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Seminars in
RADIATION
ONCOLOGY

# Emphasis on Repair, Not Just Avoidance of Injury, Facilitates Prudent Stereotactic Ablative Radiotherapy

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**Stereotactic ablative radiotherapy (SAbR) is a potent, hypofractionated treatment against cancer which puts adjacent normal tissue in potential peril. Accurate delineation of normal tissue injury risks from SAbR has been challenging, and lack of clear understanding of SAbR tolerance continues to limit its potential. In this review, we contend that SAbR effects on normal tissue could be akin to a surgical "wound," and that adequate wound repair of organs at risk is an essential component of effective SAbR therapy. To mitigate risks of clinical relevance from an SAbR wound, in addition to the traditional views on architectural organization and functional organization of an organ at risk, one should also consider the organ's predominant wound healing tendencies. We also propose that avoidance of SAbR injury to organs at risk must involve careful thought to minimize risk factors that could further impair wound healing. It is imperative that efforts aimed at determining appropriate dose constraints based on predicted SAbR wound injury repair mechanisms for a particular organ to be studied as a critically important step to furthering our understanding of SAbR-related normal tissue tolerances. This can be best achieved through thoughtful design of prospective phase I dose-escalation studies.**

**Semin Radiat Oncol 27:378-392** 

## Introduction

Historically, safe and prudent conduct in radiotherapy delivery has been considerably about avoiding toxicity. Particularly, in the 3-D era, toxicity was avoided by not crossing a line of predetermined dose or volume limits called "constraints" whereby an unacceptable percentage of patients treated previously had suffered injury. According to this point of view, practically any injury appearing after radiation treatment was scored as toxic. In contrast, medical oncologists only considered certain injuries as toxic (ie, so-called dose-limiting toxicities) while surgeons only scored events as toxic if they were unexpected or appeared outside of the perioperative window. Although radiotherapy has emerged as the "kindest and gentlest" cancer therapy capable of being used even by the most frail of patients, this approach for managing treatment potency may also have limited the potential of the therapy to eradicate cancer.

Stereotactic ablative radiotherapy (SAbR), also known as stereotactic body radiation therapy (SBRT), involves the use of highly focused, ablative doses of RT delivered over typically 1-5 fractions with the intent to eradicate the targeted tumor. Although highly effective for select tumors compared to conventional radiation treatments, a common fear that remains is that the ablative doses could also injure adjacent normal tissue. To date, the most commonly used strategy employed to mitigate such risk is optimal selection of appropriately sized tumors in favorable anatomical locations, where normal tissue exposures to high dose can be managed. Alas, this strategy limits SAbR indications significantly, particularly for targets near serially functioning tissues such as bowels.

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*Disclosure statement*: Dr. Timmerman is PI of grants to his institution for clinical research from Varian Medical Systems, Elekta Oncology, and Accuray, Inc. (all manufacturers of radiotherapy equipment). Dr. Medin receives honoraria as an instructor for courses on SRS/SBRT for Brainlab Inc. D. W. Nathan Kim has nothing to disclose.

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 http://dx.doi.org/10.1016/j.semradonc.2017.04.007
1053-4296/

More than with conventional radiation, SAbR uses effective targeting strategies including sophisticated image guidance technology, effective motion management tools, and a highly reproducible immobilization setup.[1] Nevertheless, there continues to be significant and important efforts made to determine appropriate dose constraints to improve the safety and efficacy of SAbR using clinically available data, by groups such as the AAPM SBRT Working Group, in a spirit similar to the QUANTEC data determination for conventional therapy.[2] Institutions including ours have also developed their own guidelines for dose constraints for SAbR planning (Table 2). Most recently, in a special edition of Seminars in Radiation Oncology, dose-response modeling for SAbR in a number of disease sites was performed based on the literature and institutional data review.[2] Recognized from these efforts are the challenges involved with accurate delineation of normal tissue injury risks from SAbR, which include (1) inherent bias in the selection of patients receiving SAbR, particularly for tumor sites near serially functioning tissues; (2) expert-derived, imposed dose constraints limiting the spectrum of potentially attainable dose, particularly to serially functioning tissues that are mostly mined from post hoc review of published articles; (3) nonuniform treatment (dose, fractionation), nonuniform follow-up, and nonuniform reporting; (4) retrospective nature of many studies, with nonuniform eligibility criteria for SAbR use, including lack of standard criteria for chemotherapy or systemic therapy use, and lack of uniform policy regarding prior radiation history; and most importantly, (5) paucity of prospective dose-escalation phase I studies for many of the disease sites to determine maximum tolerated dose. This last point is most problematic as without accurate knowledge of the true maximum tolerated dose derived from formal dose-escalation studies and relating to a variety of injury, the true potential of any therapy cannot be realized.

In this review, we aim to discuss normal tissue injury from a nontraditional point of view. That is, in addition to the traditional views regarding dose and/or volume limits to avoid injury, we will explore mechanism of radiation-related injury, functional subunits, serial and parallel architecture of organs at risk, and heterogeneous vs homogeneous distribution of function within an organ. Then, we will add another dimension that we believe is critical to characterizing SAbR-related injury as temporary vs permanent, the understanding of which will help us determine how to best avoid or mitigate such injury. This involves consideration of the mechanisms involved in normal tissue repair after an insult, that is, mechanisms of successful or unsuccessful injury or repair. In this view, we consider exposure of organs in the high-dose region of SAbR akin to that of a surgical wound. Every surgical wound constitutes an injury (toxicity), but the wounds clearly have potential to heal. We contend that for SAbR, like a surgical wound, the outcome of toxicity to this organ would be dependent on its ability to heal itself, particularly if it is organized in a serial architecture or has regenerative potential. We will discuss ramification of such mechanistic view of SAbR-related organ injury and repair, including implications for understanding potential for combined toxicity when agents affecting mechanisms of injury repair, such as antiangiogenic agents are used in periods surrounding SAbR.

## Radiobiology of SAbR

We predicate our discussion by first recognizing that the radiobiology of SAbR is not clearly agreed upon. There are views that the standard radiobiology concepts are sufficient to explain the clinical data seen in SAbR, asserting that the efficacy reflects the larger biologically effective dose that are delivered with SAbR.[3] However, others have suggested that novel mechanisms, so called "new biology," may be involved when a threshold dose per fraction has been exceeded.[4]

The suggested "new biology" involves SAbR's potential effects on (1) the tumor vasculature, (2) the immune response, and (3) clonal cell depletion. Endothelial apoptosis has been demonstrated to occur above ~8-10 Gy threshold,[5,6] suggesting that the SAbR can lead to tumor vasculature destruction and subsequent tumor eradication.[7-9] More recently, clinical evidence is emerging suggesting that SAbR doses can contribute to enhanced immune-mediated cell kill, including production of abscopal effects, and enhancement of efficacy of immunotherapy agents.[10,11] Finally, radiation-induced stem cell depletion effects are important to consider, as stem cells that migrate into the radiation-ablated tissue from neighboring undamaged tissue could hold the key to repair of SAbR-mediated injury.[12,13] Based on the mounting preclinical and clinical evidence for the "new biology," it is conceivable that each of these issues can contribute significantly to the understanding of the efficacy and tolerance of SAbR.

## Radiobiologic Modeling of Functional Subunits: Serial vs Parallel Functioning Organs

Yaes and Kalend[14] have proposed that tissues can be subdivided ranging from a spectrum of those that are organized in a serial fashion, that involves a "chain" of function, to those that are organized in a parallel fashion and are characterized by redundancy of function and inherent reserve. Serial structures depend on critical element (critical max dose) for organ dysfunction, whereas parallel structures depend on a critical volume for organ dysfunction.[15] However, recognizing that most organs are not simply represented by "serial" or "parallel" architecture, others have proposed that many organs, such as the heart, are better represented as combination of the 2 architectures ("serial-parallel").[16] Another view suggests that beyond organ structure, the functionality of the organs should be considered.[17] A parallel organ may have heterogeneous areas of function, and hence susceptibility to radiation injury may depend not only on critical volume irradiated but also on location where the RT is delivered to. Finally, organs may, for different circumstances, behave more parallel or serial. For example, when treating a longer length of bowel, radiation injury manifests as serial damage with catastrophic end-organ

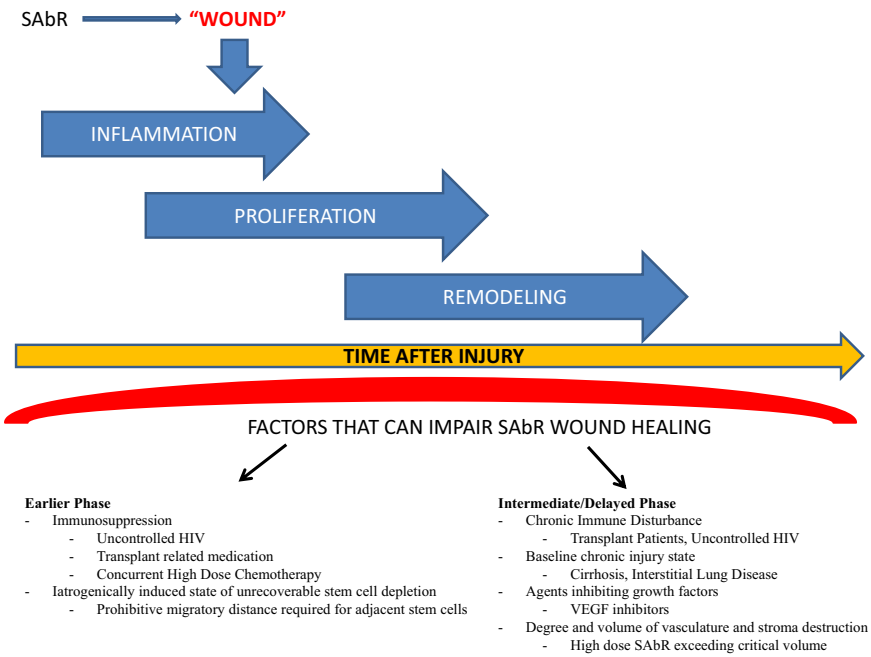


**Figure 1** Model for wound repair. (Color version of figure is available online.)

functional loss (eg, bowel obstruction). But if the radiation volume is extremely limited, say to a small, noncircumferential section of a wall, the injury response behaves more parallel. Categorization of organ is done by organization of functional subunits, and function is highly relevant in the setting of SAbR, where higher doses are delivered to a smaller area than typical with conventional fractionation.

## Principles of Wound Healing: Application to SAbR Tolerance

When considering SAbR-related injury, given the ablative nature of the therapy, one must also consider the repair mechanisms invoked when an injury occurs. Understanding the pathophysiology and mechanism of normal tissue repair can help us glean a better understanding of the potential tolerances as it relates to ablative radiation injury. In order to do so, we can first draw from the pathophysiology of repair mechanisms invoked in a traditional surgical wound. In general terms, wound repair capacity after injury ranges from regeneration to repair with fibrosis. Regeneration is obviously the more appealing form of wound healing as it is without scar, and retains and regains tissue function, but in postnatal humans this can only occur robustly in a few organ sites including primarily the parenchyma of the liver and kidney, bone, and bone marrow.[18] Mucosal sites, such as the bowel mucosa, appear to rely both on regeneration in part after migration of stem cells and classic stages of wound healing mechanisms to repair injury.[19] Some regenerating organs, such as the liver, when sustained with chronic repeated injury or repair results in chronic inflammation and fibrosis, leading to a less functional organ state, as seen in cirrhosis.[20] Therefore, when considering SAbR-related injury or repair, we hypothesize that it is important to consider the organ's repair mechanisms, in addition to consideration of the organization of its functional subunits.

For most organs that have limited or no regeneration capacity, wound repair involves complex, yet concerted stages. Although much advance has been made to identify molecular factors involved with wound healing, the molecular mechanisms that may impair wound healing are not fully understood.[21] The stages of wound healing is best studied in skin model, where stages of repair include inflammation (first 24-48 hours), new tissue formation or repair (2-10 days), and remodeling (weeks to year)[22] (Fig. 1). It involves recruitment of many different cell types and can be affected by patient-related and iatrogenic factors. These steps involve recruitment of mediators of inflammatory pathways, immune cells, angiogenic factors (eg, vascular endothelial growth factor inhibitor [VEGF] and fibroblast growth factors) and scar formation or epithelialization (or reproliferation of mucosa) or both over wound to complete the repair process.[21] Therefore, (1) clonal cell migration, (2) immune cell recruitment, and (3) angiogenesis are some of the critical factors that are thought to be involved for wound healing to occur. Disruption of any or each of these stages could theoretically contribute to impaired wound healing. For example, chronic inflammatory states can lead to poor wound healing, and a state of "chronic wound."[23] In regenerating tissues, failure to regenerate may lead to wound healing strictly by fibrosis. In organs capable of regeneration, availability of epithelial or stem cells to be able to migrate efficiently to the site of injury are thought to be critically involved in this process.

One might appreciate that some of the critical components of wound repair—angiogenesis, immune response, and stem cell–based repopulation or regeneration, are all biological processes that are potentially targeted by ablative radiation's "new biology" as facilitated by the utilized "new technology" (ie, extreme geometric avoidance of high dose). Furthermore,

**Table 1** Factors Predicted to be Important for Wound Healing in the Different Types of Organs Based on Architecture and Primary Mode of Wound Healing Mechanism

| | SR | SNR | PR | PNR |
|---|---|---|---|---|
| Wound healing: stem cells/clonal repopulation | Y | N | Y | N |
| Wound healing: angiogenesis | Y | Y | N | Y/N |
| Wound healing: immune disruption | Y | Y | N | N |
| Critical dose most important | N | Y | N | N |
| Critical dose to a critical volume most important | Y | N | Y | Y |
| Migration distance for stem cells to heal the wound important | Y | Y/N | N | N |

Categorization of representative organs by functional architecture and predominant mode of wound healing mechanism.
SR, serial regenerating: bowel structures, bronchial airways, liver ducts, and renal collecting.
SNR, serial nonregenerating: spinal cord, optic nerve, brachial plexus, major vessels, and coronary arteries.
PR, parallel regenerating: liver parenchyma and kidney parenchyma.
PNR, parallel nonregenerating: brain, parotid gland, bladder, myocardium, and lung parenchyma.

these are processes that can be affected by intrinsic patient-related factors and by systemic therapy. Therefore, in addition to being mindful of the injury caused on organs from SAbR's ablative dose, one might also consider SAbR's potential effects on impairing wound healing, the avoidance of which may be critical to mitigating significant toxicities. In other words, conventional radiotherapy has always sought to avoid toxicity by avoiding injury—a strategy that surgeons cannot employ as all surgeries cause injury starting with the incision. But for SAbR and unlike large field, conventional radiotherapy, another strategy would be to employ technology (geometric avoidance) to avoid disabling the repair capacity inherent to tissue—a strategy that is the entire basis of successful surgery.

## Normal Tissue Categorization for SAbR Tolerance Modeling

Based on these principles, we can generally categorize organs into 4 types based on functional organization and its predominant wound healing tendencies. These categories could broadly include the following: (1) serial regenerating, (2) serial nonregenerating, (3) parallel regenerating, and (4) parallel nonregenerating organs (Table 1—last row). As previously mentioned, there are shortcomings with any such blanket characterizations given the overlap of categories that can be seen in organs. Furthermore, only a few organs in the human body once it reaches adulthood are thought to maintain regenerative capacity. Some organs rely on both regeneration and nonregeneration wound healing mechanisms such as the mucosal structures. Therefore, these categories are meant to be reflective of an organ's perceived predominant response to injury. Despite the limitations, such characterization may prove useful in helping us determine SAbR tolerances by considering for each organ its organizational anatomy and function, as well as its predominant mechanism of wound healing (Table 1). This may lead to the determination of better methods of improving tolerability of SAbR via mitigation or enhancement of repair pathway of the involved organ. Owing to constraints of the review, we will discuss 1 representative example of each type of organ modeling category as it pertains to SAbR injury.

## Serial Regenerating Organ: Rectum

Components of wound healing critical to repair include immune mediators, angiogenesis, and for regenerative organs (liver, skin, and mucosal sites), availability of stem cells. When considering large bowel structures, such as the rectum, acute reparable injury, such as mucosal reaction, is typically healed via regeneration of mucosa through stem cell repopulation. When serious skin radiation injury (eg, deep ulceration or fistula) occurs, the most successful clinical approach to repair is to use a myocutaneous graft. This method of repair relies on provision of a renewed blood supply to the devascularized area via transferred muscle (ie, the myo-component), as well as epithelial stem cells (ie, the cutaneous component), which can proliferate over the denuded areas.[12] Indeed, use of this approach was found to be far more effective compared with diversions and observation alone.[24,25] Therefore, we hypothesized that the key to tolerance for SAbR would relate not only to the degree of damage inflicted by the radiation but also in maintenance of the ability for the normal tissue injury to repair itself. Using our prostate SAbR experience, we tested this hypothesis.[12]

The rectum would be considered a serial organ, with partially regenerative capabilities, if the injury is primarily involving the mucosal surface. Therefore, invoking the principles of wound healing for a regenerative organ, we hypothesized that the primary physiologic requirements that are impaired by SAbR leading to significant injury would primarily fall into 2 categories: (1) mucosal damage, including injury to stem cells and (2) vascular and/or stromal damage leading to devitalization of tissues. We further hypothesized that serious injuries manifest after SAbR when such injuries are incapable of healing due to (1) stem cell depletion at the site of injury, and the inability to efficiently recruit neighboring viable stem cells, owing to excessive distance required to migrate to the site of injury or (2) significant destruction of vasculature and stroma by excess volume of rectal wall being irradiated to a yet undetermined yet definable dose of radiation. This latter issue could lead to incapacitation of effective angiogenesis, and inability to recruit immune mediators to the site of injury, leading to a wound that cannot properly heal.

**Table 2** Mostly Unvalidated Dose Limits for SAbR and Hypofractionated Radiotherapy

| | Volume (cc) | Volume Max (Gy) | Max Point Dose (Gy)* | End Point (≥Grade 3) |
|---|---|---|---|---|
| *One fraction* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 8 | 10 | Neuritis |
| Cochlea | | | 9 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 10 | 15 | Cranial neuropathy |
| Spinal cord and medulla | <0.35 | 10 | 14 | Myelitis |
| Cauda equina | <5 | 14 | 16 | Neuritis |
| Sacral plexus | <5 | 14.4 | 16 | Neuropathy |
| Esophagus† | <5 | 20 | 24 | Esophagitis |
| Brachial plexus | <3 | 13.6 | 16.4 | Neuropathy |
| Heart/pericardium | <15 | 16 | 22 | Pericarditis |
| Great vessels | <10 | 31 | 37 | Aneurysm |
| Trachea and large bronchus† | <4 | 27.5 | 30 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 17.4 | 20.2 | Stenosis with atelectasis |
| Rib | <5 | 28 | 33 | Pain or fracture |
| Skin | <10 | 25.5 | 27.5 | Ulceration |
| Stomach | <5 | 17.4 | 22 | Ulceration/fistula |
| Bile duct | | | 30 | Stenosis |
| Duodenum† | <5 | 17.4 | 22 | Ulceration |
| Jejunum/ileum† | <30 | 17.6 | 20 | Enteritis/obstruction |
| Colon† | <20 | 20.5 | 31 | Colitis/fistula |
| Rectum† | <3.5 | 30 | 33.7 | Proctitis/fistula |
| | <20 | 23 | | |
| | <33% of rectal circumference | 24 | | |
| Ureter | | | 35 | Stenosis |
| Bladder wall | <15 | 12 | 25 | Cystitis/fistula |
| Penile bulb | <3 | 16 | | Impotence |
| Femoral Heads | <10 | 15 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 14 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 7.2 | | Basic lung function |
| Lung (right and left) | | | V-8 < 37% | Radiation pneumonitis |
| Liver | 700‡ | 11.6 | | Basic liver function |
| Renal cortex (right and left) | 200‡ | 9.5 | | Basic renal function |
| *Two fractions* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 11.7 | 13.7 | Neuritis |
| Cochlea | | | 11.7 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 13 | 19.1 | Cranial neuropathy |
| Spinal cord and medulla | <0.35 | 13 | 18.3 | Myelitis |
| Cauda equina | <5 | 18 | 20.8 | Neuritis |
| Sacral plexus | <5 | 18.5 | 20.8 | Neuropathy |
| Esophagus† | <5 | 24.3 | 28.3 | Esophagitis |
| Brachial plexus | <3 | 17.8 | 21.2 | Neuropathy |
| Heart/pericardium | <15 | 20 | 26 | Pericarditis |
| Great vessels | <10 | 35 | 41 | Aneurysm |
| Trachea and large bronchus† | <4 | 34.5 | 38 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 21.6 | 25.1 | Stenosis with atelectasis |
| Rib | <5 | 34 | 41.5 | Pain or fracture |
| Skin | <10 | 28.3 | 30.3 | Ulceration |
| Stomach | <5 | 20 | 26 | Ulceration/fistula |
| Bile duct | | | 33 | Stenosis |
| Duodenum† | <5 | 20 | 26 | Ulceration |
| Jejunum/ileum† | <30 | 19.2 | 24 | Enteritis/obstruction |
| Colon† | <20 | 25.8 | 39 | Colitis/fistula |

Table 2 (*continued*)

| | Volume (cc) | Volume Max (Gy) | Max Point Dose (Gy)* | End Point (≥Grade 3) |
|---|---|---|---|---|
| Rectum† | <3.5 | 38 | 41.3 | Proctitis/fistula |
| | <20 | 26.7 | | |
| | <33% of rectal circumference | 30 | | |
| Ureter | | | 37.5 | Stenosis |
| Bladder wall | <15 | 14.5 | 29 | Cystitis/fistula |
| Penile bulb | <3 | 20.5 | | Impotence |
| Femoral heads | <10 | 19.5 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 16.8 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 9.4 | | Basic lung function |
| Lung (right and left) | | | V-10 < 37% | Radiation pneumonitis |
| Liver | 700‡ | 15.1 | | Basic liver function |
| Renal cortex (right and left) | 200‡ | 12.5 | | Basic renal function |
| *Three fractions* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 15.3 | 17.4 | Neuritis |
| Cochlea | | | 14.4 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 15.9 | 23.1 | Cranial neuropathy |
| Spinal cord and medulla | <0.35 | 15.9 | 22.5 | Myelitis |
| Cauda equina | <5 | 21.9 | 25.5 | Neuritis |
| Sacral plexus | <5 | 22.5 | 25.5 | Neuropathy |
| Esophagus† | <5 | 27.9 | 32.4 | Esophagitis |
| Brachial plexus | <3 | 22 | 26 | Neuropathy |
| Heart/pericardium | <15 | 24 | 30 | Pericarditis |
| Great vessels | <10 | 39 | 45 | Aneurysm |
| Trachea and large bronchus† | <5 | 39 | 43 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 25.8 | 30 | Stenosis with atelectasis |
| Rib | <5 | 40 | 50 | Pain or fracture |
| Skin | <10 | 31 | 33 | Ulceration |
| Stomach | <5 | 22.5 | 30 | Ulceration/fistula |
| Bile duct | | | 36 | Stenosis |
| Duodenum† | <5 | 22.5 | 30 | Ulceration |
| Jejunum/ileum† | <30 | 20.7 | 28.5 | Enteritis/obstruction |
| Colon† | <20 | 28.8 | 45 | Colitis/fistula |
| Rectum† | <3.5 | 43 | 47 | Proctitis/fistula |
| | <20 | 30.3 | | |
| | <33% of rectal circumference | 34 | | |
| Ureter | | | 40 | Stenosis |
| Bladder wall | <15 | 17 | 33 | Cystitis/fistula |
| Penile bulb | <3 | 25 | | Impotence |
| Femoral heads | <10 | 24 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 19.5 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 10.8 | | Basic lung function |
| Lung (right and left) | | | V-11.4 < 37% | Pneumonitis |
| Liver | 700‡ | 17.7 | | Basic liver function |
| Renal cortex (right and left) | 200‡ | 14.7 | | Basic renal function |
| *Four fractions* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 19.2 | 21.2 | Neuritis |
| Cochlea | | | 18 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 20.8 | 27.2 | Cranial neuropathy |

Table 2 (*continued*)

| | Volume (cc) | Volume Max (Gy) | Max Point Dose (Gy)* | End Point (≥Grade 3) |
|---|---|---|---|---|
| Spinal cord and medulla | <0.35 | 18 | 25.6 | Myelitis |
| Cauda equina | <5 | 26 | 28.8 | Neuritis |
| Sacral plexus | <5 | 26 | 28.8 | Neuropathy |
| Esophagus† | <5 | 30.4 | 35.6 | Esophagitis |
| Brachial plexus | <3 | 24.8 | 29.6 | Neuropathy |
| Heart/pericardium | <15 | 28 | 34 | Pericarditis |
| Great vessels | <10 | 43 | 49 | Aneurysm |
| Trachea and large bronchus† | <5 | 42.4 | 47 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 28.8 | 34.8 | Stenosis with atelectasis |
| Rib | <5 | 43 | 54 | Pain or fracture |
| Skin | <10 | 33.6 | 36 | Ulceration |
| Stomach | <5 | 25 | 33.2 | Ulceration/fistula |
| Bile duct | | | 38.4 | Stenosis |
| Duodenum† | <5 | 25 | 33.2 | Ulceration |
| Jejunum/ileum† | <30 | 22.4 | 31.6 | Enteritis/obstruction |
| Colon† | <20 | 30.8 | 48.5 | Colitis/fistula |
| Rectum† | <3.5 | 47.2 | 51.6 | Proctitis/fistula |
| | <20 | 34 | | |
| | <33% of rectal circumference | 37 | | |
| Ureter | | | 43 | Stenosis |
| Bladder wall | <15 | 18.5 | 35.6 | Cystitis/fistula |
| Penile Bulb | <3 | 27 | | Impotence |
| Femoral heads | <10 | 27 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 21.5 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 12 | | Basic lung function |
| Lung (right and left) | | | V-12.8 < 37% | Pneumonitis |
| Liver | 700‡ | 19.6 | | Basic liver function |
| Renal cortex (right and left) | 200‡ | 16 | | Basic renal function |
| *Five fractions* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 23 | 25 | Neuritis |
| Cochlea | | | 22 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 23 | 31 | Cranial neuropathy |
| Spinal cord and medulla | <0.35 | 22 | 28 | Myelitis |
| Cauda equina | <5 | 30 | 31.5 | Neuritis |
| Sacral plexus | <5 | 30 | 32 | Neuropathy |
| Esophagus† | <5 | 32.5 | 38 | Esophagitis |
| Brachial plexus | <3 | 27 | 32.5 | Neuropathy |
| Heart/pericardium | <15 | 32 | 38 | Pericarditis |
| Great vessels | <10 | 47 | 53 | Aneurysm |
| Trachea and large bronchus† | <5 | 45 | 50 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 32 | 40 | Stenosis with atelectasis |
| Rib | <5 | 45 | 57 | Pain or fracture |
| Skin | <10 | 36.5 | 38.5 | Ulceration |
| Stomach | <5 | 26.5 | 35 | Ulceration/fistula |
| Bile duct | | | 41 | Stenosis |
| Duodenum† | <5 | 26.5 | 35 | Ulceration |
| Jejunum/ileum† | <30 | 24 | 34.5 | Enteritis/obstruction |
| Colon† | <20 | 32.5 | 52.5 | Colitis/fistula |
| Rectum† | <3.5 | 50 | 55 | Proctitis/fistula |
| | <20 | 37.5 | | |
| | <33% of rectal circumference | 39 | | |
| Ureter | | | 45 | Stenosis |
| Bladder wall | <15 | 20 | 38 | Cystitis/fistula |

Table 2 (*continued*)

| | Volume (cc) | Volume Max (Gy) | Max Point Dose (Gy)* | End Point (≥Grade 3) |
|---|---|---|---|---|
| Penile bulb | <3 | 30 | | Impotence |
| Femoral heads | <10 | 30 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 23 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 12.5 | | Basic lung function |
| Lung (right and left) | | | V-13.5 < 37% | Pneumonitis |
| Liver | 700‡ | 21.5 | | Basic liver function |
| Renal cortex (Right & Left) | 200‡ | 17.5 | | Basic renal function |
| *Eight fractions* | | | | |
| Serial tissue | | | | |
| Optic pathway | <0.2 | 27.2 | 29.6 | Neuritis |
| Cochlea | | | 26.4 | Hearing loss |
| Brainstem (not medulla) | <0.5 | 27.2 | 37.6 | Cranial neuropathy |
| Spinal Cord and medulla | <0.35 | 26.4 | 33.6 | Myelitis |
| Cauda equina | <5 | 34 | 38.4 | Neuritis |
| Sacral plexus | <5 | 34 | 38.4 | Neuropathy |
| Esophagus† | <5 | 36.8 | 43.2 | Esophagitis |
| Brachial plexus | <3 | 32.8 | 39.2 | Neuropathy |
| Heart/pericardium | <15 | 34.4 | 40 | Pericarditis |
| Great vessels | <10 | 55.2 | 62 | Aneurysm |
| Trachea and large bronchus† | <5 | 50 | 56 | Impairment of pulmonary toilet |
| Bronchus—smaller airways | <0.5 | 38.4 | 48.8 | Stenosis with atelectasis |
| Rib | <5 | 50 | 63 | Pain or fracture |
| Skin | <10 | 43.2 | 45.6 | Ulceration |
| Stomach | <5 | 31.2 | 42 | Ulceration/fistula |
| Bile duct | | | 48 | Stenosis |
| Duodenum† | <5 | 31.2 | 42 | Ulceration |
| Jejunum/ileum† | <30 | 28.8 | 40 | Enteritis/obstruction |
| Colon† | <20 | 35.2 | 57.5 | Colitis/fistula |
| Rectum† | <3.5 | 56 | 61.5 | Proctitis/fistula |
| | <20 | 45 | | |
| | <33% of rectal circumference | 45 | | |
| Ureter | | | 53 | Stenosis |
| Bladder wall | <15 | 22.4 | 44.8 | Cystitis/fistula |
| Penile bulb | <3 | 35 | | Impotence |
| Femoral heads | <10 | 35 | | Necrosis |
| Renal hilum/vascular trunk | 15 | 28 | | Malignant hypertension |
| Parallel tissue | | | | |
| Lung (right and left) | 1500 for males and 950 for females‡ | 14.4 | | Basic lung function |
| Lung (right and left) | | | V-15.2 < 37% | Pneumonitis |
| Liver | 700‡ | 24.8 | | Basic liver function |
| Renal cortex (right and left) | 200‡ | 20 | | Basic renal function |

*"Point" defined as 0.035 cc or less.
†Avoid circumferential irradiation.
‡One-third of the "native" total organ volume (before any resection or volume-reducing disease), whichever is greater.

When considering the Papillon technique for small low rectal cancers, with 20-40 Gy per fraction delivered every 2 weeks or so for over 100 Gy surface dose, this should have left a defect in the rectal wall, but rectal toxicity was rare, and tumor control was reported to be high.[26] This technique, however, did use contact radiotherapy with doses that fall off very quickly over short depth, and treated small areas, suggesting a potential for healing by clonal repopulation.[27] In fact, even within our own experience, when patients were treated to 45 Gy in 5 fractions and their rectum evaluated by anoscopy, all patients evaluated developed an ulcer on the anterior rectal wall which healed in all cases in 3-6 months, suggesting stem cell migration and regeneration of a wound inflicted by SAbR.[12] This was also reflected in the patient's

EPIC bowel symptom score which declined at 6 weeks but returned to normal levels by 18 months,[28] with similar trends seen from SAbR studies at other institutions.[29]

When the prostate SAbR clinical trial was initially designed, we hypothesized that sparing of adjacent, lateral, and posterior rectal wall would lead to increased tolerability to the prescription dose of radiation delivered to the anterior rectal wall which is in close proximity to the target where higher doses would be rendered. Therefore, the lateral and posterior rectal walls were imposed a much stricter dose tolerance and dose avoidance. This was based on the notion that clonal stem cell can be recruited to repair the injury imposed by the SAbR treatment, given the known regenerative properties of rectal mucosa. The recruitment of stem cells can come from the irradiated area, or from the edge of the stem cell depleted region. In the latter circumstance, which relies heavily on stem cell migration to the site of injury, the distance required for stem cell to migrate may affect the ability for injury to heal. Such dosimetric requirements helped provide data that could be later analyzed to test our hypothesis. In addition, stem cells that have migrated must find a hospitable environment, including an adequate blood supply and immune-mediated factors, in order for the tissue to heal (vascular or stromal effect). We hypothesized that (1) a prohibitive migration distance imposed by large areas of stem cell depletion and (2) devitalization of area of injury making it an inhospitable environment for stem cell recruited to heal the injury are 2 factors that relate to the development of high level of injury in the rectum.

Using preclinical models of bowel stem cell survival, we hypothesized that 24 and 39 Gy in 5 fractions would lead to 90% and 99.99% of stem cell depletion, respectively, affecting wound healing via regeneration.[12] We determined that when more than a third of the rectum was irradiated to beyond 39 Gy, this led to increased rates of high-grade rectal toxicity, suggesting that we should not irradiate more than a third of the rectum to a stem cell depletive dose, as this becomes prohibitive for adjacent stem cells to migrate and heal the wound. Evaluation of this parameter requires visualization of the dose curves, and not just a review of the dose-volume histogram (DVH) curve, as this is not the same as avoiding V39 rectum $<33\%$. The dose lines seen on the rectum reflects the pathophysiology of stem cell migration inhibition imposed by a prohibitive migration distance by stem cell depleting dose of 39 Gy in 5 fractions (Fig. 2). We also determined that there is a critical volume effect when a dose sufficient to devitalize the tissue is delivered. In this study, we determined that dose to be 50 Gy in 5 fractions, and if this dose was delivered to more than 3 $cm^3$ of the rectal wall, this was sufficient to render high-grade rectal toxicity. Both of these parameters do not fit the serial organ model, but it certainly strengthens our hypothesis that incorporation of understanding of wound healing pathway that can be inhibited by SAbR predicts for high-grade toxicity in a serial regenerating organ. Figure 3 demonstrates an example of a rectal wound after SAbR that fails to repair leading to high-grade rectal toxicity. In this patient, the injury persisted to the point of requirement of a diverting jejunostomy 24 months after SAbR. Delayed healing was via scar formation as opposed to regeneration of mucosa (Fig. 3).

## Serial Nonregenerating Organ: Spinal Cord

When potential SAbR-related toxicities related to a predominantly nonregenerating serial organ such as the spinal cord are considered, there is increased importance to understanding the factors that lead to the complication of myelopathy. For a serial organ with wound healing that is less affected by clonal repopulation, one might expect that determinants of injury are more likely to be dependent on a critical dose irrespective of volume that is irradiated. A healthy blood supply, angiogenesis, and ability to recruit immune products may still be involved in injury repair at subclinical levels, but this is difficult to prove.

Supportive of serial nonregenerating characteristics, dosimetric evaluation from multi-institutional efforts have demonstrated that the maximum point dose to the thecal sac was the most significant discriminator of myelopathy for 9 of 66 patients experiencing myelopathy after SAbR.[30,31] This was supportive of the preclinical work in swine model, where irradiation of a partial volume of spinal cord using a steep lateral gradient did not lead to increased tolerance to SAbR.[32] In a serial organ, injury at a point could lead to catastrophic consequences downstream, supporting the traditional view that a critical maximum dose must be determined and respected to avoid injury.

In contrast to the earlier observations, a dose-volume effect has been observed in situations where extremely small volumes are irradiated. Multiple groups have studied the effect of irradiated length on spinal cord tolerance. Two groups irradiated lengths of rat spinal cords less than or equal to 2 cm and both observed that tolerance increases steeply for lengths less than 1 cm.[33,34] It has been hypothesized that migration of functional cells from uninjured tissue at the periphery of the irradiated volume may be at least partially responsible for the increase in tolerance.[33] After 40 Gy irradiation to a short length of spinal cord in rats, oliodendrocyte progenitor cells can be depleted in the irradiated volume, but can be repopulated by migrating cells from adjacent healthy spinal cord, with a migration speed of approximately 0.5 mm/wk in the first month after injury.[13] In a clinical study, the spinal cord was observed to tolerate very large doses in a single-session when small lesions adjacent to the spinal cord were irradiated.[35] Increased lengths of spinal cord from 2.5-10 cm were irradiated in pigs, and no change in tolerance was observed.[36] Spinal cord tolerance has also been observed to increase in rodent models when a steep gradient is irradiated across the spinal cord, but no increase was observed in a similar study in pigs.[37-39] Fundamentally, the primary molecular mechanism for myelopathy is not fully clear. Depletion of oligodendrocyte progenitor cells or apoptosis of vascular endothelial cells or both have been implicated. A study of boron neutron capture in the spinal cords of rats supports the hypothesis of higher radiation doses causing vascular injuries that lead to white matter necrosis, suggesting the vasculature as the primary target for mediating cord injury.[40] Preclinical studies have also implicated hypoxia and upregulation of VEGF as being implicated in necrosis of cord after irradiation.[30]

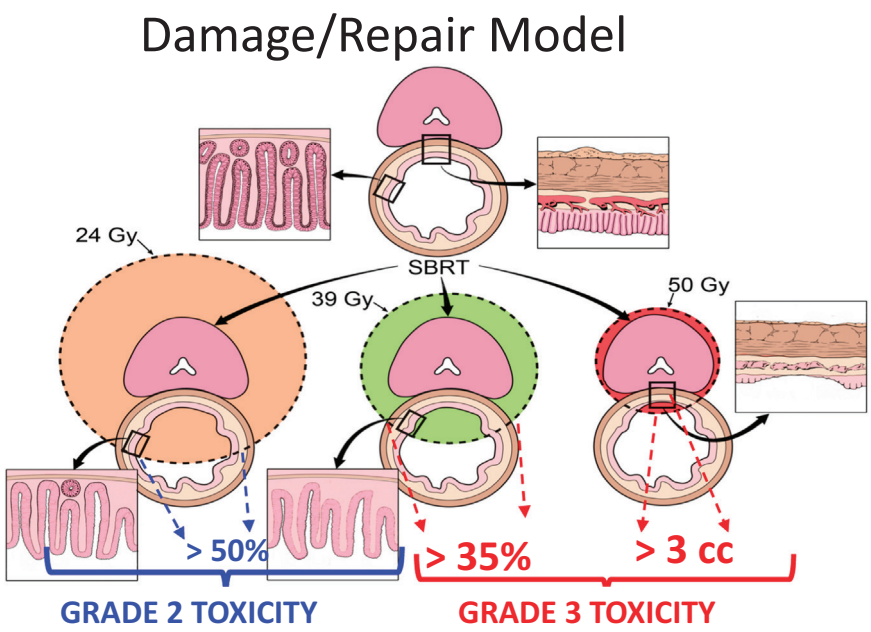


**Figure 2** Wound repair model in a serial regenerating organ, the rectum. (Modified and reused with permission from Elsevier,[12] Fig. 2C).

Regarding reirradiation experience, preclinical models have suggested a slow regenerative potential of the spinal cord. In a swine model of SBRT to spine, a history of standard conventional RT to the cord a year earlier (30 Gy in 10 fx) did not lead to reduced dose tolerance to SBRT.[41] In a preclinical study with primates, substantial recovery from injury was observed 1-3 years following conventional radiation,[42] suggesting a potential for slow regeneration when stem cells are not completely depleted. Clinical studies evaluating reirradiation suggest that a time interval (>5-6 months) is important for improved tolerance. Furthermore, the total dose tolerated from 2 courses of irradiation appears to be more than that deemed safe for a single course of radiotherapy.[43-45] Therefore, while spinal cord tolerance studies and preclinical rodent studies challenge the notion that the spinal cord is a nonregenerating organ, clinicians are reluctant to apply these studies directly to humans given paucity of clinical data.

## Parallel Regenerating Organ: Liver

The one organ in the human body, where there is little debate about the regenerative potential, is the liver. Traditionally, as it

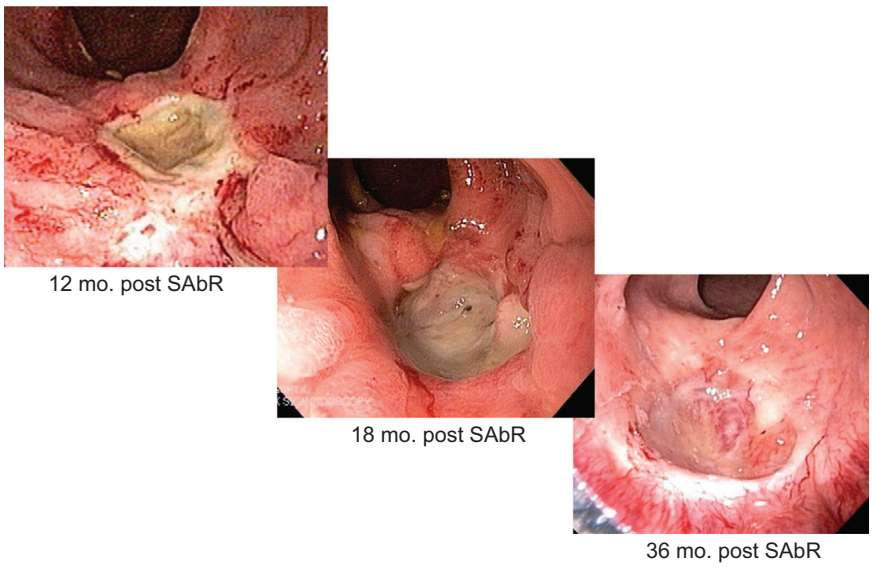


**Figure 3** Anterior rectal wall injury in a patient in whom the SAbR wound failed to repair. Chronic wound and fibrosis occurred in the first 12-24 months after therapy. This patient had a diverting jejunostomy at 24 months after SAbR.

was deemed to be a parallel organ, a critical volume constraint has been used to try to minimize the risk of toxicity to a dose that was thought to be tolerable. In many of the clinical experiences, including a prospective study, critical volume constraints of sparing greater than one-third of the "native" organ volume from receiving a critical dose (eg, $<700$ cc receiving 15 Gy in 3 fractions in this study) is typically employed to minimize risk.[46] The "native" organ is that unaffected by disease or surgical removal for an otherwise healthy adult of that sex and body habitus. Given the regenerative property of this organ, one would expect not to have the same concerns of migration distance thresholds limiting clonal repopulation as a prerequisite for repair. In conventionally fractionated radiotherapy experience, dose-volume effect for toxicity has been reported.[47] Interestingly, when reviewing the literature, very few episodes of RILD have been reported in studies of SAbR involving the liver in patients without significant baseline liver disease.[48] For example, in a phase I/II study, there were no incidence of RILD reported.[46] In another study of patients with hepatocellular carcinoma treated with SAbR, dose relationship of 18 Gy or less being delivered to at least 800 mL of the organ was found to minimize the risk of Child-Pugh class progression.[49] However, when considering the principles of regenerative wound healing, it would be imperative that there are sufficient healthy uninjured cells with sufficient amount of stem cells for effective regeneration to occur. In both conventional and SAbR experiences, patients with underlying baseline liver disease are found to be at higher risk for radiation-induced liver toxicity. In a phase I dose-escalation study of SAbR in 3 fractions,[50] tolerance to SAbR was decreased in Child-Pugh Class B patients even when the same critical volume constraints were used with Child-Pugh Class A patients, where no dose-limiting toxicity was seen.

Finally, a recent study calls into caution the importance of avoiding dose to adjacent or embedded serial organs or both that are critical to functionality of the liver. Reminiscent of the experiences in the central lung, there are suggestions of increased risk of toxicity with increasing exposure of central biliary tract region to increased dose of SAbR.[51] In this series, 21.5% grade 3 or higher toxicity was reported. This toxicity was associated with a biologically effective dose (using $\alpha$-$\beta$ ratio of 10) exceeding a specified volume of a critical area ($V_{BED10}$ 40 Gy $\geq$ 37 cc, and $V_{BED10}$ 30 Gy $\geq$ 45 cc to the 15 mm expansion from the portal vein, which was felt to represent the central biliary tract, was associated with toxicity). This suggests once again that within parallel structures, injury that is more reminiscent of a serial injury can occur due to association of serial nonregenerative architecture in close proximity to the parallel organ.

## Parallel Nonregenerating Organ: Lung

Lung is an organ thought to be classically defined as having functional subunits that are of parallel architecture and generally thought to have little or no capacity for regeneration. This notion is being challenged, with a case report of a patient who appears to have demonstrated new lung growth after pneumonectomy,[52] and there are significant preclinical research efforts being made in the field of stem cell research attempting to elucidate potential methods of inducing lung regeneration.[22] However, most clinical studies to date would support the notion that lung behaves as a parallel nonregenerating organ as it pertains to its response to injury. Therefore, even at lower doses, critical injury is likely to occur, but owing to its parallel architecture of redundancy of function, a critical volume of functional subunits would need to be injured to cause clinically apparent toxicity. It is, therefore, predicted that there would be less dependence on wound healing factors and clonal repopulation to help mitigate the risk of serious toxicity given the parallel nonregenerating properties of this organ. Clinical data would support this notion.

When only a small volume of lung parenchyma is treated with a high dose of radiation that would certainly inflict often nonreparable injury, clinical tolerability is seen due to the redundancy of homogeneous function afforded by the parallel architecture of this organ. As proof of principle, small ($<5$ cm) peripheral lesions were able to be treated to a higher than expected dose using SAbR in the phase I/II studies.[53] Furthermore, with the exception of experiences from centrally located tumor,[54] lung SAbR is generally thought to be well tolerated with a fairly low incidence of grade 3+ toxicity reported.[55] Interestingly, in the initial dose-escalation experiences, treating tumors exceeding 10 mL of gross tumor volume was shown to demonstrate an 8-fold increased risk of high-grade toxicity.[54] This seems to support the notion that SAbR lung toxicity is not likely to occur as long as there is sufficient functional reserve remaining, primarily achieved by avoidance of a large area of functional lung from the cytotoxic effects of high-dose radiation. Experiences from central lung tumors also highlight the importance of appreciation of potential for injury that can occur when serial organs in close proximity to the lung are exposed to critical doses of radiation.[54] These structures include central airway structures, esophagus, and the large vessels. In another experience, 8 of 9 patients with central tumors treated to 40-60 Gy in 3-4 fractions on consecutive days demonstrated partial or complete bronchial stricture and secondary loss of normal lung volume. Median time to bronchial stricture was 20.5 months.[56]

## Assessment of Wound Healing Properties in Considering Potential for Increased Risk of SAbR-Related Toxicities

### Angiogenesis

An important aspect of wound healing relies on recruitment of angiogenic factors to permit growth of new blood vessels into the wound. Given SAbR's capacity to produce a wound, impairment of angiogenesis may lead to further risk of increased toxicity by impairing the wound healing process. Therefore, it would be prudent to exercise caution when it

relates to the use of antiangiogenic factors for cancer therapy, and given that angiogenesis may play an important aspect of wound repair in a delayed manner, use of antiangiogenic agents even at a time point long after SAbR has been concluded, may still pose an increased risk by impairing wound healing.

There are several clinical studies and case reports suggesting potential for increased toxicities with SAbR.[57] One of the larger series comes from Mayo Clinic, where 74 patients treated to the abdominal region with an SAbR dose of 50 Gy in 5 fractions of whom 20 patients also underwent (VEGFI) therapy within 2 years of SAbR were reviewed.[58] Owing to similarity of dose and fractionation used in our prostate SAbR experience, we will highlight this series as it pertains to our hypothesis that wound healing repair inhibition may be a critically important determinant of serious toxicities. Of the 74 patients in this series, 9% developed serious bowel injury, all of whom had received VEGFI therapy within 13 months of completion of SAbR, and 5 of these patients received VEGFI within 3 months of SAbR. Furthermore, 38% of patients who had received VEGFI therapy within 3 months of SAbR developed serious bowel injury, compared to a historical standard of 1%-2% rate of bowel perforation reported with VEGFI therapy. No patients treated with SAbR without VEGFI therapy developed serious bowel injury. Interestingly, although dosimetric analysis in view of potential clonal repopulation and wound repair was not performed, it was interesting to note that no patients with bowel max dose of 18 Gy developed serious bowel injury. By our estimates, 18 Gy in 5 fraction would be far below the threshold dose of 24 Gy in 5 fraction that we had hypothesized would lead to greater than 90% stem cell depletion based on preclinical modeling.[12] Therefore, in this group, any acute injury may have been healed via clonal repopulation, and therefore less likely to have manifested a symptomatic injury. Interestingly, the 7 patients who had serious bowel injury in their series had maximum bowel doses ranging from 18.3-46.2 Gy in 5 fractions, with 4 of these patients having max bowel dose below 39 Gy (dose at which we found stem cell depletion to be $>99.9\%$, and requiring migration of adjacent stem cells to be recruited for wound healing to occur). This would suggest that when such patients with reparable wounds are exposed to antiangiogenic agents, this may further impair the wound repair that may have been otherwise feasible.

In patients expected to be treated with antiangiogenic agents, we may need to consider stricter dose recommendations to avoid late bowel toxicity. In our prostate SAbR series, the rectal ulceration seen in patients treated to 45 Gy in 5 fractions took weeks to months for full resolution.[12] Therefore, it may be worthwhile to inspect the bowel that has been exposed to SAbR with endoscopy if feasible, to ensure that there is no obvious nonhealing wound remaining, before initiation of VEGFI therapy.

However, one would suspect that the use of VEGFI should have less effect in patients treated with organs at risk that are primarily parallel regenerating or nonregenerating given that these toxicities are less directly related to wound repair issues, as it is expected that these organs will be clinically tolerant of SAbR as long as threshold volumes are not exceeded. In support of this notion, use of stereotactic radiosurgery (SRS) in a parallel nonregenerating organ (brain), for treatment of recurrent gliomas, and adjuvant bevacizumab was retrospectively analyzed at Duke University, with suggestion of good tolerance to this regimen.[59] This led to a prospective study of SRS and concurrent bevacizumab at the same institution, without report of excessive toxicity.[60] Similarly, investigators from China employed SRS followed by adjuvant bevacizumab in patients with brain metastases with extensive cerebral edema, without mention of excess toxicity.[61]

Experience of spine SAbR from Cleveland Clinic, with concurrent tyrosine kinase inhibitors that included patients treated with VEGF inhibitors in renal cell carcinoma metastases did not demonstrate increased toxicity. This suggests that serial nonregenerating organs, with less reliance on wound healing after SAbR, also may be less likely to have increased toxicity to SAbR as long as SAbR parameters for critical dose are respected.[62]

In a prospective clinical study of liver SAbR concurrent with the VEGFI sorafenib, significant bowel toxicities were reported.[63] Therefore, even when treating tumors involving primarily a parallel nonregenerating organ such as the liver with SAbR, one must be mindful of other neighboring organs in close proximity that could be affected by systemic agents that could impair wound healing.

## Immune Suppression

Another important factor in wound healing and repair involves recruitment of immune factors to the site of injury. Therefore, patient factors contributing to immune suppression, or chronic use of medications or agents that impair immune response severely, may be hypothesized to lead to wound repair inhibition, particularly if occurring concurrently, or during the earlier period following SAbR, given the role that immune mediators play in the earlier phase of injury repair. This would be particularly relevant in serial regenerating organs due to the potential for catastrophic outcome due to the serial nature of the injury. In our experience, during our phase I prostate SAbR study, one transplant patient who was on immunosuppresants at the time of SAbR developed significant high-grade rectal toxicity after 50 Gy in 5 fractions.[28] This was also the only patient who experienced high-grade toxicity in this phase I cohort. Interestingly, this patient's transplanted kidney was dysfunctional but the patient was being treated with immunosuppresants to avoid graft vs host problems before the SAbR. Therefore, after the toxic event, when the patient's antirejection medications were withdrawn, his symptoms improved. Given these concerns, amendment was made to this clinical protocol excluding enrollment of patients on immune suppressants.

A series from Washington University and Mayo Clinic of 28 patients undergoing SAbR for inoperable HCC has been reported.[64] Following standard liver constraints, and with prescription doses ranging from 40-55 Gy in 5 fractions, 2 occurrences of grade 5 toxicities were reported. One of these 2 patients had primary sclerosing cholangitis with a renal transplant history and who was on immunosuppressant medication

(Tacrolimus).[65] This patient developed RILD, which progressed to hepatic failure and death.[64] Dosimetric parameters for liver constraints in this patient were met. However, when considering SAbR as the source of the injury, in the setting of a likely chronic fibrotic state and a less than healthy liver, use of immune suppressants that may impair recruitment of immune mediators necessary for wound healing may have led to a nonhealing wound. Interestingly, in both experiences, patients were actively immunosuppressed during and immediately after the SAbR, a time duration, when recruitment of immune mediators would be deemed to be important for the wound healing process (Fig. 1).

There is otherwise a paucity of reports of clinical experiences of the use of SAbR in immune-compromised patients to further support this hypothesis. This is likely due to patient selection, as most investigators on or off clinical trials may be hesitant to offer SAbR to immune-compromised patients. Outside of a clinical study, we would recommend exercising caution in the use of SAbR in these situations, particularly when serial regenerating organs (eg, bowel) are in close proximity to the treatment site.

## Chronic Fibrotic States

In a phase I dose-escalation study of SAbR in 3 fractions,[50] tolerance to SAbR was decreased in Child-Pugh Class B patients even when the same critical volume constraints were used with Child-Pugh Class A patients, where no dose-limiting toxicity was seen.[50] The initial thought was that this was likely due to reduced reserve of less healthy cells remaining in the liver. However, another possibility is that the chronic fibrotic state of the injured organ led to a reduced regenerative capacity and a reduced ability to recruit appropriate wound healing factors to heal to a more functional form after sustaining SAbR injury.

There are also other examples of chronic fibrotic states demonstrating increased toxicity; Yamaguchi et al[66] reported on pneumonitis rates on patients treated with SAbR, with subclinical interstitial lung disease (SILD). Although there was no correlation of grade 2-5 pneumonitis with presence or absence of SILD, 3 patients who were found to have high-grade pneumonitis extensively outside of the radiation field all had SILD. There was a significant difference in occurrence of extensive pneumonitis between patients with and without SILD ($P = 0.0035$). Of these 3 patients, 1 endured grade 4 toxicity while another died due to this toxicity (grade 5). Patients with SILD who developed this toxicity did not have dosimetric profiles that could explain this event, suggesting that the chronic fibrotic state may have created a less hospitable environment for healing, and for tendencies toward a dysregulated inflammatory state leading to toxic events affecting organ outside of the primary irradiated volume.

# Conclusion

In our view, SAbR is a potent treatment that is potent on the cancer, and also potent on the normal tissue in its high-dose path, and likely to cause a SAbR-related "wound." To mitigate risks of clinically relevant toxicity, this "wound" needs to be repaired, and for this, multiple issues need to be considered. These include consideration of the architectural organization of the organ at risk in proximity to the tumor target. For parallel organ architecture, it is imperative that a critical volume of functioning parenchyma be spared the disabling dose. The volume needing to be spared is likely to be higher for the nonregenerating organ, such as the lung or salivary gland, and lower for a regenerating organ, such as the liver. For serial organs, the dogma has been that critical dose must not be exceeded, particularly for predominantly nonregenerating structure such as the spinal cord. For serial organs with capacity to regenerate, we would consider a critical volume in addition to the critical dose, beyond which wound repair may be impaired due to devitalization of this tissue. This critical dose would be typically reflective of the dose required to destroy vasculature, and stromal supportive structures, as opposed to the clonal stem cells. In addition, we would also consider a critical circumferential length that is treated to a critical dose, as exceeding this length may inhibit clonal repopulation due to excessive migratory distance that becomes difficult to achieve for the clonal stem cells from adjacent uninjured portion of the organ to travel to heal the injured region effectively. This critical dose may be different from the tissue devitalizing dose, as this dose would be impairing repair through a different mechanism, one that would involve depletion of stem cells to the region. In addition, we would have to carefully consider the use of concurrent therapies that could impair wound healing such as antiangiogenic agents and immune suppressants. Antiangiogenic agents may need to be avoided even much after SAbR has been completed, as delayed wound repair stages may be impaired by these agents, once again particularly in the serially organized organs.

Future research into mitigating SAbR toxicity might start with simply using a "sharper" beam (eg, charged particles) for better geometric avoidance but should also include approaches that exploit molecular mechanisms of wound healing for patients treated with SAbR. The latter could range from the use of strategies aimed at promoting wound repair by elucidating molecular pathways, to use of stem cells aimed at regeneration of organs without scar.[21] Preclinical studies of stem cells to regenerate organs injured with RT have been reported.[67-69] More importantly, efforts aimed at determining appropriate dose constraints based on predicted SAbR wound injury repair mechanisms for a particular organ would be a critically important step to moving our understanding of SAbR-related normal tissue tolerances forward. It is imperative that we go beyond the traditional view of DVH analysis, as DVHs would not reflect these biological processes. Such analysis can best be achieved from evaluation of experiences of prospective, dose-escalation phase I studies rather than post hoc mining of historically treated patients.

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