

# Challenges and opportunities of using stereotactic body radiotherapy with anti-angiogenesis agents in tumor therapy

Xiaowen Sun, Lei Deng, You Lu

Department of Thoracic Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

*Correspondence to:* Prof. You Lu, Department of Thoracic Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China. Email: radyoulu@hotmail.com.

## Abstract

Microvessels promote proliferation of tumor cells by delivering oxygen and nutrients, but rapid growth of tumors results in unmet demands for oxygen and nutrients, thereby creating a hypoxia microenvironment. Under hypoxic conditions, vascular endothelial cells (ECs) initiate the formation of immature and abnormal microvasculature. This results in leakage and tortuosity that facilitates tumor cell invasion, metastasis and resistance to cytotoxic treatment. Radiotherapy (RT) is a vital tumor treatment modality. Currently, more than 60% of patients with malignant tumors receive RT at certain points during their treatment. Hypoxia induced by abnormal microvessels can hamper the cytotoxic effect of ionizing radiation, particularly, stereotactic body radiotherapy (SBRT). Anti-angiogenesis (AA) agents are known to reduce and renormalize microvessels in tumors, and hence alleviate hypoxia. The combination of AA agents with SBRT may have a synergistic role in inhibiting the growth of tumors. On the contrary, large doses of irradiation may affect tumor microvessels itself. In this review, we aim to clarify the relationship between SBRT and microvessel formation in tumors. In addition, we provide a retrospective analysis of the combination therapy involving SBRT and AA agents in preclinical and clinical practice to define its role in anti-tumor treatment.

**Keywords:** Body radiotherapy, stereotactic; radiation effect; microvessel; agents, anti-angiogenetic

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## Introduction

Though stereotactic body radiotherapy (SBRT), also called as stereotactic ablative radiotherapy (SABR) or stereotactic radiosurgery (SRS), was developed over 60 years ago, due to serious collateral damage to surrounding normal tissue, SBRT could not be applied extensively in clinic until the arrival of precision radiotherapy (RT) about two decades ago. Both radiation delivery and image guidance are vital technological advances that enable delivery of large doses of radiation to tumors thereby reducing damage to surrounding normal tissues. SBRT has been approved as an important treatment modality in patients with cancers of the lung, liver, spine, kidney, pancreas tumors and

oligometastatic disease. Typically, SBRT involves the delivery of one or a few large dose fractions of 5 to 30 Gy per fraction (usually applied at 1 to 5 dose fractions). Variations of SBRT include a single relatively large dose RT, i.e. single fraction radiotherapy (SFRT), or more than one dose or hypo-fractioned radiotherapy (HFRT). The latter being a major paradigm (usually no less than 5.0 Gy per fraction) shift from conventional fraction radiotherapy (CFRT) which delivers several fractions of small doses ranging from 1.8 to 3.0 Gy.

While normal blood vessels aid the delivery of oxygen, nutrients and immune cells to every part of body, abnormal microvasculature within tumors play a critical role in its growth. Pro-angiogenic overwhelm anti-angiogenic factors

resulting in the proliferation and migration of vascular endothelial cells (ECs) resulting in abnormalities in organization, structure and function of the tumor microvasculature. The excessive ECs and abnormal perivascular cells become disorganized and form dilated, tortuous, hyperpermeable and dysfunctional microvessels. This impedes immune cell migration and function during angiogenesis, and makes the tumor more likely to metastasize. This abnormal microvasculature with poor transportation efficiency causes hypoxia, acidosis and high interstitial fluid pressure in tumors.

Here, we review the negative effects of abnormal tumor microvasculature on SBRT and comb through literature for a better understanding of the relationship between SBRT and microvasculature in tumors, and end by discussing the combination of SBRT with anti-angiogenesis (AA) agents for cancer treatment in preclinical and clinical practice, examining the current situation of this combination therapy in anti-tumor treatment.

### Microvasculature in tumor

Folkman in 1971 hypothesized that the most common pathway for new microvessel development in malignancy is angiogenesis. Under physiological conditions, pro-angiogenic factors and anti-angiogenic factors maintain a dynamic balance during the normal development of blood vessels. However, in malignant tumors, this balance is perturbed by hypoxia. Excessive pro-angiogenic factors induce abnormal growth of microvessel, which results in poor transportation efficiency and intensifying hypoxia and acidosis within the tumor microenvironment.

Hypoxia had long been identified as a direct negative factor for RT since irradiation is dependent on the existence of molecular oxygen ( $O_2$ ) for its cytotoxic effects. In hypoxic microenvironments, free-radicals mediate DNA damage, since  $O_2$  is necessary to produce DNA damaging free radicals produced by irradiation (1). Previous studies have proven that the linear-quadratic (LQ) model overestimates tumor cell killing by SFRT/HFRT by 20%–50% (2,3). The differential properties of SFRT/HFRT and CFRT on subpopulations of hypoxic cells are the reason for this overestimation (3). Several cellular and molecular processes caused or intensified by hypoxia, including but not limited to, induction of cancer “stem cell” phenotype, tumor growth and genomic instability, epithelial to mesenchymal transition, invasion and metastasis, have been identified to affect tumor treatment modalities when subjected to RT (4).

### Microvasculature response to SFRT/HFRT/AA agents in preclinical tumor models

It remains unclear that with a similar biologically effective dose (BED) in LQ models, SFRT/HFRT kills fewer tumor cells directly compared to CFRT because of hypoxia, while SFRT/HFRT achieves better local control than CFRT (2,3). One thought is that microvessels may respond to SFRT/HFRT, which enhance the anti-tumor effect of irradiation.

In 2003, Garcia-Barros and his group discovered that high-dose SFRT (more than 8–11 Gy) facilitates apoptosis of ECs in a dose-dependent manner and normalize tumor vasculature (5). Then Fuks *et al.* observed that EC damage appears to be induced by both SFRT and CFRT. The different outcomes after irradiation between these two approaches may lie in the fact that EC apoptosis contribute significantly to tumor cell lethality in SFRT and EC damage induced by low-dose exposure of CFRT. This does not enhance tumor cell death effectively, as death signaling pathways in ECs are repressed by concomitant activation of tumor cell hypoxia inducible factor-1 (HIF-1) (6). A recent study came to the conclusion that using a pancreatic tumor model, irradiation with SFRT (24 Gy/1 fraction) could cause temporary vascular dysfunction and expression of HIF-1 (7). Lan *et al.* confirmed that SFRT/HFRT (both 12 Gy/1 fraction and 12 Gy/3 fractions) could reduce microvessel density (MVD) significantly in Lewis lung carcinoma (LLC) models (8). These results suggest that SFRT/HFRT may reduce MVD and normalize tumor microvasculature. However, more evidence is needed to explain the difference in mechanism in ECs responding to CFRT and SFRT/HFRT.

Compared to SFRT/HFRT, the mechanism of MVD reduction and microvessel normalization of AA agents in tumor is more explicit. AA agents can inhibit angiogenesis, normalize microvasculature and alleviate hypoxia by increasing vascular pericyte coverage, and reducing tumor hyperpermeability, vessel calibers, hypoxia and interstitial fluid pressure. Normalization of blood vessels occurs when there is a “window of opportunity” (4,9–11). An increase in transient perfusion during the acute phase (1 to 3 days after medicine infusion) progressively decreased tumor microvessel density on the 5th to 7th day post-AA agent therapy, resulting in decreased blood perfusion (9,12). Duration of this “window” is dependent on dose and potency of AA therapy.

In addition, microvessels may play a role in post-

SFRT/HFRT tumor progression. Lan *et al.* observed that tumor MVD increased along with tumor regrowth after 3 weeks of a single dose of 12 Gy irradiation (8). Furthermore, irradiated tumors secrete various cytokines to inhibit apoptosis in ECs, thereby preventing vascular damage and impairing the anti-tumor effects of irradiation. HIF-1 regulates cytokines such as vascular endothelial growth factor (VEGF), which have been shown to weaken the effects of RT (13). Moreover, irradiation (6 Gy, single dose) upregulates endothelial nitric oxide synthase (eNOS) expression and activity. This activates the nitric oxide (NO) pathway in ECs. NO signaling post-irradiation induces profound transformation of the EC phenotype to generate tumor angiogenesis (14). Moreover, post-irradiation microvessels regrowth may be triggered by irradiation-induced and caspase-3-mediated cell death in both human colon cancer and human glioma xenografts (15,16).

It is still controversial whether ECs originate from bone marrow-derived cells is the key process in the revascularization of post-irradiated tumors. In certain murine and human tumors, an increase in intratumoral SDF-1/CXCR4 pathway is activated by irradiation. This recruits myeloid-derived monocytes, particularly tumor-associated macrophages, which subsequently promote tumor regrowth (17,18). Further investigations indicated that myeloid-derived monocytes, recruited post-RT in glioblastomas facilitate vasculogenesis but not angiogenesis, which subsequently results in tumor re-growth (19). However, Kozin suggested that although tumor-associated macrophages and certain subgroup of monocytes promote post-RT tumor revascularization, some ECs in growing tumors may be derived from cancer stem-like cells through trans-differentiation (20).

AA agents may be more effective for the treatment of post-HFRT relapsing tumors than HFRT-naïve tumors in human tumor xenograft models (21). Various cytokines and cells have been demonstrated to play a role in regulating angiogenesis after SFRT/HFRT, which supports the use of AA agents for improved efficacy.

### Effects of SFRT/HFRT/SBRT with AA agents in preclinical and clinical studies

As mentioned earlier, SFRT/HFRT kills fewer tumor cells than CFRT due to the hypoxic microenvironment in tumors. AA agents may alleviate hypoxia to improve sensitivity of tumor cells to irradiation. Combination of AA agents might be effective with SBRT where microvessel redistribution plays an important role in post-SBRT

relapse. From another aspect, SBRT itself could reduce MVD and normalize microvessels in tumor. Therefore, it is important to explore whether a synergistic effect exists using a combination of SBRT and AA agents. This has been tested in various preclinical and clinical studies.

### Efficiency of SFRT/HFRT with AA agents in preclinical research

Using the preclinical LLC model, VEGF was induced after exposure to RT. Pre-treatment with angiostatin or a VEGF-neutralizing antibody before HFRT (20 Gy/2 fractions) was associated with a synergistic than an additive anti-tumor effect (22,23). Endostatin, an anti-angiogenic factor, showed disparate effects on tumor growth and hypoxia between high (MCA-35) and low (MCA-4) vascularized murine mammary carcinomas. The poorly-vascularized tumor (MCA-4) responded better to endostatin therapy than the highly-vascularized tumor (MCA-35) (22-24). In a follow-up study, the team found that in MCA-4 models, a combination of HFRT (6 Gy/5 fractions) and a monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2; DC101) inhibited tumor growth significantly when compared to the MCA-35 models (25). In addition, hypoxia-activated chemotherapy or using a HIF-1 $\alpha$  inhibitor enhanced the effect of SFRT (8 Gy or 10 Gy/1 fraction) in sarcoma models (26,27). Gao *et al.* determined that bevacizumab radiosensitizes non-small cell lung cancer (NSCLC) xenografts by inhibiting the repair of DNA double-strand break in ECs and re-normalizes the tumor microvasculature (28). Supplementing this observation, several other AA agents have been noted to enhance the effects of SFRT/HFRT (12,28-33).

### Efficacy of combined SBRT with AA agents in clinical trials

Nearly 100 clinical trials evaluating the combination of CFRT and AA agents have been performed over the last decade. The majority of these were phase I or II trials with most ending with disappointing results. However, two recent phase III trials (AVAGLIO and RTOG0815) demonstrated that bevacizumab improved progression-free survival (PFS) (AVAGLIO: 11 vs. 6 months; RTOG0815: 11 vs. 7 months) but not overall survival (OS) (AVAGLIO: both 17 months; RTOG0815: both 16 months) with CFRT (60 Gy/30 fractions) in patients with glioblastoma (34,35).

These trials raise the potential for combining AA agents with SBRT in the clinic. Although a number of AA agents,

mainly targeting VEGF or VEGFR, have been tested with or without chemotherapy in clinical practice, these agents were seldom combined with SBRT in phase III clinical trials.

Bevacizumab together with SRS/HFRT + temozolomide, achieved a PFS of 10.0–14.3 months and an OS of 16.3–19.0 months when used as a first line of therapy against glioblastoma multiforme (GBM) (36,37). Because irradiation-induced necrosis is higher in HFRT/SRS than CFRT and bevacizumab may reduce vascular permeability, rapidly reducing peritumoral edema and alleviating subsequent radiation necrosis, bevacizumab may amplify the effect of SBS in GBM (38). Two phase II clinical trials in newly diagnosed GBM patients compared “bevacizumab + HFRT + temozolomide” and “HFRT + temozolomide” and concluded that bevacizumab in combination therapy did not prolong PFS (12.8 vs. 9.4 months,  $P=0.58$ ) or OS (16.3 vs. 16.3 months) (39). The results did however indicate that bevacizumab offset the development of symptomatic radiation necrosis in small volume tumors (36), but it did not act as a radio-protective factor to these patients with large tumors after HFRT (37).

In two phase III trials (AVAGLIO and RTOG0815) in patients with newly diagnosed glioblastoma, using “CFRT (60 Gy/30 fractions) + bevacizumab + temozolomide” achieved the median PFS of 11 months for both and the median OS of 16–17 months. When the trials used HFRT/SBRT instead of CFRT (60 Gy/30 fractions), it did not make a significant difference in PFS or OS (16.3–19.0 months) (34,35).

After the initial radiation to the tumor bed, 72%–93% of GBM patients relapsed (40). The use of the combination of bevacizumab and HFRT (30 Gy/5 fractions) achieved promising outcomes in previously heavily treated GBM patients with the median tumor volume of 34 cm<sup>3</sup>: the overall response rate (ORR) was 50%, the 6-month PFS was 65%, and the median OS was 12.5 months (41). This trial provided a choice for GBM patients who relapsed. These outcomes were better than previous retrospective and prospective studies using either HFRT or CFRT without AA agents, excepting the trials that recruited patients with much smaller tumor volumes (42). In a single-institution retrospective study of high-grade glioma patients treated with CFRT (36 Gy/18 fractions) with concurrent bevacizumab, the OS (12.1 months) appeared to be similar when compared with those who received HFRT with bevacizumab, better than that of CFRT alone or CFRT with concurrent temozolomide (8.0 months) (43). However, this retrospective study did not provide the

target tumor volume, which is a recognized prognostic factor. Additional studies are needed to confirm this.

Oligometastasis (defined as five or less clinically detectable metastatic lesions from any primary site) signifies a limited tumor burden that is potentially curable with appropriate local treatment. The use of SBRT could benefit patients with liver or lung oligometastatic disease (44,45). Sunitinib in combination with SBRT has been used to treat patients with oligometastasis of head and neck, liver, lung, kidney and prostate tumors. Sunitinib combined with SRS to treat intracranial oligometastasis resulted in shorter median PFS than with SBRT to the extracranial lesions (4.8 vs. 12.2 months) (46–48). On the other hand, when compared with the results of a phase Ib trial for brain CFRT + sunitinib, the median PFS was 5 months, and the median OS was 8.8 months (49). We could infer that using SBRT or CFRT to brain did not make a difference in combination with sunitinib. Presumably, these combination trials involved different types of tumors, since sunitinib, as a single agent, was ineffective at controlling extracranial disease. The small sample size and possible biases may have led to misinterpretation of the results. In fact, patients with a large tumor burden were associated with worse survival prognosis when treated with SBRT alone. Patients with kidney or prostate primary carcinoma suggested improved OS when treated with SBRT and sunitinib (47,50).

Since sorafenib alone has been verified to improve the PFS and OS of patients with hepatocellular carcinoma (HCC) (51), it has been hypothesized that combining sorafenib and SBRT may increase the efficacy in patients with HCC or liver metastases. A phase I clinical trial, using “SBRT + sorafenib” in HCC patients, reported prematurely because of unacceptable toxicities with an estimated median PFS (12.1 months) and estimated median OS (26.3 months) (52). However, earlier phase I and II trials carried out using SBRT alone in HCC patients had a median PFS of 6.0 months and a median OS of 17.0 months (53). Another phase II clinical trial that used CFRT (40–60 Gy/20–30 fractions) with sorafenib in advanced HCC patients resulted in an ORR of 55%, a median PFS of 8.6 months and a median OS of 14 months (54). Two other clinical trials in patients undergoing SBRT with or without sorafenib for liver metastases indicated no differences in ORR (47% vs. 49%) nor median OS (20.9 vs. 17.9 months) (55,56).

### *Toxicities in clinical practices*

In general, SBRT with AA agents had a moderate effect for

certain tumors, such as heavily treated GBM, renal cell carcinoma and prostate carcinoma (41,47). However, grade 4 toxicities were seldom observed in patients receiving AA agents with CFRT, while the combination of AA agents and SBRT had much higher rates of serious toxicities (56-58). These toxicities were also observed in SBRT/SRS/AA agents alone or in combination therapy. These severe and relatively high-frequency toxicities are particularly gastrointestinal and hepatic toxicities in combination of SBRT with AA agents. Additional studies are needed to determine whether any particular agent is safer to use with SBRT than others.

Large doses of irradiation could cause damage to normal adjacent tissue. This usually results in severe inflammation, pain, dysfunction, radioactive gastritis, esophagitis, pneumonitis, liver dysfunction and intracranial radiation necrosis (45,55,59). Radioactive pneumonitis may progress to pulmonary fibrosis without effective anti-inflammatory treatment. Radionecrosis is due to SRS and usually occurs 6 months after irradiation. In a clinical trial using SBS + bevacizumab in GBM patients with large tumor volumes [median planning target volume 1 (PTV1) of 131 cm], there was an unexpected high risk of radionecrosis, which developed in 30 out of 35 patients. However, the incidence of radionecrosis in patients receiving CFRT + bevacizumab has not been reported for the two phase III trials (34,35).

AA agent-associated toxicities are numerous and mainly consist of cardiovascular and non-cardiovascular toxicities, which depend on the category of AA agents used. Hypertension and thromboembolic diseases are common cardiovascular toxicities induced by AA agents, while others include myocardial ischemia, left ventricular dysfunction and prolongation of the QT interval. Non-cardiovascular adverse effects include proteinuria, gastrointestinal toxicities, delayed wound healing, fatigue, stomatitis, thyroid dysfunction, myelosuppression, dysphonia and cutaneous effects. Additional rare or agent-specific toxicities include reversible posterior leukoencephalopathy, microangiopathic hemolysis, osteonecrosis of the jaw, hypoglycemia and pancreatic enzyme elevations.

Bevacizumab induces more gastrointestinal toxicity than other AA agents (60). This may be due to bevacizumab's ability to form immune complexes and induce vascular inflammation and clotting. Gastrointestinal toxicities are significantly reduced with a multi-fraction regimen (25-45 Gy in 3-5 fractions with median BED3 of 105.6 Gy; range, 66.7-180.0 Gy) compared with a single fraction (25 Gy in 1 fraction or BED3 of 233.3 Gy) for SBRT in pancreatic

tumor (61). Thus, adopting HFRT in addition to SFRT, and using the lowest BED, which provides high local control, and establishing an optimal dose should be investigated for concurrent or possible sequential AA therapy.

The most common grade  $\geq 3$  non-surgery-associated toxicities are diarrhea (12%, 6/50), pulmonary embolisms (12%, 6/50) when using "bevacizumab + capecitabine + oxaliplatin + HFRT (5 Gy/5 fractions)" as a neoadjuvant scheme for metastasized rectal carcinoma (62). However, when HFRT is replaced by CFRT in this neoadjuvant scheme, grade  $\geq 3$  toxicities were substantially reduced with only 2 of 55 patients developing deep vein thrombosis but having similar rates of diarrhea (12.7%, 7/55) (63). Lymphopenia (36%, 9/25), thrombocytopenia (12%, 3/25) and hyponatremia (24%, 6/25) were common toxicities for combination of bevacizumab + HFRT (6 Gy/5 fractions) for recurrent gliomas (41). A retrospective study found that esophageal fistula was a rare complication (5.8%, 3/52) in patients with irradiated volume within 2 cm of the esophagus. The fistulas occurred only when doses exceed 51 Gy and were only observed in the patients treated with AA agents post SBRT (64). Most of these hematopoietic toxicities were reversed by effective medication. Other rare toxicities observed were renal failure, wound healing complications, infections, ischemic stroke and central nervous system bleeding.

Sunitinib seems to be associated with less serious toxicities than bevacizumab. Patients with oligometastasis irradiated with SBRT experienced grade  $\geq 3$  toxicities including anemia (5.4%, 3/56), neutropenia (10.7%-14.3%, 6/56 and 2/14), thrombocytopenia (12.5%, 7/56), bleeding (5.4%, 3/56), liver function test abnormality (5.4%, 3/56), metabolic abnormality (3.6%, 2/56), fatigue (35.7%, 5/14), lymphopenia, rash, mucositis and hemolysis (7.1%, 1/14) (46,47).

Sorafenib with SBRT, used in hepatic metastasis and HCC patients, manifested the unexpected rapid reduction of liver volume (52,58). It might necessitate individualized assessments for probable liver volume reduction prior to SBRT in patients taking sorafenib. Significant gastrointestinal toxicities experienced with this combination may be attributed to gastrointestinal structures receiving larger doses of irradiation than planned because of liver deformation (58,65). However, combination of sorafenib with CFRT revealed acceptable toxicities, with 7.5% (3/40) of patients experiencing diarrhea and 5.0% (2/40) suffering from impaired liver function,

which subsequently lead to sorafenib reduction or discontinuation (54).

It is undetermined whether a “wash-out” period should be observed between AA therapy and SBRT. Presumably, a “wash-out” period after radiation is dependent on the half-life of the specific AA agent. The optimal timing, duration and dosing of AA agents when combined with SBRT also remain unknown. It is however not recommended that concurrent sorafenib with SBRT be a strategy for further clinical testing in patients with locally advanced HCC, particularly with irradiation of a large area of the liver (52). Sequential SBRT plus sorafenib (half dose for the first 4 weeks) in RTOG 1112 in locally advanced HCC is a strategy being currently investigated. *Table 1* lists the outcomes of completed clinical trials testing the combination of AA agents with SBRT.

Results of a search in “*clinicaltrials.gov*” using the phrases, “stereotactic body radiation therapy” or

“stereotactic ablative radiotherapy” or “stereotactic radiosurgery” for completed, not completed or terminated clinical trials involving both SBRT and AA agents are listed in *Table 2*. However, it is too early to conclude whether AA agents synergize the cytotoxicity of SBRT.

### Summary and perspective

More compact evidence is needed to confirm and optimize the combination of SBRT and AA therapy, as well as to determine optimal timing, dose and washout periods. A number of clinical trials are underway to answer these questions. Although preclinical models have indicated that SBRT with AA agents has a synergistic effect on efficacy, the treatment tends to induce more adverse events compared to CFRT with AA agents. Due to the small number of patients with successful outcomes, subsequent clinical trials may need to be more selective when

**Table 1** Reported clinical trials on combination of SBRT and AA agents

Trial	Type of tumor	SBRT (dose/fraction)	AA agent	Chemotherapy with combined	Line of therapy	Phase of trial/No. of patients	Toxicity (grade ≥4)	Median PFS (month)	Median OS (month)
Omuro <i>et al.</i> (36)	Glioblastoma	36 Gy/6 f	Bevacizumab, 10 mg/kg, d1, d15	Y	1st	II/40	Y	10	19
Ney <i>et al.</i> (37)	Glioblastoma	60 Gy/10 f	Bevacizumab, 10 mg/kg, d1, d15	Y	1st	II/25	Y	14.3	16.3
Gutin <i>et al.</i> (41)	Malignant gliomas	30 Gy/5 f	Bevacizumab, 10 mg/kg, d1, d15;	N	≥2nd	II/25	Y	GBM: 7.3; AG: 7.5	GBM: 12.5; AG: 16.5
van Dijk <i>et al.</i> (62)	Metastatic Rectal Cancer	25 Gy/5 f	Bevacizumab, 7.5 mg/kg, d1	Y	Neoadjuvant	II/50	Y	13	N/A
Tong <i>et al.</i> (48)	Oligometastases	50 Gy/10 f	Sunitinib, 37.5 mg qd, 28 d,	N	ND	II/25	Y	12.2	14.1
Kao <i>et al.</i> (47,66)	Oligometastases	40–50 Gy/10 f	Sunitinib, 37.5–50 mg qd, 28 d	N	ND	I/21	Y	4.6	N/A
Ahluwalia <i>et al.</i> (46)	Brain oligometastases	SRS	Sunitinib, 37.5–50 mg qd, 28 d	N	1st for brain metastases	II/14	N	4.8	11.7
Swaminath <i>et al.</i> (58)	Liver metastases/HCC	Focal: 33–54 Gy/6 f; Diffuse: 21.6 Gy/6 f	Sorafenib, 400–600 mg qd	N	ND	I/15	Y	N/A	N/A
Goody <i>et al.</i> (56)	Liver metastases	30–60 Gy/6 f	Sorafenib, 200–400 mg bid	N	ND	I/17	Y	2.9	22.3
Brade <i>et al.</i> (52)	HCC	30–50 Gy/6 f	Sorafenib, 200–400 mg qd or bid	N	ND	I/16	Y	20.5*	26.3*

SBRT, stereotactic body radiotherapy; AA, anti-angiogenesis; PFS, progression-free survival; OS, overall survival; Y, yes; N, no; GBM, glioblastoma multiforme; AG, anaplastic gliomas; N/A, not available; ND, not demanded; SRS, stereotactic radiosurgery; HCC, hepatocellular carcinoma; \*, estimated value.

**Table 2** Ongoing clinical trials involved combination of SBRT with AA agents on *clinicaltrial.gov*

Agent (identifier)	Type of tumor	Status	Phase of trial
Bevacizumb			
NCT02672995	Brain metastases	Recruiting	I
NCT01392209	Recurrent malignant glioma	Active, not recruiting	I
NCT02120287	Glioblastoma multiforme	Recruiting	II
NCT01925573	Recurrent glioblastoma	Recruiting	II
NCT02162537	Non-squamous NSCLC with brain metastases	Recruiting	III
Sorafenib			
NCT02989870	HCC	Recruiting	I
NCT01730937	HCC	Recruiting	III
NCT02794337	HCC	Recruiting	II
Apatinib			
NCT02998242	Symptomatic bony disease in prostate cancer	Recruiting	II
Sunitinib			
NCT02019576	Metastatic RCC	Recruiting	II
NCT00981890	Brain metastases	Active, not recruiting	I
Cabozantinib			
NCT02132598	NSCLC with brain metastases	Recruiting	II

SBRT, stereotactic body radiotherapy; AA, anti-angiogenesis; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

recruiting patients. We have listed some of the reasons why combined therapy has not achieved greater success in clinical practice to date as follows:

Firstly, only limited RT clinical trials and even fewer SBRT trials have been conducted. Of the 200 clinical trials supported by the American National Cancer Institute (NCI), only 11 involved RT (67). Nevertheless, brighter prospects lie ahead as a new era dawned with hypofractionation in general, and SBRT in particular, promising to give RT an edge over other cancer therapies.

Secondly, experimental designs and animal models need to be improved. In general, tumors in animal models are simple at genetic level and grow so rapidly that they tend to be more sensitive to AA agents than corresponding tumors in humans. Improvement of patient-derived xenograft models depends on the evolution of more humanized immune system in mouse. Thus, the findings with preclinical models may not corroborate with treatment setting in clinical practices (4).

Thirdly, safety should be given particular attention. Combined treatment may cause significant side effects, including prominent gastrointestinal or hepatic toxicities and other severe potential adverse reactions.

In the near future, more clinical trials on SBRT and AA combination therapy will reveal the benefit to patients with certain types of cancer. In addition, personalized medicine is warranted since tumor heterogeneity within a patient can lead to varied responses to combination therapy.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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