (6). The tumor dose can be as high as technically achievable but should at least be 15 Gy in a single fraction. Conventional dose prescription in radiotherapy is based on tumor volume, not on the OAR tolerance. An example of a conventional dose prescription is a fixed single-fraction dose of 15 Gy prescribed on the target volume for every individual patient. However, uniformity in TTD prescription does not guarantee uniformity in NTCP. Because of the difference in tumor volume amongst patients, for some the OAR dose-volume constraint will not be met, whereas for others it is exceeded unless the prescribed tumor dose is lowered. With IDP, it is possible to individually tailor the dose prescription to a predefined level of acceptable toxicity (also see Figure 1). OAR = organ at risk; RT = radiotherapy.

study on patients treated with SABR for oligometastases, several fractionation schedules were used depending on the location of the metastasis and its proximity to an OAR, resulting in the vast majority of patients being treated with a 2 Gy equi-effective dose of less than 100 Gy (9). Not surprisingly, local control two years after SABR was only 33% and was statistically significantly ($P = .02$) better for lesions treated with a 2 Gy equi-effective dose greater than 75 Gy compared with a dose of less than 75 Gy. Life expectancy also plays a role. If the tumor is near an organ that is at risk for radiation toxicity (eg, spinal cord, brain, bowel) or the tumor volume is unfavorably large, fractionation schedules are often protracted to a relatively large number with an accordingly low dose per fraction in order to decrease the risk of late toxicity. An example of such a risk-adapted fractionation schedule in early-stage NSCLC is eight fractions of 7.5 Gy for centrally located tumors instead of three fractions of 18 to 20 Gy for peripherally located ones. In general, the fractionation sensitivity (characterized by the reciprocal α/β -value) of a relevant biological endpoint of late-responding normal tissue is lower than that for tumors. If the α/β -value of the tumor is higher than that of the late-responding normal tissue, then a reduction of dose per fraction improves the therapeutic ratio, provided the overall treatment time is not extended (10). Although the concept of SABR has been around for more than half a century, its clinical use has strongly expanded over the last decade, mainly because of high local control rates at acceptably low proven toxicity rates (11).

Furthermore, the concept of the “oligometastatic disease state” has widened the indication for SABR to patients with stage IV solid tumors that were previously not eligible for (stereotactic) radiotherapy except for palliative purposes (12). The aim of SABR in patients with a limited number of metastases (oligometastases typically comprise up to five lesions in a maximum of three visceral organ sites) is the prolongation of progression-free survival, postponing systemic treatment, and the long-term maintenance of quality of life (13). For patients with one to three brain metastases, SABR is currently a standard treatment (14,15). In stage I lung cancer treated with SABR, local control rates are comparable with surgery while simultaneously avoiding the morbidity and mortality of invasive approaches (16,17). Randomized clinical trials are currently being designed to directly compare the outcome of SABR to surgery in operable patients, although patient accrual may be problematic because of the lack of equipoise from different specialties (18,19). Other applications of SABR are the treatment of metastases or primary tumors in the liver, vertebra, adrenal gland, kidney, prostate, or lymph nodes (13). There are several studies suggesting that the hypofractionated SABR of metastases may induce a so-called “abscopal” effect, ie, when highly immunogenic tumor antigens resulting from local SABR activate the immune system causing shrinkage of other metastases at nonirradiated sites (20,21). This phenomenon has been described in primary tumor types such as melanoma, lymphoma, and renal cell carcinoma. It is hypothesized that cytotoxic T-cells and natural killer cells play a crucial role in the underlying biological mechanisms (22,23). The widespread use of SABR at intra- and extracranial tumor sites has become possible because of several technical advances, making SABR a safe and patient-friendly technique (24–27). Randomized studies are needed to identify which oligometastatic patients really benefit from ablative doses of SABR (12).

Toxicity of SABR

Local control rates of SABR on small tumors at noneloquent locations are high (>90%) when applied according to current state-of-the-art procedures (28). However, severe complications have been described in other situations because nearby OARs receive doses that can lead to organ dysfunction. Examples of severe toxicities are the following:

- SABR in early-stage NSCLC: risk of radiation pneumonitis in large-volume lung tumors (eg, planning target volume >80 cm³) if the V_{5Gy} (the volume that receives at least 5 Gy) of the contralateral lung is ≥ 26% (29);
- SABR in centrally located lung tumors: bronchial stenosis and/or necrosis (30);
- SABR in brain metastases: symptomatic brain necrosis if more than 10 cm³ of the uninvolved brain tissue is irradiated with a single dose of at least 12 Gy (6);
- SABR in abdominopelvic tumors: bowel obstruction, perforation, and bleeding (31);
- SABR in spinal metastases: myelopathy and vertebral fracture (32,33);
- SABR in close to mediastinal structures: esophageal fistula (34).

To minimize the risk of the severe toxicity of SABR, clinical researchers have developed dose-volume constraints for OARs (35,36). However, most of these constraints remain unvalidated and only serve as a starting point of sorts in order to develop some uniform guidelines to guide practitioners in the rapid proliferation of SABR.

Current Guidelines for Dose Prescription in Conventionally Fractionated RT and SABR

In radical, conventional, fractionated RT, the TTD is prescribed according ICRU guidelines at the planning target volume (PTV) (37). The PTV comprises the tumor with margins for microscopic extension (margin from gross tumor volume, GTV, to clinical target volume, CTV) and uncertainties of patient positioning, inter-observer variation, treatment delivery, and imaging (margin from CTV to PTV). Typically, the dose distribution within the PTV is relatively homogeneous, in the range of 95% to 107% of the prescribed dose. The TTD in SABR is also prescribed at the rim of the PTV, but it differs from conventional fractionated RT in that the dose distribution within the PTV is deliberately heterogeneous. The maximum dose often exceeds 130% of the prescribed dose (19,28). The aim of the steep dose gradient at the rim of the PTV is to achieve optimal sparing of nearby OARs while simultaneously allowing for dose escalation within the PTV in order to achieve maximal TCP. Typically, the used GTV-CTV and CTV-PTV margins are minimized by the use of dedicated onboard imaging and patient immobilization devices.

Limitations of Dose Prescription Based on Tumor Volume

Currently, several clinical trials with SABR are ongoing. In these studies, a fixed dose level is prescribed to the PTV in the same way for every patient. During treatment planning, the OAR dose constraints are respected and, if necessary, nearby OARs are actively spared. If the OAR is very close to the PTV, there is an insurmountable conflict because it is technically not feasible to respect the OAR dose-volume tolerance while simultaneously achieving sufficient PTV coverage. Several potential solutions are chosen in daily practice:

1. A more fractionated approach is chosen in order to increase the therapeutic ratio. SABR is delivered as conventionally fractionated RT, which may result in protracted schemes of multiple fractions over several weeks. However, long fractionation schedules are undesirable in a metastatic setting where disease progression at other metastatic sites may occur within months. One to five fractions are more desirable for patient convenience.
2. Underdosage of the PTV is accepted in a region near the OAR while the number of fractions remains unchanged. This may result in a decreased TCP. Moreover, when reporting SABR, it is often unclear exactly what dose has been delivered in the PTV and in the OAR.
3. Underdosage of the PTV is achieved by reducing the number of fractions in order to respect the OAR constraint.
4. PTV coverage is not compromised by altering the dose prescription, although the OAR constraint is not respected, which results in increased NTCP rates.

Evidently, these four solutions have the substantial clinical disadvantages of protracted treatment duration, decreased TCP, and increased NTCP. Another disadvantage of SABR dose prescription based on the tumor volume is its application in phase I dose escalation trials. A paradox may occur because tumors typically have different volumes. SABR of large tumors causes a large volume of the nearby OAR to be irradiated at certain doses. A patient with a large tumor volume in a phase I study in a low-dose treatment arm may have a higher NTCP than a patient with a small tumor volume in a high-dose treatment arm. For

example, with the SABR of brain metastasis NTCP (eg, radionecrosis) is dependent on the $V_{12\text{Gy}}$ and increases rapidly above 10% if the $V_{12\text{Gy}}$ is 10 cm³ or larger (6,35,36). The $V_{12\text{Gy}}$ of nearby uninvolved brain tissue may be above 10 cm³ in the low-dose arm with large-volume metastasis and less than 10 cm³ in the high-dose arm with a small-volume metastasis. This was also shown in a randomized trial on SABR in brain metastases, in which a 1 mm GTV-PTV margin was compared with a 3 mm GTV-PTV margin with a primary endpoint of a 12-month local control (38). Dose prescription was based on the maximum diameter of the PTV as shown in Table 1. In the 3 mm GTV-PTV arm, prescription dose was generally lower, with an equal GTV diameter as that of a 1 mm GTV-PTV arm. BED and TCP are calculated based on the method described by Wiggenraad et al. (39), with an α/β -ratio of 12 Gy. In this study, the median GTV in both arms was the same (0.38 cm³ in both arms). The median $V_{12\text{Gy}}$, which corresponds with NTCP, was higher in the 3 mm arm compared with the 1 mm arm: 11.4 cm³ vs 6.0 cm³. The therapeutic ratio was higher in the 1 mm margin arm with a higher prescribed dose to the PTV and TCP and a lower $V_{12\text{Gy}}$ and NTCP (Table 1). Therefore IDP, especially in a fractionated approach, may increase the therapeutic ratio of SABR in large brain metastases.

Isotoxic Dose Prescription Based on OAR Tolerance

We propose an isotoxic dose prescription (IDP) strategy to overcome the limitations of current tumor volume-based dose prescription protocols, especially in the design of phase I SABR-based clinical trials. In IDP, the SABR dose is prescribed in relation to a volume of a dominant OAR based on an acceptable normal tissue complication probability (NTCP) level. The TTD is escalated up to the technically highest achievable level but within a specified range of minimal TCP. If the TCP is unacceptably low because of limitations by NTCP, more fractionated SABR will allow a more favorable therapeutic ratio and the allowance of a higher TCP with a constant low NTCP. In the context of IDP and NTCP, it is essential to achieve international consensus in OAR delineation and the reporting of RT dose in OAR (40). Moreover, IDP will help to determine the exact OAR tolerance dose in a prospective setting and will validate current predictive NTCP models (41,42). If OAR dose volume tolerance levels are unknown for a certain fraction scheme, phase I studies may discern this. There are several potential designs for phase I studies with IDP:

1. The TTD is escalated until a predefined OAR dose volume tolerance level is met (with an accompanying NTCP rate). The volume of the OAR in relation to which the dose is prescribed is fixed, and the number of fractions is fixed. An example of this strategy is illustrated in Figure 3.

2. The OAR volume in relation to which the dose is prescribed is escalated while maintaining the RT dose in the OAR and the number of fractions fixed.
3. The number of fractions is increased until the predefined OAR dose volume constraint is met. The RT dose for each fraction is fixed, and the volume of the OAR to which the dose is prescribed is fixed.

For a phase I study, a time-to-event continual reassessment methodology (TiTe-CRM) design is suitable, which utilizes a Bayesian approach to reassess the dose on all patients in the study and permits short- and long-term adverse events to be incorporated as an alternative approach to a commonly used 3x3 designs (43,44). For the design of a phase I study, the OAR constraint based on available literature is determined. Next, the TCP is calculated using an in silico study with the available treatment planning and delivery technique and using the margins of several tumor sizes. If there is no potential with the current technique and GTV-PTV margins, critical evaluation of the GTV-PTV margins will be needed to investigate whether a decrease in the margins is safe at the treatment department. This will provide the potential for further dose escalation with equal NTCP. If the TCP is still unsatisfactory (<90%), more fractionated approaches are used. However, the OAR constraint of common used fractionation schedules is often relatively well described but is often unknown for uncommon used fractionation schedules. For example, the $V_{12\text{Gy}}$ for a common used single-fraction SABR in brain metastases is well described, but the OAR constraint for a five- or 10-fraction approach is poorly documented. It is not trivial to convert the particular OAR constraint from a given fractionation scheme into an equivalent constraint for a new scheme. Therefore, it is important to perform a phase

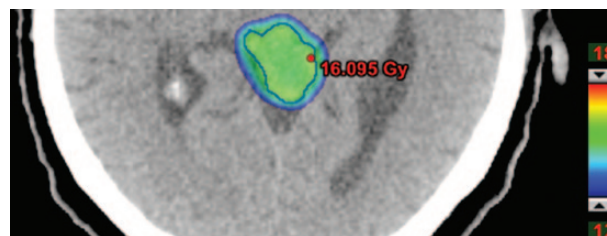


Figure 3. Potential gain in tumor complication probability (TCP) with isotoxic fractionated dose prescription in a patient with a large brain metastasis. Treatment plan (Eclipse, Varian, Palo Alto, CA) of a single fraction of 15 Gy with stereotactic ablative body radiotherapy of a large brain metastasis with a diameter of 28 mm. The illustrated radiation doses are in the range of 12 to 18 Gy. The TCP of a single dose of 15 Gy is 40%. In this treatment plan, the $V_{12\text{Gy}}$ is 5 cm³. If isotoxic dose prescription (IDP) is applied and the $V_{12\text{Gy}}$ is escalated up to 10 cm³, the total tumor dose increases to 18.9 Gy with a TCP of 65%. Thus, the gain in TCP for this brain metastasis with IDP is 25% if an NTCP of 10% on symptomatic radionecrosis is accepted. Wiggenraad calculated TCP estimates based on the review article (39).

Table 1. SABR dose prescription schedule for brain metastases in a randomized trial comparing outcomes for 1 mm vs 3 mm GTV-PTV margins*

PTV diameter, cm	GTV diameter with 1 mm GTV-PTV margin, cm	GTV diameter with 3 mm GTV-PTV margin, cm	Prescribed dose	BED (Gy)	TCP, %
<2.0	<1.8	<1.4	1 fraction of 24 Gy	72	90
2.0–2.9	1.8–2.7	1.4–2.3	1 fraction of 18 Gy	45	65
3.0–3.9	2.8–3.7	2.4–3.3	1 fraction of 15 Gy	34	40

* BED = biologically effective dose; GTV = gross tumor volume; PTV = planning target volume; SABR = stereotactic ablative body radiotherapy; TCP = tumor control probability.

I study for fractionated approaches in order to carefully assess the OAR tolerance level.

Predictive modeling studies for IDP have already been published. In an *in silico* trial for advanced NSCLC, an individualized isotoxic dose prescription enabled therapeutic gains (ie, TTD escalation) in 79% of case patients compared with conventionally prescribed fractionated RT (45). This was achieved by altering the dose per fraction and/or the number of fractions based on a clinically relevant mean or a maximum OAR tolerance dose for the uninvolved healthy lungs, brachial plexus, spinal cord, esophagus, and heart. Two different approaches were described in order to assess the predicted gain in a tumor-effective dose, either based on an IDP approach or on a maximum tolerable dose. Clinical experience has also been gained with IDP. In a prospective single-arm study in stage I to III NSCLC, a radical dose of chemotherapy was prescribed using a sequential approach by increasing the number of fractions until the first dose-limiting OAR tolerance level was met (46). The observed toxicity rates were acceptable (grade 3 or more toxicity was 24%), and survival was comparable with the results achieved with historical controls of concurrent radiotherapy and chemotherapy. In a predictive modeling study, the authors had already published an expected increase in TCP of 25% with this approach (47). Recently, favorable clinical results were published with IDP in NSCLC in a concurrent radiotherapy and chemotherapy setting (48). The observed gain in a therapeutic ratio encourages further exploration into this approach for disease entities other than NSCLC with fractionated approaches, but also in extreme hypofractionated approaches with SABR. Fractionated approaches (eg, up to 30 fractions) are needed when the tumor is abutting a radiosensitive organ with a relatively low tolerance dose for serious complications. Examples are gastro-intestinal organs such as the stomach (eg, bleeding) and bowel (eg, perforation). Obviously, when employing more fractions at a lower fraction size, the dose to the GTV is to a lesser extent limited by the maximum tolerable dose to the surrounding radiosensitive organs, and it may be possible to cover the GTV to an ablative BED of 100 Gy. For this means, a schedule of 12 fractions may not be sufficient, and more fractionated approaches may be needed to achieve a better therapeutic ratio. For designing prospective IDP trials with both conventional fractionated and more hypofractionated approaches, published tolerance dose of OARs should be used. The QUANTEC group has published comprehensive reports of known tolerance doses for conventional multiple fractionat approaches (6). For example in the QUANTEC paper, the tolerance dose of the bowel for grade 3 or higher toxicity is a V_{45Gy} value of less than 195 cm³ using a conventional fraction schedule with fractions of 2 Gy. For a hypofractionated approach, Lo and Timmermans have also published OAR constraints (35,36). For example, the tolerance dose of the small bowel in a single SABR fraction is only a $V_{9.8Gy}$ value of less than 5 cm³ (36). If the therapeutic ratio is unsatisfactory with a hypofractionated SABR IDP schedule, a treatment schedule with more fractions IDP is used. The OAR tolerance dose for this multiple fractions schedule may be unknown. Then a phase I study is needed to determine the OAR tolerance level for this specific fractionation schedule. Another option is to choose a multiple fractions schedule from which the OAR tolerance dose is known, such as a conventional 2 Gy fractionation schedule. In Maastricht, an *in silico* study for SABR in brain metastases is ongoing, which aims to explore the theoretical therapeutic gain obtained by using IDP followed by a prospective clinical trial to validate the predictive modeling with clinically observed outcomes.

Future Challenges

By further applying IDP, more evidence becomes available regarding the exact tolerance doses of OARs. This may pave the way towards personalized medicine where shared decision-making aids physicians and patients in making evidence-based treatment decisions and balancing the benefit and toxicity of SABR in an individually tailored manner (49). The TCP achieved by IDP may depend on the technology and the size of the margins that are used. Future research will focus not only on exploration of IDP in SABR but also on improving the prediction of outcomes based on multifactorial decision support systems (50). An example of multifactorial predictive models can be found at www.predictcancer.org. Another area of research is the further improvement of radiation modalities such as particle therapy (eg, protons and carbon ions), which may further increase the therapeutic ratio of IDP (51,52). With these techniques, an even higher degree of normal tissue sparing may be achieved, which could potentially lead to a reduction of the number of fractions, making these modalities less expensive per treatment course, with implications for increasing the number of patients who could benefit from them.

Conclusion

Isotoxic dose prescription is a new paradigm in stereotactic ablative radiotherapy. The radiation dose is prescribed based on nearby organs-at-risk tolerance dose. Simultaneously, the prescribed total tumor dose is maximized to the technically highest achievable level to increase the probability of tumor control. This strategy has the potential to overcome several limitations of traditional radiotherapy dose prescription based on tumor volume, and this strategy is expected to improve the overall therapeutic ratio of tumor control and toxicity.

Notes

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