ROLE OF SRS/SBRT IN OLIGOMETASTATIC DISEASE

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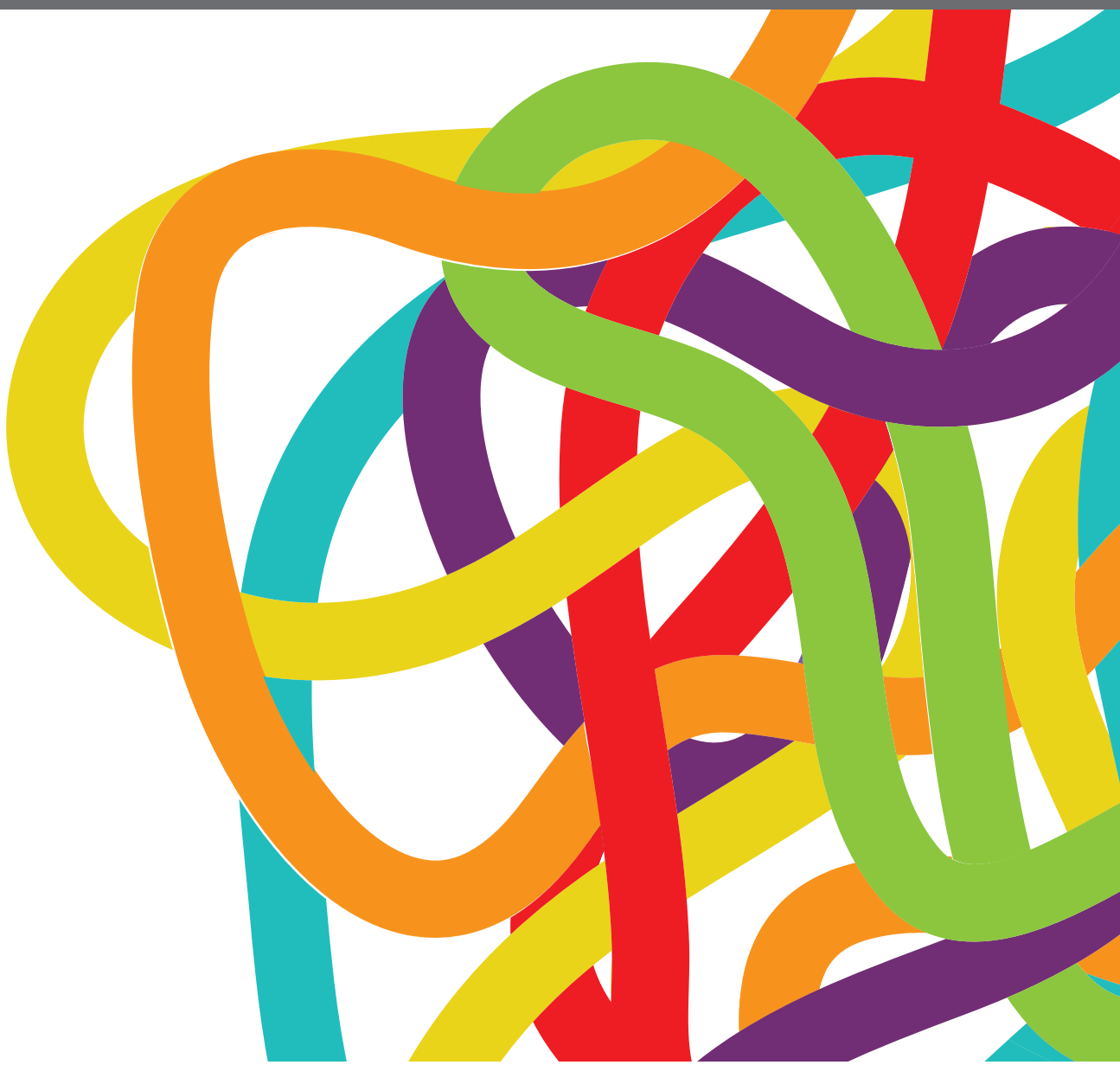

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ROLE OF SRS/SBRT IN OLIGOMETASTATIC DISEASE

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Oligometastatic disease represents an intermediate state between the early localized disease and widespread metastatic malignancy. Some patients with oligometastatic disease, treated by ablative therapies to all sites of metastatic disease, can achieve long disease-free survival and sometimes cure. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are accepted treatment options for these patients, achieving high rates of local control. While most of the studies report outcomes of SBRT for solitary oligometastasis, patients with oligometastatic disease might present with multiple concurrent lesions either in the same organ or in neighboring organs. There are few studies addressing the role of SBRT in patients with multiple concurrent oligometastases. Furthermore, these patients likely recur either in the same organ or at distance. Therefore, the need for retreatment with SBRT might be required. There remains a dearth of data regarding the re-irradiation after prior SBRT, toxicity, and dose volume constraints.

Particularly as it related to significant improvements in systemic therapies (including immunotherapies), it is likely that patients with widespread metastases can become oligometastatic after systemic treatments. While targeted, immune therapies and SBRT are increasingly used in patients with oligometastatic disease, their sequencing, interaction, and toxicities have not been studied and are poorly understood.

In this e-book, we discuss the state of the science of oligometastatic disease & SBRT in a variety of locations and outline potential future direction of research efforts.

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CASE REPORT
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Chemo-Radiotherapy of Oligometastases of Colorectal Cancer With Pegylated Liposomal Mitomycin-C Prodrug (Promitil): Mechanistic Basis and Preliminary Clinical Experience

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Hypo-fractionated radiotherapy and stereotactic body radiotherapy are viable options for treatment of oligometastases. A prodrug of mitomycin-C is under clinical testing as a pegylated liposomal formulation (Promitil) with an improved safety profile over mitomycin-C. Promitil was offered to two patients with oligometastases from colorectal cancer as radiosensitizer. Each derived durable clinical benefit from Promitil administered immediately prior to and following irradiation. Transient toxicity to normal tissues of moderate to severe degree was observed. Promitil appears to have potential clinical value in this setting.

HIGHLIGHTS

- Delivery of radio-sensitizing drugs with pegylated (long-circulating) liposomes is a pharmacologically rational approach which remains largely clinically untested.
- A mitomycin-c prodrug delivered by pegylated liposomes (Promitil) is activated by thiol groups, which are produced in excess by radiation-damaged cells, thus potentiating the radio-sensitizing effect of Promitil.
- Two durable clinical responses in patient with colorectal oligometastases to Promitil and radiotherapy suggest that this approach may be of value in cancer chemo-radiotherapy.

Keywords: colorectal cancer, oligometastases, liposomes, mitomycin-C, prodrug, radiotherapy, radiosensitizer

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the USA (1). During recent decades, advances in surgical technique, diagnostics, and new oncologic drugs have improved outcomes in metastatic disease. Radiation therapy may be used in metastatic colon cancer for palliation at the site of primary tumor or for metastatic lesions. Radiotherapy is effective for palliation in pelvic recurrence of rectal cancer (2, 3). Although hypofractionated treatments may

correlate with a higher risk of toxicity, careful selection of palliative patients minimizes those risks (4).

Adding chemotherapy to radiation can increase the anti-tumor effect of radiotherapy. Mitomycin-C (MMC) is a particularly attractive candidate for radiosensitization since it may target the hypoxic population of tumor cells which are considered to be relatively resistant to radiation when compared to well oxygenated cells (5). Promitil is a pegylated liposomal formulation of a lipidated prodrug form of mitomycin C (abbreviated as MLP), developed by Gabizon et al. (6). Promitil reduces MMC toxicity (7), and retains activity against multidrug resistant tumors (8, 9). Liposomes, as other nanoparticles and macromolecules, preferentially accumulate in tumors as a result of the enhanced permeability and retention effect (10). In a recent study (11), we have shown that radiation enhances MMC release from Promitil *in vitro*. Released MMC will sensitize further tumor cells to radiation damage. This background information on Promitil led us to hypothesize that Promitil may be an attractive therapeutic option in palliative therapy of patients with oligometastases treated with radiotherapy.

METHODS

Between 2015 and 2017, Promitil was given immediately prior and following RT to five patients with advanced cancer under individually-named patient compassionate approvals of the Israel Ministry of Health. We focus here on two of these patients[1], who suffered from advanced CRC with oligometastatic disease confined to active disease in retroperitoneal and pelvic lymph nodes. Both patients gave written informed consent to have their clinical history cases published. All Promitil treatments were given at Shaare Zedek Medical Center (SZMC) at dose levels between 1.0 and 2.0 mg/kg body weight. Promitil was infused as previously described (7), while radiotherapy was delivered at Hadassah Medical Center using Truebeam STX linear accelerator with daily on-board cone beam CT scan image guidance.

RESULTS

The first case is a 58-year old woman, diagnosed in June 2011 with stage 4 rectal adenocarcinoma, RAS-mutant type. On initial diagnosis, she had a rectal tumor and a single liver metastasis which were surgically resected by low anterior resection and partial hepatectomy, followed by a 4-month course of the FOLFOX-bevacizumab regime (9 cycles). In 2013 she developed a single metastasis in the lung, which was treated by SBRT (50 Gy in 5 fractions of 10 Gy), and shortly thereafter retroperitoneal lymphadenopathy. She was treated with standard fractionated radiotherapy to a small retroperitoneal field (42 Gy in 21 fractions of 2 Gy) and chemotherapy was resumed. Between June 2013 and June 2015, she was treated on and off with the FOLFIRI-bevacizumab regime. After further disease progression of lymphadenopathy in the pelvis (in distal location to previous radiation field), suspected recurrence in the liver, and a rise of tumor markers, she was enrolled into a phase 1 clinical trial with a combination of Promitil and capecitabine. After 3 cycles, there was no response by CT scan. Because of increasing pelvic pain, we offered the patient to continue with Promitil, off study, and give palliative radiotherapy for the pelvic recurrence (39 Gy in 13 fractions of 3 Gy delivered in October 2015). She went on to receive 4 more cycles of Promitil together with bevacizumab. The treatment resulted in significant pain relief, complete regression of affected nodes by FDG PET-CT (**Figure 1**) and a significant and durable drop of tumor marker levels (**Figure 2**). However, 3–4 months later, the patient developed painful hemorrhagic proctitis requiring weekly blood transfusions. There was a slow and gradual symptomatic improvement with less bleeding, yet, the patient chose to undergo a palliative abdomino-perineal resection and colostomy in April 2017. There was no evidence of residual tumor in the pelvis intra-operatively, nor in the surgical pathological specimen. FDG PET/CT in December 2016 showed a single focus of active disease in the liver. In September 2017, she had IMRT to the liver metastasis (33 Gy in 11 fractions of 3 Gy), but no further treatment with Promitil. Following her last course of Promitil in March 2016, she was without chemotherapy for nearly 2 years. Recently, she resumed chemotherapy due to systemic disease progression in another medical center. She is now surviving 34 months since her first exposure to Promitil and RT.

The second patient is a 67-year old male, diagnosed in February 2013 with T3N1 colon cancer, RAS wild-type, who underwent Lt. hemicolectomy (March 2013), and had adjuvant capecitabine and oxaliplatin. In March 2014, he recurred in a solitary mesenteric node which was surgically removed followed by a second round of adjuvant treatment with bevacizumab and capecitabine. In February 2015, he developed retroperitoneal lymph node metastases, and received single agent cetuximab until January-2016, when disease progression was noted in a group of porto-caval lymph nodes near the hepatic hilum. Cetuximab was discontinued and a combination of irinotecan-bevacizumab was given. However, there was no tumor response, and he was referred for standard fractionated radiotherapy on May 2016 (30 Gy in 10 fractions of 3 Gy) concomitantly with compassionate use of Promitil (5 cycles), which was given along with bevacizumab. He responded with a metabolic CR of the porto-caval hilar lymphadenopathy by FDG PET/CT (**Figure 3**). In November 2016, following upper abdominal pain, endoscopy revealed a radiation-induced ulcer in the duodenum, which healed slowly but completely with medical treatment (proton pump inhibitors). In September 2017, another group of retroperitoneal lymph nodes in the left para-aortic chain grew. The patient was referred for chemoradiotherapy with Promitil and received protracted retroperitoneal lymph nodes radiotherapy (44 Gy in 22 fractions of 2 Gy to paraaortic nodes and additional 10 Gy in 5 fractions of 2 Gy as boost to the involved nodes) with 2 more cycles of Promitil. For the last 6 months, he remains asymptomatic with ECOG performance status 0 and has been without any active treatment. His last FDG PET/CT shows persistent metabolic

[1]The other 3 patients are: 2 patients with urinary tract cancer and widespread metastases who received Promitil and RT for palliation of painful metastases, and 1 patient with locally advanced pancreatic cancer after failure to Folfirinox chemotherapy who received Promitil and SBRT.

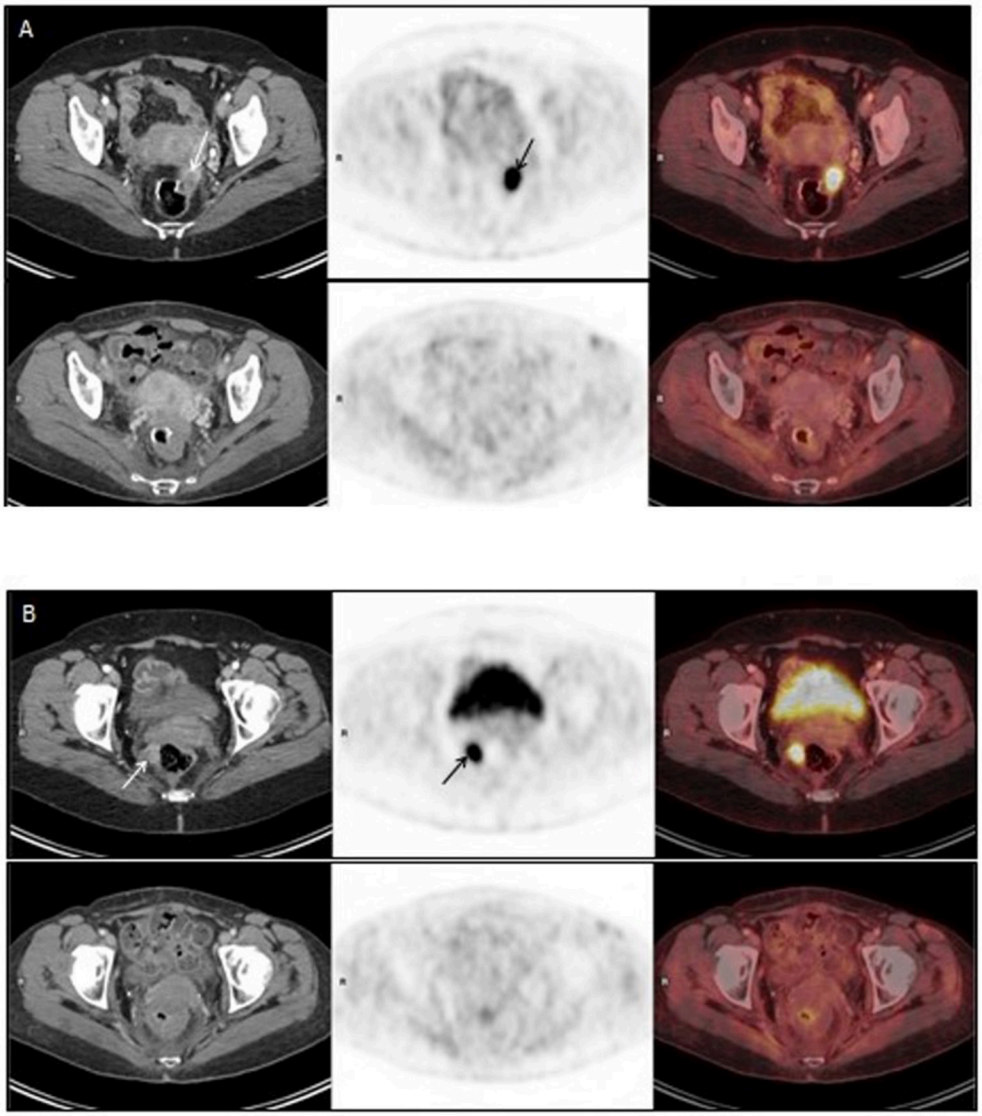

FIGURE 1 | (A,B) represent PET-CT images of two different pelvic metastases in the radiation field. Upper panel of **(A,B)**: PET/CT on 30Sep2015, before Promitil with radiotherapy. Lower panel of **(A,B)**: PET/CT on 28Dec2016, 15 months after Promitil with radiotherapy. Axial CT (left panel), FDG PET (middle panel) and fused FDG PET/CT (right panel) images of two metastatic lesions. The intense pathological uptake in a left nodule anteriorly to the rectal anastomosis (**A**, arrows) and in a right para-rectal nodule (**B**, arrows) has completely resolved with therapy on both PET and CT, along a prolonged follow-up (**A**,**B**, lower panel). Note post radiation rectal wall thickening on post-therapy CT images.

response in porto-caval nodes, size reduction of some of the irradiated lymph nodes, and overall mixed response of this retroperitoneal disease. His disease remains confined to abdominal lymph nodes with no visceral spread, and he is now surviving 27 months after first exposure to Promitil-RT.

DISCUSSION

While early stages of CRC have a relatively good prognosis, and many patients can be cured by surgery alone, the 5-year survival rate declines to 14% for patients diagnosed with metastatic disease. Hellman and Weichselbaum (12, 13) suggested that, in various cancer types, there is an initial oligometastatic phase characterized by the presence of isolated metastases, followed by a second metastatic phase typified by widespread dissemination. The term oligometastases indicates an intermediate state of few metastatic sites and low disease burden in the transition between loco-regional disease and widespread metastases.

Although systemic therapy represents the backbone of metastatic colorectal cancer management, surgical resection in selected patients with oligometastases has been shown to prolong survival, as observed for hepatic (14) and pulmonary (15) metastases. In a population-based study with 13,599 patients

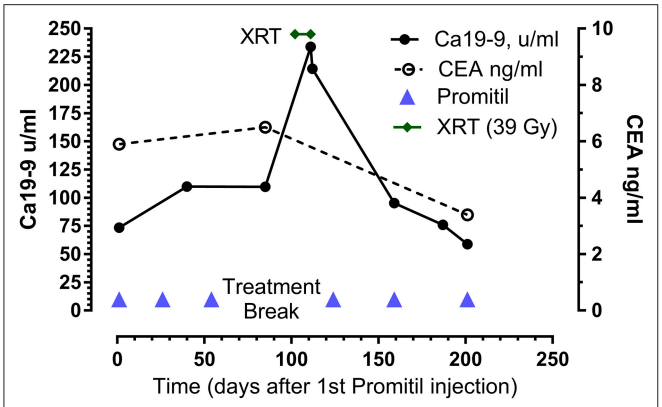

FIGURE 2 | Tumor marker response to Promitil with radiotherapy. Same patient as in **Figure 1**. Note the sustained decrease of CEA and Ca19-9 levels after chemo-radiotherapy.

from SEER[2] data, the 5-year overall survival (OS) was 32.8% and 10.5% among patients who did or did not undergo resection of hepatic metastases, respectively ($p < 0.0001$) (16). Far less data are available regarding surgery for less frequent sites of metastases, for example adrenal, ovarian, and retroperitoneal sites. There are no randomized data to strongly support surgical or locally ablative approaches in these scenarios.

Hypofractionated RT is an adequate option for palliative treatment of metastases and may also be effective in control of oligometastatic disease (17). Furthermore, stereotactic body radiotherapy (SBRT)[3] provides high rates of local control with minimal morbidity for oligometastatic disease and delivers a significantly higher biologically equivalent dose compared to conventional regimens. Two-year local control rates following SBRT for hepatic and pulmonary oligometastases of CRC are ∼80% for patients treated with high-dose regimens (18). Retrospective studies have indicated that SBRT for various metastatic lesions results in good outcomes with low morbidity, both in the curative and palliative setting (19–21). Yet, most strategies utilizing radiation with concurrent chemotherapy are still conducted in the setting of conventionally-fractionated radiation therapy.

Adding chemotherapy to radiation can increase the anti-tumor effect of radiotherapy. This is standard therapy in the neoadjuvant setting for rectal adenocarcinoma and for the definitive therapy of tumors of the esophagus, head and neck, anus, as well as uterine cervix and specific stages of gastric and non-small cell lung cancer. Mitomycin C (MMC) is a well-known radiosensitizer. As a DNA crosslinking agent, MMC forms DNA adducts that hinder the ability of cells to repair radiation induced DNA breaks (22), thus increasing the anti-tumor effect. A landmark phase-III trial showed that adding MMC to radiation in the treatment of anal cancer led to better colostomy-free survival and disease-free survival and was also associated with improved 5-year overall survival (78.3 vs. 70.7%, $p = 0.026$) over neoadjuvant cisplatin and 5-FU followed by chemoradiation with cisplatin (23). MMC is a particularly attractive candidate for radiosensitization since it may target the hypoxic population of tumor cells which are considered to be relatively resistant to radiation when compared to well oxygenated cells (5).

Promitil reduces MMC toxicity as shown in humans in a phase 1 study (7) and retains activity against multidrug resistant (MDR-1 type) tumors (8, 9). Its pharmaceutical ingredient is MLP, a prodrug of MMC, which consists of a conjugate of MMC linked to glycerol lipids through a cleavable dithiobenzyl bridge and requires cleavage of the disulfide bond by reducing agents for conversion of the inactive MLP prodrug to active MMC. The MLP prodrug is entrapped in the lipid bilayer of long-circulating pegylated liposomes of similar composition to that of the well-known Doxil/Caelyx formulation (24, 25). Liposomes, as other nanoparticles, preferentially accumulate in tumors as a result of the enhanced permeability and retention (EPR) effect (10). Reducing agents are found in high concentrations within tumors (26).

In a recent study (11), we demonstrated that radiation enhances MMC release from Promitil *in vitro* by increasing the levels of thiol-reducing agents secreted from radiation-damaged tumor cells to the surrounding medium. Released MMC, in turn, will sensitize further tumor cells to radiation lethal damage. This bidirectional interaction of radiation and Promitil will conceivably enhance the synergy and final therapeutic efficacy of this combination, particularly if we consider the EPR effect which will contribute to high accumulation of Promitil liposomes in the tumor bed. A graphical depiction of this mechanism of action is presented in **Figure 4**.

Indeed, *in vivo* studies in human tumor models of colon cancer indicate a superior anti-tumor effect of Promitil and radiotherapy (RT) over MMC or 5FU and RT (11). In this study, a single injection of Promitil potently sensitized colorectal tumor xenografts to fractionated RT; however, a single injection of equitoxic free MMC with or without 5-FU did not. In addition, animals treated with Promitil could receive more than twice the equivalent dose of MMC than animals in the free MMC group because of the reduced toxicity of Promitil, thus conferring an additional pharmacological advantage to the combination of Promitil and RT.

This background information on Promitil led us to hypothesize that Promitil may be an attractive therapeutic option in palliative therapy of patients with oligometastases. Herein, we report two patients with heavily pretreated metastatic colorectal cancer and a clinical course characterized by a persistent oligometastatic phase and a major and lasting clinical benefit after treatment with Promitil and RT.

While the presence of any type of metastases from most solid tumors are generally regarded as being representative of disseminated cancer and are not considered to be curable, evidence has emerged that the subgroup of patients with oligometastases can be cured or at least palliated for long periods of time by resection or ablation of these lesions. This theory provides a rationale for pursuing aggressive local management of oligometastases in well selected CRC patients.

[2]Surveillance, Epidemiology, and End Results Program (SEER) Program of the National cancer institute, National Institute of Health, US.
[3]SBRT is also known as Stereotactic Ablative Radio-Therapy.

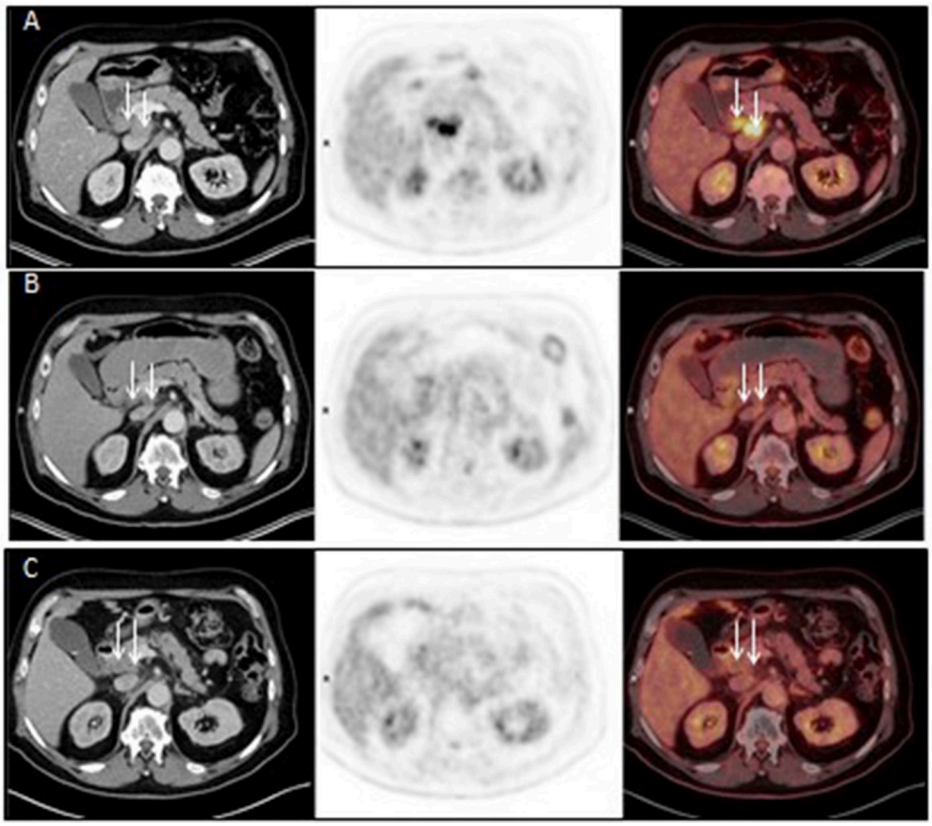

FIGURE 3 | Axial CT (left panel), FDG PET (middle panel) and fused FDG PET/CT (right panel) images before Promitil with radiotherapy (**A**, 07Apr2016), 3 months after Promitil with radiotherapy (**B**, 04July2016), and on a recent re-evaluation 22 months later (**C**, 19Feb2018). Initial pre-therapy intense pathological uptake in two adjacent porto-caval lymph nodes (arrows) resolved after therapy, with significant interval reduction in lymph nodes dimensions.

Pharmacokinetic advantages of Promitil include increased circulation time of the prodrug vs. free MMC (t½ in humans ∼24 h for prodrug and <0.5 h for MMC), enhanced accumulation within tumors by the EPR effect, and controlled sustained release depending on the rate of prodrug activation and/or liposome breakdown. Extended intra-tumoral release of activated prodrug from nanoparticles may be particularly important in fractionated radiation schedules to enable synergistic effects.

Promitil has reduced systemic toxicity when the dose of its active ingredient, MLP, is compared to molar-equivalent doses of free MMC in animals and in humans (7, 27). This feature is probably related to various factors. First, pegylated liposomes are very stable and leakage in plasma of MLP prodrug or cleavage to MMC is negligible (7, 27). Second, tissue distribution of the liposomal prodrug may relatively spare some tissues (e.g., kidney, lung, bone marrow) that are sensitive to MMC damage. Third, prodrug cleavage and release of MMC occur gradually, thereby reducing the damage of acute exposure.

It should be noted that the two patients described here developed radiation-induced hemorrhagic proctitis and duodenal ulcer, respectively. This suggests a radiation-enhancing effect of Promitil, but it is also a warning of potential toxicities on normal tissues of this potent combination. These are worrisome complications for the safety profile of this combination although, in the proctitis case, bevacizumab treatment may have contributed to toxicity by inhibiting tissue repair. As mentioned in Methods, we treated another 3, non-CRC, patients with Promitil and RT. In none of these patients we observed toxicity to normal tissues. Two of these patients with widespread metastases of urinary tract cancer died within 6 months after RT. The 3rd patient with locally advanced pancreatic cancer responded extremely well and is alive 16 months after RT with local control in the irradiated site but tumor outgrowth outside the field margins. At any rate, given some concern for increased normal tissue toxicity, close attention to the technique, dose, and fractionation of radiotherapy should be paid in future trials of RT with Promitil. In summary, the triggered release of Promitil by radiation combines the pharmacologic benefits of rapid drug onset and prolonged drug release, making it a potent radiosensitizer.

These are the first reported cases of RT given with Promitil treatment. Based on these encouraging clinical cases, and on the strong preclinical rationale, Promitil is an attractive tool for chemoradiotherapy of patients with

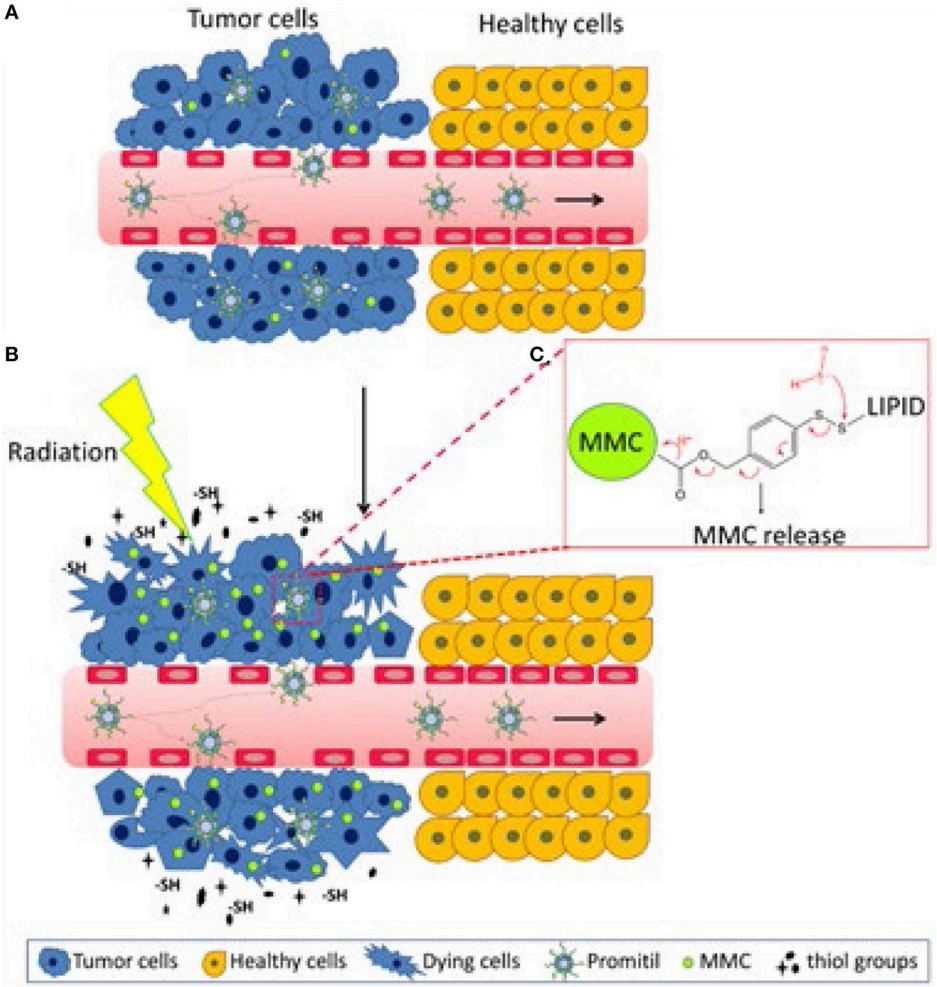

FIGURE 4 | Graphical representation of the proposed mechanism of radio-sensitization by Promitil. The process includes the following steps in sequence. **(A)** Promitil reaches tumor site via EPR effect, limited prodrug activation and MMC release takes place in tumor initiating the radio-sensitizing effect. **(B)** Radiation-damaged cells secrete SH compounds that activate the prodrug MLP amplifying the generation of MMC and subsequent radiosensitizing effect by alkylation and formation of DNA adducts. **(C)** Schematic drawing of the prodrug MLP with the disulfide bridge sensitive to free thiols and leading to the release of MMC. Adapted with permission from Tian et al. (11).

CRC oligometastases. To confirm these observations, a phase 1B clinical study to explore further the combined activity of Promitil and RT in palliative treatment of patients with advanced and/or metastatic disease has been recently launched.

ETHICS STATEMENT

The cases presented in this study were treated under the compassionate named patient approval procedure of the Israel Ministry of Health. All subjects gave written informed consent for treatment in accordance with the Declaration of Helsinki and our hospital ethical regulations. We confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

AUTHOR CONTRIBUTIONS

ET drafting the work and revising it for important intellectual content, acquisition, analysis, and interpretation of data. RB-S acquisition, analysis and interpretation of data. ES acquisition, analysis, and interpretation of data. RP and BWC revising the work for important intellectual content. IN, YT, and MG acquisition of data. PO revising the work for important intellectual content. AZW conception of the work, revising the work for important intellectual content. AAG conception and design of the work, acquisition, analysis, and interpretation of data, revising the work for important intellectual content, provide approval for publication of the content, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Hypofractionated Stereotactic Radiotherapy for Non-breast or Prostate Cancer Oligometastases: A Tail of Survival Beyond 10 Years

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Purpose and Objective(s): We sought to analyze the long-term follow-up of patients treated with hypofractionated, stereotactic radiotherapy (HSRT) for oligometastases from malignancies other than breast or prostate cancer.

Materials and Methods: From 2001 to 2006, 82 cancer patients with 1–5 radiographically apparent metastatic lesions (in 1–3 organs) from primary sites other than breast or prostate cancer, were enrolled on a prospective study of HSRT. Freedom from widespread metastasis (FFWM) was defined from date of enrollment until death, an event (i.e., widespread distant metastasis not amenable to local therapy), or last radiographic study. Local recurrence was scored as an event if pathologically confirmed or if a treated lesion increased by ≥20% using RECIST criteria. Prognostic variables were assessed using Cox regression analysis.

Results: The mean age was 61 ± 11 years, with a male to female ratio of 46:36. The most common metastatic sites were liver (50%), lung (48%), thoracic lymph nodes (18%), and bone (5%). Sixty-one patients (74%) had 1 involved organ and 18 (22%) had 1 lesion treated. The preferred dose-fractionation scheduled was 50 Gy in 10 fractions (52 patients). The median follow-up was 1.7 years. Eleven patients lived >5 years, and 6 lived >10 years. The 5-year OS, PFS, FFWM, and LC rates were 13.4, 7.3, 18.3, and 63.4%, and the 10-years OS, PFS, FFWM, and patient LC rates were 7.3, 6.1, 13.4, and 62.2%, respectively. A greater net gross tumor volume (GTV) was significantly adverse for OS ($p < 0.01$) and LC ($p < 0.01$). For FFWM, net GTV was not a significant factor ($p = 0.14$). Four patients remain alive at >13 years from enrollment and treatment, without evidence of active disease.

Conclusion: A small subset of select non-breast, non-prostate cancer patients with limited metastasis treated with HSRT are long-term survivors. Net GTV is a significant factor for tumor control and survival. Further research is needed to help better select patients most likely to benefit from local therapy for metastatic disease.

Keywords: oligometastases, radiotherapy, metastases, stereotactic radiation, survival

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INTRODUCTION

In 1995 Hellman and Weichselbaum hypothesized a "clinical significant state of oligometastases," in which metastases limited in number and extent represented a relatively indolent disease state before reaching full metastatic potential (1). It has since been postulated that oligometastases may possess unique genetic characteristics, and are potentially amenable to definitive, metastases-directed (i.e., surgery or ablative) treatment (2). The interest in metastasis directed therapy dates back decades (3, 4). In 1968 Rubin questioned "Are metastases curable?" in a JAMA editorial (5) in addition to writing a book "Solitary Metastasis" (3) in which localized therapies were discussed. In 1983, Peters, Milas, and Fletcher explored the concept of systemic therapy to sterilize occult metastatic disease, followed by radiation therapy to overt sites of disease as a curative treatment (6).

Systemic therapy remains the standard of care for metastatic disease. As the efficacy of systemic therapy continues to improve with the development of novel agents, durable tumor control becomes more important in patients with limited metastatic disease. Recent advances in radiographic and functional imaging, ablative techniques, and radiotherapy have again made the hypothesis of metastasis-directed therapy for oligometastases more compelling. Hypofractionated, stereotactic radiotherapy (HSRT), or stereotactic body radiation therapy (SBRT) if delivered in up to 5 fractions, is an advanced treatment technique enabling the delivery of high biologically effective doses to the target while limiting normal tissue volume receiving therapeutic doses (7). The high fractional doses of radiation are postulated to have the ability to overcome intra-tumor regional hypoxia as well as potentially stimulate an immune response (8), and have become an acceptable treatment for oligometastases.

There is a growing body of evidence supporting the use of radical irradiation for oligometastases (9, 10). The recently reported multi-national SABR-COMET, randomized 99 patients in a 1 to 2 ratio between standard of care ± SBRT ($n = 65$ non-breast, non-prostate cancer) with 1–5 oligometastases. SBRT significantly increased the median progression-free survival (PFS; 12 vs. 6 months $p = 0.001$); the median overall survival (OS) difference (41 vs. 28 months, $p = 0.09$) met the study's randomized phase II endpoint of $p < 0.20$ (11).

While breast and prostate cancer tend to have better outcomes, both overall and in the oligometastatic setting (12), several studies have shown potential benefits for oligometastatic therapy for other primaries. Gomez et al. randomized stage IV NSCLC oligometastatic patients with three or fewer metastatic lesions after first line systemic therapy to either local consolidative therapy with or without subsequent maintenance treatment, or to maintenance treatment alone in a randomized phase II trial. The study was terminated early after 49 patients were randomized, with the interim analyses showing a significant improvement in median PFS in the local consolidative group (11.9 vs. 3.9 months) (13). Iyengar et al. conducted a similar trial assessing consolidative radiotherapy in limited metastatic (primary plus up to 5 metastatic sites) NSCLC, and also stopped early after an interim analysis showed improved PFS for local consolidative therapy (9.7 vs. 3.5 months) (14). Studies of oligometastatic colorectal patients have long shown a survival benefit with resection of limited lung or liver metastases (15–17). There are now multiple series showing excellent outcomes with metastasis-directed therapy in lung, liver, adrenal, lymph nodes, and bone oligometastases (18–23), (23).

Long-term (10+ year) data on metastasis-directed radiotherapy for oligometastatic cancer are lacking. There are even more limited data for non-breast, non-prostate metastatic primaries. We previously published the survival and tumor control outcomes of 121 patients with five or fewer radiographically apparent metastases from any primary site (including 39 breast cancer patients, and no prostate cancer patients), metastatic to any organ, treated with HSRT with curative intent (24). We sought to analyze the 10-year outcomes of the non-breast, non-prostate oligometastatic patients treated with HSRT on a prospective Phase II protocol in an effort to better understand long-term outcomes and factors that may impact these outcomes.

METHODS AND MATERIALS

Between February 2001 and December 2006, 82 patients with one to five radiographically apparent metastatic lesions were enrolled on a University of Rochester Medical Center (URMC) prospective pilot study, using HSRT to treat limited oligometastatic disease (25). The URMC research subjects review board approved the study, and all patients provided written informed consent. The eligibility requirements included age ≥18 years, Karnofsky performance status (KPS) ≥70, and one to five extra-cranial metastases. Prior treatment of metastatic tumor (including radiation or surgery) did not exclude patients from the study unless the treating physician determined that radiation could not be delivered safely. Prior chemotherapy for metastatic disease was allowed. Four patients (each with fewer than five total metastases) also had brain metastases (six lesions among 4 patients) treated with single-fraction radiosurgery. The patients who experienced local recurrence after HSRT in one or more sites, or who developed additional metastatic disease, were allowed to undergo additional courses of HSRT (26). The net GTV represented the sum of each lesion's GTVs according to the contoured volumes on the planning computed tomography scan. The net GTV was calculated at SBRT planning; thus, previously resected metastases were not included in the net GTV. Likewise, changes in the tumor volume resulting from previous systemic therapy were not accounted for. The net GTV did not include oligometastases that developed, and were subsequently treated, after completion of the initial protocol HSRT.

HSRT Technique

The HSRT technique has been discussed in greater detail in previous publications (27–29) and briefly summarized here. During initial simulation and with all treatments, the patients were immobilized with a vacuum cushion, and the treatment setup was reproduced using a relaxed end-expiratory breath hold technique and the Novalis ExacTrac® patient positioning platform (BrainLAB AG, Heimstetten, Germany). Treatment planning was performed using the BrainSCAN system

(BrainLAB AG). The PTV was generated with a minimal GTV expansion of 10 mm in the craniocaudal direction and 7 mm in other directions. Treatment was prescribed to the 100% isodose line, and the PTV was covered by the 80% isodose line. HSRT was delivered using conformal arcs or multiple fixed coplanar beams, shaped with multileaf collimators. The protocol described a range of recommended prescribed doses for 3, 4, 5, 6, 8, and 10 Gy fractional doses(as described in detail previously, but allowed the treating physician discretion, in order to adhere to protocol mandated normal tissue dose constraints (30). The required normal tissue dose-volume constraints have been reported in previous publications (8, 27, 28). Because of various dose-fractionation schedules used, we also analyzed biologically equivalent dose (BED), using an assumed alpha-beta ratio of 10 Gy. Most (63%) of the 202 non-brain lesions were treated to 50 Gy in 10 fractions.

Endpoints

Widespread distant metastases are defined as distant progression not amenable (at the discretion of the treating physician) to resection or locally ablative therapy (i.e., SBRT, HSRT, stereotactic radiosurgery, radiofrequency ablation, and embolization) due to the bulk and/or number (generally more than 3) of metastases. The freedom from widespread distant metastasis (FFWM) and OS rates were calculated using Kaplan-Meier actuarial survival analyses. OS was defined from the date of enrollment until death or the last follow-up visit, and FFWM was defined from the date of enrollment until death, an event (widespread distant progression), or the last radiographic study. Lesion local recurrence was scored as an event if any treated lesion increased by $\geq$20%, using the Response Evaluation Criteria in Solid Tumors criteria (31), or local recurrence was confirmed pathologically. The treating physician would generally opt to follow with serial imaging, or obtain PET imaging (commissioned in 2005) if there was concern about post-radiation changes mimicking progression. Stata version 15.1 (StataCorp, College Station, TX), was used for all data analysis.

RESULTS

Patient Characteristics

The patient and tumor characteristics are summarized in **Table 1**. Twenty-four patients presented with metastatic disease during their initial diagnostic workup for cancer. For the remaining fifty-nine patients, the interval between initial diagnosis and metastasis was from 3 to 98 months (median 16 months). Fifty patients had a >6 month interval between initial diagnosis and metastatic diagnosis. The patients were generally referred for radiation if they were not candidate for, or declined, systemic therapy (21 patients); for disease progression after

TABLE 1 | Patient Characteristics at initial presentation of oligometastatic disease.

Characteristics	No. of patients (%)	Characteristic	No of patients (%)
Total no. of patients	82	Primary Histology	
No. alive at last follow up	4	Adenocarcinoma	50 (61%)
No. with no evidence of disease	4	Other	9 (11%)
Age, y		Squamous Cell Carcinoma	7 (9%)
Median (range)	61(41-88)	Sarcoma	7 (9%)
Mean±SD	61 ± 11	Carcinoid	3 (4%)
Male/Female	46/36	Hepatocellular Carcinoma	3 (4%)
Primary cancer		Renal Cell Carcinoma	3 (4%)
Colorectal	31 (38%)	Sites involved with metastatic disease	
Lung, head and neck, or esophagus	23 (28%)	Lung	39 (48%)
Liver, Pancreas	9 (%)	Thoracic lymph node	15 (18%)
Other	9 (11%)	Liver	41 (50%)
Sarcoma	7 (9%)	Pelvic or abdominal lymph node	2 (2%)
Renal	3 (4%)	Brain	4 (5%)
Sum of GTVs ml		Adrenal Glands	4 (5%)
Median (range)	32 (0.3–422)	Bone	4 (5%)
Mean ± SD	55 ± 8	No. of oligometastatic lesions	
Prior curative-intent local therapy	29 (35%)	1	22
Previously had > 5 metastatic lesions	16 (20%)	2	20
Reason for Treatment (Rx)		3	22
No systemic Rx for metastasis	21 (26%)	4	10
Disease Progression after systemic Rx	20 (24%)	5	8
CR/PR/SD after systemic Rx	20 (24%)	No. of involved organs	
New Limited metastasis	14 (17%)	1	61
Growing metastasis, >6 months after systemic Rx	7 (9%)	≥2	21

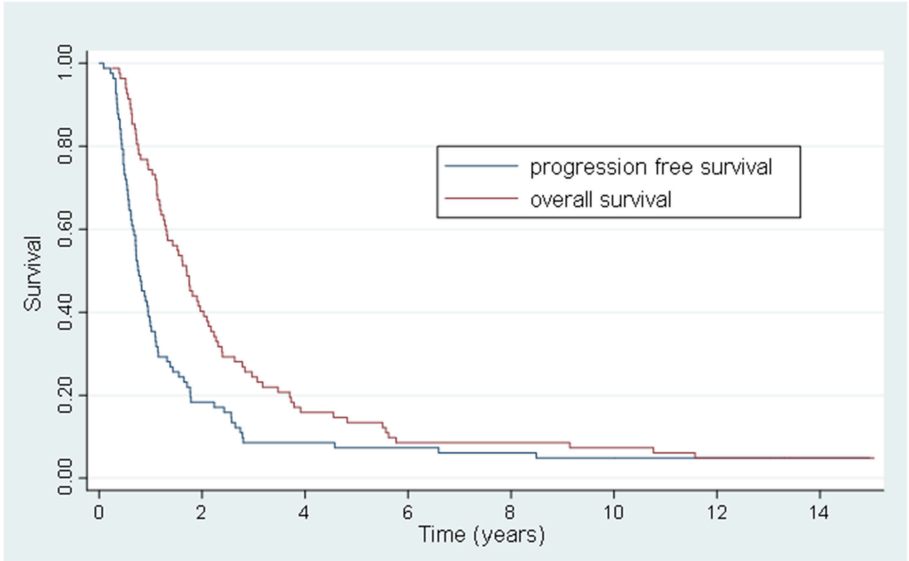

FIGURE 1 | Kaplan-Meier actuarial overall and progression-free survival.

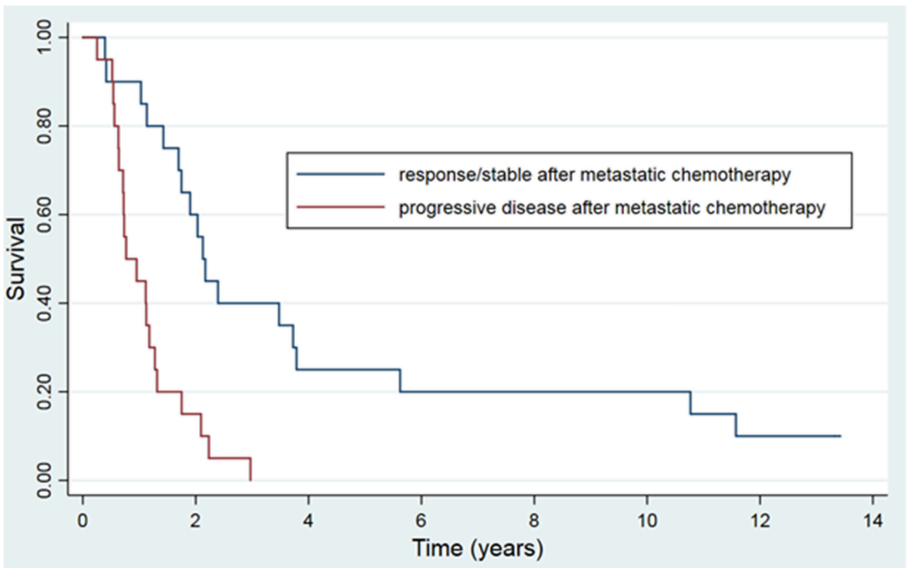

FIGURE 2 | Kaplan-Meier actuarial overall survival, grouped by response to systemic therapy prior to HSRT.

receiving systemic therapy (20 patients); after experiencing a clinical response or stable disease after systemic therapy (and therefore referred for consolidative HSRT) (20 patients); for local therapy of new limited metastasis (in conjunction with systemic therapy starting just before or after HSRT) (14 patients); or for growing metastases occurring >6 months after completing systemic therapy (7 patients). The median time from metastasis diagnosis to enrollment was 6.5 months. There were 61 patients that underwent systemic therapy at some point after metastases diagnosis, 40 of those patients underwent systemic treatment prior to HSRT. No patient received immunotherapy. There was radiographic progression after systemic therapy in 20/40 patients, and stable or regressive disease in 20/40 patients. The majority of patients were treated with 10 fractions to a total dose of 50 Gy (52 patients), with 58 patients getting a biological equivalent dose of 75 Gy or greater.

There were twenty-nine patients who underwent curative intent local therapy for metastases prior to enrollment including; 14 colon, 6 sarcoma, 5 lung, 2 utero-cervical, 1 parotid, and 1 ovarian primary cancer. Sixteen patients were diagnosed with

TABLE 2 | Characteristics of long-term (≥ 5 years) survivors.

Characteristics	No. of patients (%)	Characteristic	No of patients (%)
Number of patients	11	Number of involved organs	
Alive at last follow up	4	1	8 (72%)
Follow up of living patients (years)	13.3–15.1 (median 13.4)	2	3 (27%)
Deceased with survival ≥5years	7	Primary Histology	
Survival (years)	5.5–11.5 (median 5.8)	Adenocarcinoma	5 (45%)
Age (years)	57 (49–77)	Squamous Cell Carcinoma	1 (9%)
		Other	5 (45%)**
PRIMARY CANCER			
Colorectal	3 (27%)	Sum of GTVs (ml)	4-239 (median 15)
Lung, head and neck, or esophagus	2 (18%)	No. of involved organs	
Other	6 (54%)**	1	2 (18%)
		2–3	6 (54%)
Initial sites involved with metastases		4–5	3 (27%)
Lung	5 (45%)		
Thoracic lymph node	2 (18%)	Additional therapy for metastases	7 (63%)
Liver	6 (54%)	Local therapy for local recurrence	2 (18%)
Bone	1 (9%)	Local therapy for new oligometastases(es)	6 (46%)

**Other primary cancers/histologic types included sarcoma (n = 7), pancreas (n Z 4), hepatocellular (n Z 3), carcinoid (n = 3), urinary bladder (n = 3), renal (n Z 3), adrenocortical (n = 1), ovarian (n = 1), endometrial (n = 1), endocervical (n = 1), and melanoma (n = 1).*

≥ 5 metastatic lesions at some point before enrollment. These patients were treated with either systemic therapy or radiation, which ultimately resulted in ≤5 detectable metastases at the time of enrollment. Among 82 patients, there were 108 organs involved by metastases. Sixty-one patients (74%) had 1 involved organ and 18 (22%) had 1 lesion treated. The most common site for metastases was the liver (50%) with 21/41 of the metastases arising from a colon primary. The next most common sites involved were lung (48%) and thoracic lymph nodes (18%). Fourteen of the fifteen patients with thoracic lymph nodes metastasis also had lung metastases (**Table 1**).

Toxicity of HSRT

No patient experienced Grade 4–5 toxicity, and only 1 patient experienced Grade 3 toxicity of non-malignant pleural and pericardial effusion while undergoing liver HSRT as described previously (25). Lower grade toxicities were also described previously (25). No additional toxicity was reported in the subsequent follow-up period.

Follow-Up Duration

Follow–up ranged from 0.3 to 15 years (median 1.7). Eleven patients lived ≥5 years, the duration ranged from 5.5 to 15 years (median 10.8). Four patients were alive at the last follow up with no evidence of disease (median 13.4). There are seven patients deceased with ≥5 years survival (median 5.8), and two patients deceased with ≥10 years survival (median 11.1). For all patients who died, survival ranged from 0.3 to 11.6 years (median 1.6).

Survival Outcomes

The 5 and 10-year OS rate was 13.4 and 7.3% and the 5 and 10-year PFS rate was 7.3 and 6.1%, respectively (**Figure 1**). For the 20 patients that were treated with HSRT after progression of lesions after systemic therapy vs. the 20 patients who had stable or regressive disease, the mean survival was 1.1 years vs. 4.2 years ($p < 0.01$) and the mean PFS was 0.6 years vs. 2.6 years ($p < 0.01$) (**Figure 2**). The characteristics of long-term survivors (≥ 5 years) are shown in **Table 2**. Ten out of the eleven patients underwent systemic therapy, and 5 out of the 11 had systemic treatment prior to HSRT with stable or good response to chemotherapy. Four patients had prior curative intent local therapy, and 2 patients initially presented with >5 distant metastasis. There were no long-term survivors with more than 2 organs initially involved. At 10 years there were 6 patients that went on to develop either local (6) or distant (5) progression of disease with a PFS range of 1.7–9.3 years (median 4.8 years). There were 6 patients with survival ≥10 years from treatment, with 1 out of the 6 developing new liver metastasis at 9.4 years after initial treatment, and was retreated with local-directed therapy.

Among 78 deaths, 67 occurred in patients who had developed widespread distant metastases, which was likely the cause of, or major contributor to, death in these patients. One >10-year survivor died from progression of a second primary lung cancer. One patient died at 3 months, with evidence of local progression of liver disease. Three died from other causes, and 6 died from unknown causes (though most were likely from cancer progression). As most deaths were cancer-related, and the cause of death not available for all patients, cancer-specific survival was not analyzed.

TABLE 3 | Univariate and multivariate analyses of prognostic factors for overall survival and progression free survival.

Variable	OS	PFS
Age (y) (UVA Cox)	0.20	0.76
PRIMARY CANCER (UVA LOG RANK)		
Colorectal, *p*	0.71	0.31
Lung, head/neck, esophagus, *p*	0.28	0.49
SITE INVOLVED (UVA LOG RANK)		
Lung, *p*	0.97	0.66
Thoracic lymph nodes, *p*	0.77	0.95
Liver, *p*	0.85	0.39
Oligometastatic lesions treated UVA (Cox), *p*	0.77	0.91
involved organs (1 vs. 2-3) UVA (Cox), *p*	0.53	0.77
History of >5 metastases prior to enrollment (UVA Cox)	0.35	0.59
Systemic therapy for metastasis (UVA Cox)	0.20	0.25
BED 75 Gy or greater (UVA Cox)	0.10	0.14
History of prior curative local treatment (UVA Cox)	0.81	0.65
SUM OF GTV (CM^3)		
UVA (Cox), *p*	<0.01	0.01
UVA HR (95% CI) per 10 cm^3	1.04 (1.014–1.075)	1.04 (1.009–1.07)
MVA (Cox), *p*	<0.01	0.03
MVA HR (95% CI) per 10 cm^3	1.05 (1.014–1.099)	1.04 (1.005–1.09)

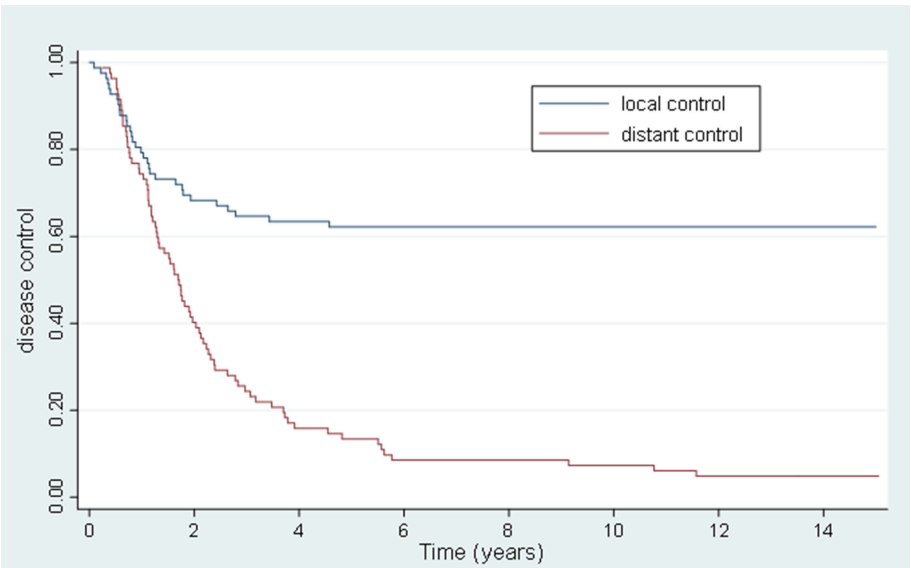

FIGURE 3 | Kaplan-Meier actuarial local (treated-metastasis) and distant control.

As expected, having widespread distant recurrence was a strong predictor for worse overall survival ($p < 0.01$, HR 3.41), but local recurrence was not ($p = 0.59$). Fifty patients had a >6 month gap between initial diagnosis and diagnosis of metastasis, but the time between diagnosis and metastasis did not predict for overall survival ($p = 0.15$). The hypothesis-generating univariate and multivariate analysis of other potential prognostic variables for OS and PFS are listed in **Table 3**. The net GTV in cm^3 (cc) was the only analyzed variable significant for OS ($p < 0.01$) and PFS ($p < 0.01$). We categorized each patient's net GTV in bins of 10 cm^3 to better characterize the significance. For OS and PFS, every increase of 10 cc in net GTV was predictive of a 4% increase in risk of death or progression. This variable was consistently significant for both survival outcomes on MV analysis. In contrast the total number of lesions treated, the site of metastasis, or the number of involved organs did not prove to be significant. On univariate analysis a BED of 75 Gy

or greater was borderline significant, though not significant with multivariate analysis.

Lesion Local and Distant Control

The 5 and 10 year local control (LC) was 63.4 and 62.2%, respectively, and the 5 and 10 year FFWM was 18.3 and 13.4%, respectively. **Figure 3** summarizes the long-term rate of disease control. The median time to local recurrence was 1.2 years. In comparison there were 69 patients that had distant recurrence also with a median time of 1.2 years. Forty-nine of the patients with distant recurrence had received some form of systemic therapy. The hypothesis-generating univariate and multivariate analyses of potential prognostic factors for disease control are listed in **Table 4**. Net GTV was shown to be highly significant predictor for local control ($p < 0.01$) with a HR of 1.09 for every 10 cc of net GTV for both univariate and multivariate analyses. A BED of 75 Gy or greater was significant on univariate analysis (HR = 0.37), though was not significant on multivariate analyses. There were 11/39 recurrences for patients with oligometastases lesions treated in the lung, and 20/41 recurrences for patients with liver lesions ($p = 0.16$ and $p = 0.12$, respectively). Nine out of the 31 recurrences had previously undergone prior curative intent local therapy, and eight patients initially had more than 5 metastasis (NS). The number of lesions treated also did not predict for overall survival. Systemic therapy during metastases diagnosis was the only variable that approached significance for FFWM on MV analyses ($p = 0.09$). Out of the 69 patients who had distant recurrence, 20 were unable to get systemic treatment. On UV and MV for both LC and FFWM the primary site of disease (colorectal, lung/esophagus/head and neck) were not significant.

TABLE 4 | Univariate and multivariate analyses of prognostic factors for local control and freedom from distant progression.

Variable	LC	FFWM
Age (y) (UVA Cox)	0.94	0.81
PRIMARY CANCER (UVA LOG RANK)		
Colorectal, *p*	0.38	0.30
Lung, head/neck, esophagus, *p*	0.20	0.50
SITE INVOLVED (UVA LOG RANK)		
Lung, *p*	0.16	0.48
Thoracic lymph nodes, *p*	0.52	0.91
Liver *p*	0.12	0.25
Number of oligometastatic lesions treated UVA (Cox), *p*	0.90	
Involved organs (1 vs. 2-3) UVA (Cox), *p*	0.78	
History of >5 metastases prior to enrollment (UVA Cox), *p*	0.59	0.98
Systemic therapy for metastasis (UVA Cox), *p*	0.25	0.15
MVA (Cox), *p*	0.45	0.09
BED≥75 GY		
BED≥75 Gy (UVA Cox), *p*	<0.01	0.15
UVA HR (95% CI)	0.37 (0.18-0.76)	
MVA (Cox), *p*	0.34	0.39
MVA HR (95% CI)	0.61 (0.23-1.68)	
History of prior curative local treatment (UVA Cox)	0.25	0.97
SUM OF GTV (CM^3)		
UVA (Cox), *p*	<0.01	0.14
UVA HR (95% CI) per 10 cm^3	1.09(1.05–1.13)	
MVA (Cox), *p*	<0.01	0.17
MVA HR (95% CI)	1.10 (1.04–1.16)/10cm3	

DISCUSSION

To our knowledge, this study represents the longest follow-up after HSRT for oligometastatic cancer. Specifically, in our study of 82 oligometastatic patients from "less-favorable" primaries (non-breast, non-prostate), we demonstrate that roughly 13% experience long-term (>5-year) survival, with six patients alive past 10 years. At last follow-up, there were 4 patients alive without any evidence of disease. Patients with a lower gross tumor burden fared significantly better in terms of OS, PFS, and lesion LC; however the tumor burden was not significant in predicting for FFWM. Patients whose metastatic lesions were treated with systemic treatment, before HSRT, and had demonstrated radiographic progression after systemic therapy fared significantly worse than patients with stable or regressing disease.

In comparison to the 5 year OS (46%) and PFS (16%) presented for the local ablation arm of SABR-COMET, our 5 year OS (13.4%) and PFS (7.3%) is much lower. One possible explanation is the differences in the site of original primary tumor. Out of the 66 patients treated on the SABR-Arm, 13 (19.7%) had breast cancer primaries and 14 (21.2%) had prostate cancer primaries. The investigators addressed a discrepancy of number of prostate cancers between the control and SABR-Arm, by performing a sensitivity analysis that showed an expected improvement in PFS for prostate primary vs. others. Despite removing these favorable patients, SABR-COMET still showed improved PFS for local ablative therapy (13). There were no specific results presented for the breast cancer patients, but we have previously reported long-term outcomes (4 and 6 years) for both breast and the non-breast oligometastatic groups on this prospective study. Breast cancer patients fared significantly better in terms of OS, LC, and FFWM in comparison to all other primaries (24). The long-term overall survival for breast patients at 10 years was 31%; with osseous-only oligometastases doing significantly better than non-osseous sites ($p = 0.002$) (32). Yet, despite having "less favorable" primaries, our patient cohort showed potential for long-term survival.

Local recurrence was not significantly associated with OS, likely reflecting potential salvage of local recurrence with surgery or re-irradiation. As expected, FFWM was a strong predictor for OS. The only other factor that significantly predicted for OS and PFS was net GTV, with a 4% increase in risk for every 10 cc of tumor burden. The number of metastatic lesions, potentially another parameter of tumor burden, was not a significant factor, as seen in other studies (33).

The predictive role of tumor burden is consistent with the important characteristics for metastasis as first demonstrated by RTOG 9508, which analyzed 1 vs. more than one metastasis (34). In a recent review, Palma, Louie and Rodrigues further described the four key prognostic variables, which they term "four aces," for patients in the setting of oligometastatic disease: young age (i.e., <65–70), patient fitness (i.e., KPS ≥70), slow growing cancers (i.e., metachronous vs. synchronous; longer duration to develop metastases) and minimal burden of disease (35). A "wild card" for outcome in these patients may be the primary site (i.e., breast or prostate cancer). Synchronous vs. metachronous development of oligometastases (relative to the primary tumor), was not a significant factor for any outcome in this study, as it was in other studies (36).

Other postulated predictors for oligometastatic characteristics include molecular factors measured both before treatment (37, 38), and in the surveillance period (39). These factors were not considered in our study, but they show promise in predicting outcomes. Post therapy surveillance is especially important since the majority of patient's cancer will progress, as seen in our study (5 year PFS 7.3%). However, roughly two-thirds of patients living >5 years underwent additional local therapy (HSRT/SBRT or surgery) for local recurrence/or for new oligometastatic lesions, and better surveillance can help guide these salvage opportunities.

One limitation of the current study is the variable dose-fractionation schedules used. As described previously (24), fractional doses in excess of 8 Gy were just beginning to be investigated when this study began, and thus the physicians treating patients on this study opted to be somewhat conservative (relative to the SBRT dose-fractionation schedules commonly used today). We attempted to address the discrepancy by converting prescribed dose to BED, and assessed for outcome based on a BED cutoff of 75 Gy (NS). There is compelling evidence for higher doses and lower fractionation (40, 41), though a less aggressive dose-fractionation is seemingly effective (42), and the optimal dose-fraction is unclear. Similarly the PTV expansions in this trial predate improvements in technology that today allow for smaller geometric expansions. Another study limitation is that patients were not randomized, as done in SABR-COMET (11) and other studies. Also, the wide variety in timing of systemic therapy (e.g., before HSRT, after HSRT, and/or after developing widespread metastases) and agents used (with many patients undergoing several different regimens over time) preclude meaningful analysis of the impact of systemic therapy on outcomes. Finally, 74% of patients in our study had only one involved organ, and thus our results may not be generalizable to patients with more extensive oligometastatic or oligoprogressive disease.

In summary, while relatively few patients in the present study have survived >10 years (**Figure 1**), it is remarkable that non-breast, non-prostate oligometastatic patients have survived for such a long duration. There has been an increasing use of locally aggressive treatments for various oligometastatic primaries in the United States, and further research is needed to help better identify patients most likely to benefit from metastases-directed radiotherapy (43). Recently published randomized trials (11, 13, 14) and ongoing studies will continue to provide additional insight into both survival and control outcomes after SBRT/HSRT for a variety of oligometastatic cancers.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

PO, AK, and MM contributed conception and design of the study. MM and KA organized the database. MM and KA performed the statistical analysis. KA and MM wrote the first draft of the manuscript. KA, AK, DS, PO, and MM wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Efficacy and Tolerance of Post-operative Hypo-Fractionated Stereotactic Radiotherapy in a Large Series of Patients With Brain Metastases

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Purpose: The aim of this study was to assess, in a large series, the efficacy and tolerance of post-operative adjuvant hypofractionated stereotactic radiation therapy (HFSRT) for brain metastases (BMs).

Materials and Methods: Between July 2012 and January 2017, 160 patients from 2 centers were operated for BM and treated by HFSRT. Patients had between 1 and 3 BMs, no brainstem lesions or carcinomatous meningitis. The primary endpoint was local control. Secondary endpoints were distant brain control, overall survival (OS) and tolerance to HFSRT.

Results: 73 patients (46%) presented with non-small cell lung cancer (NSCLC), 23 (14%) had melanoma and 21 (13%) breast cancer. Median age was 58 years (range, 22–83 years). BMs were synchronous in 50% of the cases. The most frequent prescription regimens were 24 Gy in 3 fractions ($n = 52$, 33%) and 30 Gy in 5 fractions ($n = 37$, 23%). Local control rates at 1 and 2 years were 88% [95%CI, 81–93%] and 81% [95%CI, 70–88%], respectively. Distant control rate at 1 year was 48% [95%CI, 81–93%]. In multivariate analysis, primary NSCLC was associated with a significant reduction in the risk of death compared to other primary sites (HR = 0.57, $p = 0.007$), the number of extra-cerebral metastatic sites (HR = 1.26, $p = 0.003$) and planning target volumes (HR = 1.15, $p = 0.012$) were associated with a lower OS. There was no prognostic factor of time to local progression. Median OS was 15.2 months [95%CI, 12.0–17.9 months] and the OS rate at 1 year was 58% [95% CI, 50–65%]. Salvage radiotherapy was administered to 72 patients (45%), of which 49 received new HFSRT. Ten (7%) patients presented late grade 2 and 4 (3%) patients late grade 3 toxicities. Thirteen (8.9%) patients developed radiation necrosis.

Conclusions: This large multicenter retrospective study shows that HFSRT allows for good local control of metastasectomy tumor beds and that this technique is well-tolerated by patients.

Keywords: radiotherapy, hypofractionated stereotactic radiation therapy, brain metastasis, surgery, Cyberknife

INTRODUCTION

Brain metastases (BMs) are the most frequent brain tumors, and, throughout disease course, 20–40% of cancer patients will develop a BM (1). In subjects in good general health and presenting with a single BM, surgical resection has been shown to improve survival (2, 3). After surgery, adjuvant whole-brain radiotherapy (WBRT) allows to significantly reduce local and brain recurrence rates, as well as the risk of death from neurological cause (4, 5). Nevertheless, WBRT has not been shown to be beneficial in terms of overall survival (4–6) and the length of time in which patients remain functionally independent (4, 5). In addition it contributes, in the short term, to a poorer quality of life in patients (6) and causes acute toxicities including asthenia, alopecia, nausea, and a decline in learning and memory functions (7). Stereotactic radiosurgery (SRS) allows for good local control of the disease while avoiding the neurocognitive decline triggered by WBRT (8). Consequently, after resection of a BM, SRS and Hypofractionated stereotactic radiation therapy (HFSRT) are increasingly being used and could be considered as an alternative treatment standard to WBRT allowing to limit toxicity (7, 8).

To date, there is no consensus on the optimal dose, fractionation, or prescription regimens of HFSRT on the surgical cavity. Several prescription patterns are described in the literature, including schemas of 3 fractions with doses ranging from 7.7 to 11 Gy, (9–12) or schemas of 5 fractions (13, 14). Such heterogeneity in prescription doses prevents any direct comparison between studies. The largest phase III randomized study, comparing SRS to WBRT published by Brown et al. showed a longer cognitive-deterioration-free survival in patients assigned to SRS (median 37 months) than in patients assigned to WBRT (median 30 months) ($p < 0.0001$) (8). Overall survival (OS) was identical in the 2 arms, but local and distant brain control were lower in the SRS arm.

The aim of this study was to evaluate the efficacy and safety of post-operative HFSRT in resection cavity of secondary brain lesions in a large cohort of patients.

Abbreviations: HFSRT, Hypofractionated Stereotactic Radiation Therapy; BM, Brain Metastase; OS, Overall Survival; NSCLC, Non-Small Cell Lung Cancer; WBRT, Whole-Brain Radiotherapy; HFSRT, Hypofractionated Stereotactic Radiation Therapy; SRS, Stereotactic Radiosurgery; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; CTV, Clinical Target Volume; GTV, Gross Tumor Volume; PTV, Planning Target Volume; DBC, Distant Brain Control; PET, Positron Emission Tomography; HR, Hazard Ratio; RMSTD, Restricted Mean Survival Time Difference; RPA, Recursive Partitioning Analysis; DS-GPA, Diagnostic-Specific Graded Prognostic Assessment; CTCAE, Common Terminology Criteria for Adverse Events.

MATERIALS AND METHODS

Population

Between July 2012 and January 2017, patients treated with post-operative HFSRT to the resection cavity in two French centers were included. Data were retrospectively collected. Inclusion criteria were: adult patients, with 1 to 3 BMs, no previous radiotherapy treatment to the brain, treated by surgery for BM of a solid tumor and with anatomical pathology data, no brainstem lesion or carcinomatous meningitis, eligible to be treated by HFSRT as decided in a multidisciplinary meeting, with a life expectancy of more than 3 months, and not opposed to the use of their medical data for research and educational purposes.

HFSRT Technique

Patients were immobilized using a thermoplastic mask system. Computed tomography (CT) scan and gadolinium contrast-enhanced magnetic resonance imaging (MRI) were used for treatment planning. Imaging was performed using millimetric slices and rigid registration. Target volumes and organs at risk were contoured on MRI and concordance with CT was controlled. Contouring software's used were Oncentra (version 4.3.0) and Multiplan (Accuray, version 3.2.0).

Target volumes were contoured using the surgical and anatomical pathology assessment of resection specimens. The clinical target volume (CTV) included the surgical cavity, contrast enhancement of tumor border and a 1–2 mm margin which delineates it on the CT scan and planning MRI. In the case of metastasis in contact with dura, the CTV included a larger margin (5–10 mm) beyond the area where there was contact before surgery. The gross tumor volume (GTV) was defined if macroscopic disease could be identified by nodular contrast enhancement by T1-Gadolinum MRI imaging. The planning target volume (PTV) was defined as CTV + 1 mm.

HFSRT treatment was delivered using a CyberKnife®-type robotic accelerator (Accuray, Inc., Sunnyvale, CA), using 6 MeV photon beams, in Centre Oscar Lambret in Lille and Centre François Baclesse in Caen. Dose was prescribed at the 80% isodose and patients were treated every 2 days.

Follow-Up

Follow-up of patients included collection of clinical data and brain perfusion MRI at 2 months and then every 3 months after the end of irradiation during the first year, and every 4 to 6 months thereafter. Local recurrence was defined as the appearance or growth of nodules in the surgical cavity visible on a T1-gadolinium MRI sequence. OS was defined as the time from HFSRT until death from any cause. Time-to distant brain control (DBC) was defined as to the time from HFSRT until progression in the brain outside of the surgical cavity. Radiation necrosis

was diagnosed based on clinical, morphological, and metabolic criteria, and was validated by experts. MR spectroscopic imaging and 18F-DOPA PET (Positron emission tomography) were used to support the diagnosis if needed.

Statistical Analysis

Patient and disease characteristics were analyzed using descriptive statistics. Quantitative variables were expressed as median and range. Survival curves were estimated using the Kaplan Meier method. For time to progression, patients were censored at the date of last news or date of death from any cause. Time interval for overall survival was calculated from the date of HFSRT to the date of death from any cause. Patients alive were censored at the date of last news. Patients were censored at day 1 in case of missing information on the event.

After having checked the proportional hazard assumption (Schoenfeld residuals), prognostic factors of survival were identified using a univariate Cox regression model. *Hazard Ratios* (*HR*) and the 95% CI as well as the calculated probability (*p*-value) were presented for each model. In cases of non-proportional hazards, the "restricted mean survival time difference" (RMSTD) was used (15). Significant variables at $p = 0.10$ in the univariate model were included in the multivariate Cox stepwise backward model analysis. The following factors were analyzed: sex, age, primary disease, primary histology, RPA (recursive partitioning analysis) score, DS-GPA (Diagnostic-Specific Graded Prognostic Assessment) score, controlled primary tumor, location of BM, extracranial metastasis status, number of BM, time between primary tumor and BM diagnosis, partial resection and gross total resection, interval time between surgery and HFSRT, dose of HFSRT, salvage WBRT, SRS or HFSRT, pre- and post-operative volumes, conformity index, and homogeneity index.

The association of the radiation necrosis with the different factors was analyzed with the Fisher exact test for qualitative variables and with the Wilcoxon Mann-Whitney test for quantitative variables.

Statistical analyses were performed using Stata 13.1 (StataCorp. 2013 Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) and significance level was set at a *p*-value of 0.05 for all analyses.

RESULTS

Population

This was a retrospective study involving 160 patients and 167 surgical cavities. Patients were 76 women (47.5%) and 84 men. The median age at diagnosis of BM was 58 years (range, 22–83 years) (**Table 1**). Seventy-three patients (46%) presented with primary lung cancer, 23 patients (15%) with melanoma and 21 patients (13%) with breast cancer. The median time interval between the primary tumor diagnosis and BM surgery was 8.4 months (range, 0–148.6 months).

TABLE 1 | Patient characteristics.

Patient characteristics	*n*	%
Patients	160 (167 cavities)	
Sex	160/160	
Female	76	47.5%
Male	84	52.5%
Age (y)		
Median (range)	58	(22; 83)
Primary disease	157/160	
NSCLC	**73**	**46%**
Cutaneous	**23**	**15%**
Breast cancer	**21**	**13%**
Gastrointestinal	16	10%
Gynaecologic	9	6%
Renal cell carcinoma	6	4%
Other	9	6%
Histology	160/160	
Adenocarcinoma	**102**	**64%**
Melanoma	**24**	**15%**
Squamous cell carcinoma	**12**	**8%**
Other	22	14%
Metachronous BM	**78/157**	**50%**
Synchronous BM:		
Controlled systemic disease	63	40%
Uncontrolled systemic disease	16	10%
Number of other extra BM sites	157/160	
0	74	47%
1	52	33%
2	26	17%
≥3	5	4%
RPA score	156/160	
1	**75**	**48%**
2	**78**	**50%**
3	3	2%
DS-GPA score	134/160	
Median (range)	**3**	(1; 4)
PS scale	156/160	
0	**56**	**36%**
1	**86**	**55%**
2	13	8%
3	1	1%

BM, Brain Metastases; DS-GPA, diagnosis-specific GPA; GPA, Graded prognostic assessment; NSCLC, Non-small cell lung cancer; RPA, Recursive partitioning analysis; PS Scale: Performance Status scale.

Description of BM and Treatment by HFSRT

At the time of diagnosis, 115 patients (72%) had a single BM; 77 patients (50%) had symptoms of intracranial hypertension and 126 patients (81%) had neurological symptoms (**Table 2**). Seventy-eight patients (50%) presented with synchronous BM, 63 patients (40%) with a metachronous BM and a controlled primary tumor, and 16 patients (10%) with a metachronous and a non-controlled primary tumor. Pre-operative MRI revealed a median tumor size of 32 mm (range, 7–78 mm) and 75% of the cases ($n = 124$) were supratentorial. Planning MRI was performed in 151 patients (94%). The median surgery cavity size was 27 mm (range, 5–66 mm) and in 46 patients (30%) a nodular

contrast enhancement by planning MRI led to the diagnosis of an early relapse in the surgical cavity. Most frequent prescription regimens were 24 Gy in 3 fractions ($n = 52$, 33%) and 30 Gy in 5 daily fractions ($n = 37$, 23%). Median CTV and PTV volumes were 10.6 mL (range, 0.9–98.8 mL) and 15.2 mL (range, 2.2–129.8 mL), respectively.

Local Control

The median follow-up was 30.6 months. At the end of the follow-up, 23 local recurrence (14.4%) were observed. Local control rates at 6 months, 1 year and 2 years were 91% [95% CI, 85–95%], 88% [95% CI, 81–93%], and 81% [95% CI, 70–88%], respectively (**Figure 1A**). No factor appears to be prognostic of local control.

Distant Brain Control

At the end of the follow-up, 86 patients (53.7%) presented with DBC. The median time to brain recurrence was 11.2 months (range, 8.4–18.0 months). DBC rates at 6 months, 1 and 2 years were 71% [95% CI, 63–78%], 48% [95% CI, 39–56%], and 34% [95% CI, 24–43%], respectively (**Figure 1B**). No factor appears to be prognostic of time to distant brain progression. The progression free leptomeningeal progression rate were 80% [95% CI, 73–86%] at 1 year and 72% [95% CI, 59–82%] at 3 years.

Overall Survival

At the end of the follow-up, 113 deaths (70.6%) were observed, including 33 deaths (42%) due to disease brain progression. Median OS was 15.2 months [95% CI, 12.0–17.9 months], and 6 months, 1 and 2 year OS rates were 81% [95% CI, 74–86%], 58% [95% CI, 50–65%] and 32% [95% CI, 24–39%] (**Figure 2**).

In the univariate analysis, different prognostic factors appears to be associated with overall survival. Lung primary tumor was associated with a significant reduction of the risk of death compared to other primary tumors ($HR = 0.65$, [95% CI, 0.44–0.94], $p = 0.023$). The number of extra-cerebral metastatic sites ($HR = 1.19$, [95% CI, 1.02–1.39], $p = 0.027$), the number of BM ($HR = 1.17$, [95% CI, 1.00–1.35], $p = 0.046$), the absence of systemic control of the disease ($HR = 1.39$, $p = 0.035$) and larger PTV ($HR = 1.12$, [95% CI, 1.01–1.26], $p = 0.040$) were associated with a significant increase of the risk of death. In multivariate analysis, lung cancer ($HR = 0.57$, [95% CI, 0.38–0.86], $p = 0.007$), the number of extra-cerebral metastatic sites ($HR = 1.26$, [95% CI, 1.08–1.48], $p = 0.003$) and the larger PTV ($HR = 1.15$, [95% CI, 1.03–1.28], $p = 0.012$) were prognostic of OS (**Table 3**). The number of BM did not achieve significance with a $HR = 1.16$ ($p = 0.055$).

Salvage Treatments

Among the 23 patients presenting a local recurrence, 7 were treated by stereotactic re-irradiation, 6 by a WBRT, and 9 did not receive additional irradiation (**Table 4**). Overall, 72 patients (45%) underwent another brain irradiation: 38 (24%) received exclusively SRT at a median delay of 7.3 months (range, 1.3–58 months) and 34 (21%) received WBRT at a median delay of 7 months (range, 1.8–33 months). Sixty-six patients (41.8%) presented new neurological sign related to disease progression, at

TABLE 2 | Brain Metastases and HFSRT treatment characteristics.

Brain metastases and treatment characteristics	***n***	
Resection cavities treated	167	
Preoperative size	136/167	
Median (mm)–(range)	**32**	(7; 78)
Resected cavity size	104/167	
Median (mm)–(range)	**27**	(5; 66)
Location	167/167	
Supratentorial	124	74%
Infratentorial	43	26%
Synchronous BMs at time of HFSRT	160/160	
None	115	72%
1	29	18%
2	16	11%
Local relapse on planning MRI		
No	107	70%
Yes (nodule)	**46**	**30%**
Time between diagnostics and surgery	161/167	
Median (months)–(range)	**0.4**	(0; 138)
Time between surgery and CK treatment		
Median (days)–(range)	59.5	(21;181)
Gross total resection	$n = 117/127$	**92%**
Associated treatment during CK	$n = 68/139$	**43%**
None	71	
Chemotherapy	30	
Targeted therapy	8	
Immunotherapy	8	
Anti-angiogenic	1	
Unknown	*21*	
Delivered dose regimen		
24 Gy in 3 fractions	**52**	**33%**
30 Gy in 5 fractions	**37**	**23%**
27–30 Gy in 3 fractions	**34**	**22%**
30 Gy in 6 fractions	15	9%
Other	22	14%
Clinical target volume (CTV)		
Median (cm^3)–(range)	**10.6**	(0.9; 98.8)
Planning target volume (PTV)		
Median (cm^3)–(range)	**15.2**	(2.2;129.8)
D2 CTV		
Median (Gy)–(range)	**33.6**	(25–50)
Mean (Gy) (±standard deviation)	**34 ± 5.3**	
D50 CTV		
Median (Gy)–(range)	**31.6**	(22–46)
Mean (Gy) (±standard deviation)	**32 ± 4.9**	
D98 CTV		
Median (Gy)–(range)	**30.2**	(20.7–43.1)
Mean (Gy) (±standard deviation)	**29.4 ± 4.6**	
Brain $V_{12\text{-}Gy}$		
Median (cm^3)–(range)	**53.2**	(4.0; 380)
Brain $V_{21\text{-}Gy}$		
Median (cm^3)–(range)	**22.9**	(0.01; 230)
Brain D50		
Median (Gy)–(range)	**1.3**	**(0.2; 6.2)**

BM, Brain Metastases; CK, CyberKnife; DX, Dose received by x% of the volume of interest; MRI, Magnetic Resonance imaging; V_{12-Gy} and V_{21-Gy}, Volume (cm^3) of brain that received doses of 12 and 21 Gy.

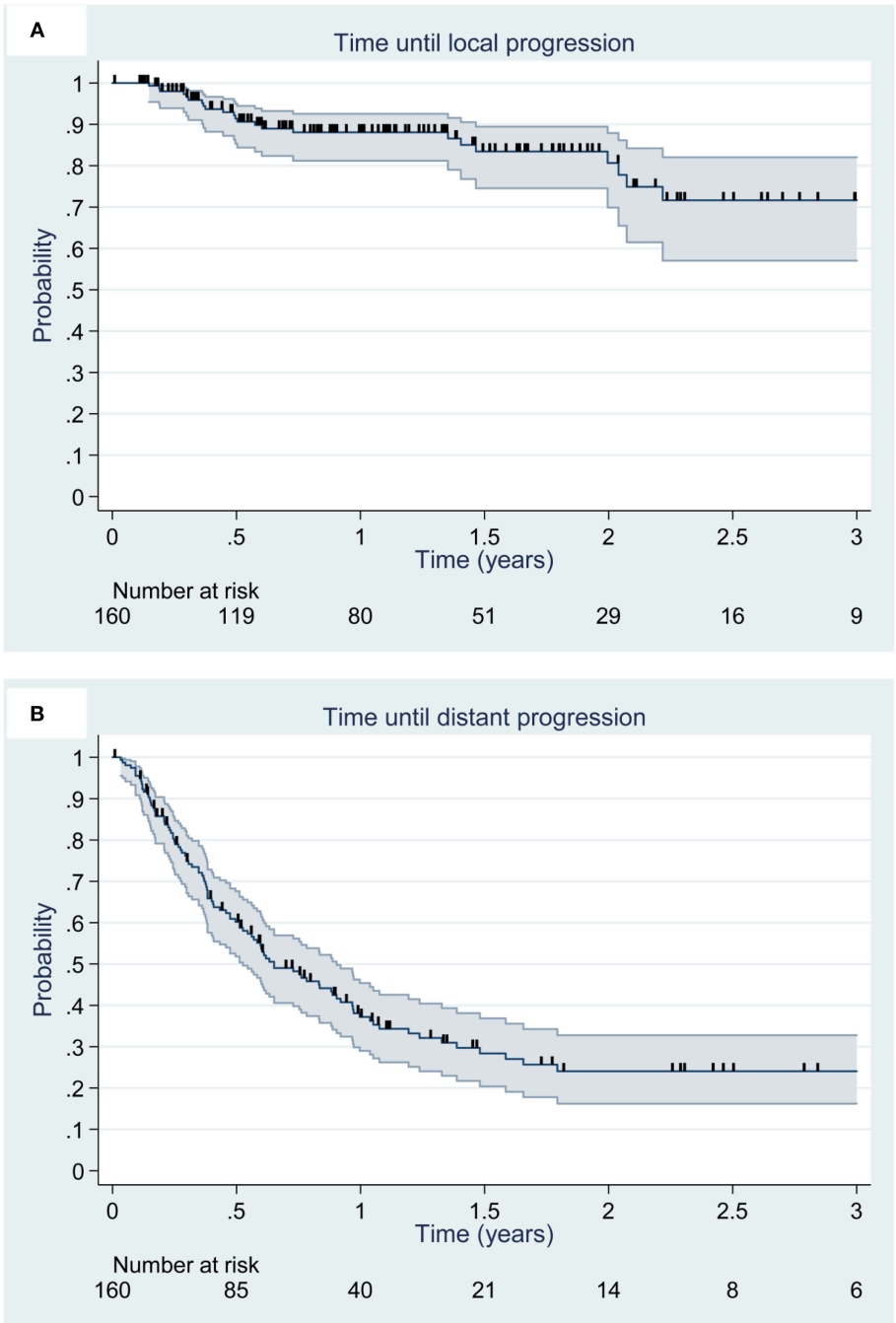

FIGURE 1 | Kaplan Meier estimation (95% CI) of local **(A)** and distant **(B)** control. Deceased patients and patients alive at the date of last news were censored and are illustrated by vertical lines.

a median delay of 6.3 months (range, 0.9–32.2 months) after the initial radiotherapy treatment.

Tolerance

According to the Common Terminology Criteria for Adverse Events (CTCAE) grading system, version 4.03, 5 patients (3.4%) presented an acute grade 2 toxicity and 1 patient (0.7%) presented an acute brain hemorrhage of grade 3. Ten patients (7.2%) developed late toxicity of grade 2 and 4 patients (2.7%) a late toxicity of grade 3 (two brain necroses, one seizure and one stroke). Radiation necrosis during follow-up occurred in 13 patients (8.9%). The stereotactic re-irradiation or WBRT was the only factor associated with an increased risk of developing a radiation necrosis ($p < 0.001$, Fisher exact test). Among patients that received HFSRT exclusively, the rate of radiation necrosis at the end of follow-up was 6.9% and among the 7 patients treated

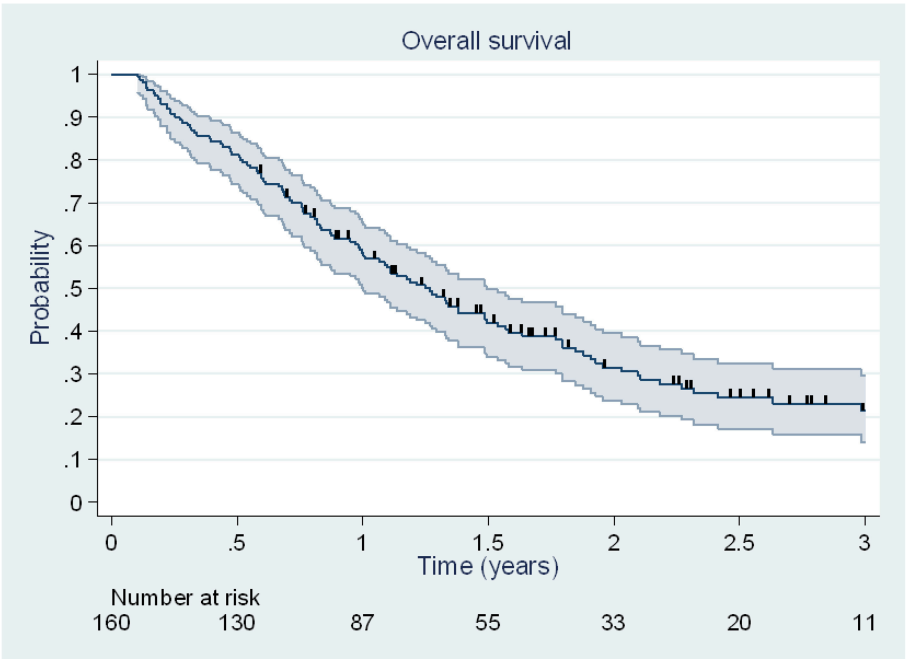

FIGURE 2 | Kaplan Meier estimation (95% CI) of overall survival. Patients alive at the date of last news were censored and are illustrated by vertical lines.

TABLE 3 | Prognostic factors of overall survival in multivariate analysis (Cox model).

Predictive factors	*HR*	95% CI	*p*
Primary disease			**0.007**
Other	1		
NSCLC	0.57	0.38–0.86	
Number of other extra cerebral metastatic sites	1.26	1.08–1.48	**0.003**
Planning target volume	1.15	1.03–1.28	**0.012**
Number of BM	1.16	0.99–1.35	**0.055**

NSCLC, Non-Small Cell Lung Cancer; BM, brain metastases.

TABLE 4 | Radiotherapy treatment for brain recurrence.

Patient characteristics ($n = 160$)	*n*	%
Treatment of local recurrences	**23**	
- WBRT	6	26%
- SRT	7	30%
- No re-irradiation	9	39%
- *Missing data*	*1*	4%
Treatment of brain recurrences	**72/160**	**45%**
- WBRT	23	14%
- SRT	38	24%
- WBRT + SRT	11	7%

WBRT, Whole Brain Radiotherapy; SRT, Stereotactic Radiation Therapy.

with stereotactic re-irradiation in the surgical cavity, 4 (57%) presented with a radiation necrosis.

DISCUSSION

This large series, the second largest after Keller et al.'s to our knowledge (12), shows that post-operative HFSRT to the surgical cavity of BM allows for a good local control with acceptable acute and late toxicity profiles.

Local Control

Local control rates achieved in our series with HFSRT to the surgical cavity are comparable to those of the larger retrospective series. Keller et al. reported local control rates of 92.9% at 6 months, 88.2% at 1 year and 86.5% at 2 years in a series involving 181 patients and 189 surgical cavities (12) (**Table 5**). In this study, the prescribed dose was 3 × 11 Gy to the isocenter. Factors associated with a greater rate of local relapse in multivariate analysis were larger PTV (>24 mL), a greater GPA score and meningeal contact of the BM. Patel et al. and Mahajan et al. also demonstrated in their series that the tumor volume was predictive of local control (16, 19). The 1 year local control rate of 88% [95% CI, 81–93%] in our study is similar to the 85% revealed by the meta-analysis involving 629 patients treated by SRT to the surgical cavity (17).

The phase III study from Kocher et al. evaluated the combination of WBRT or SRS with surgery to treat 359 patients with 1 to 3 BMs (4). Of 160 patients treated with surgery, 79 patients were randomized to the observation arm and 81 to the adjuvant WBRT arm. The 2 years local control rate was 41% in the observation arm vs. 73% ($p < 0.001$) in the surgery and WBRT combination arm, close to the rates observed in our study.

TABLE 5 | Post-operative HFSRT and SRS for brain metastases literature data.

Trials	Study	*n*	Median OS	Local control	Distant Brain Control
Brown et al. (8) (Post-operative SRS)	Phase III	98/194	12.2 months	6 months: 80% 1 year: 61%	6 months: 72% 1 year: 65%
Mahajan et al. (16) (Post-operative SRS)	Phase III	63/128	17 months	6 months: 85% 1 year: 72%	1 year: 42%
Gans et al. (17) (Post-operative SRS)	Review 14 studies	629	14 months	1 year: 85%	Median: 8.4 months
Ling DC et al. (18) (Post-operative SRS or HFSRT)	Retrospective	99	12.7 months	6 months: 84% 1 year: 72% 2 years: 55%	1 year: 36% Median: 7.9 months
Keller et al. (12) (Post-operative HFSRT)	Retrospective	181	17.3 months	6 months: 93% 1 year: 88% 2 years: 87%	6 months: 70% 1 year: 61%
Current study (Post-operative HFSRT)	Retrospective	160	15.6 months	6 months: 91% 1 year: 88% 2 years: 81%	6 months: 71% 1 year: 48% 2 years: 34%

HFSRT, Hypofractionated stereotactic radiation therapy; OS, Overall survival; SRS, Stereotactic radiosurgery.

A randomized study, recently published by Brown et al., included 194 patients from 48 centers and compared radiosurgery and WBRT as adjuvant treatment (8). The surgical cavities had to be smaller than 5 cm. Patients treated by WBRT had 6 months and 1-year local control rates of 87.1 and 80.6%, respectively. In addition, this study showed weak local control rates in the radiosurgery arm (80.4% at 6 months and 60.5% at 1 year), well-below the local control rates obtained in the WBRT arm ($p = 0.00068$). The lower local control rate in this study could be explained by the weak dose delivered. Indeed, patients treated by SRS received 12 to 20 Gy in one fraction, while patients in the WBRT arm received 37.5 Gy in 15 fractions or 30 Gy in 10 fractions. Robbins et al. demonstrated in their study the use of radiosurgery to the surgical cavity as adjuvant therapy for resected BM that a marginal dose in SRS under 16 Gy was predictive of local control (20). Mahajan et al. reported in a phase III study the local control rates of 85% at 6 months and of 72% at 1 year after adjuvant SRS after surgery for patients with 1 to 3 BM (16).

Early Local Recurrence

In our study, 46 (30%) patients presented a nodular contrast enhancement by planning MRI, even though resection was macroscopically complete in 92% of the cases. This diagnosis is difficult, and because RANO and RECIST 1.1 criteria are not adapted in the post-surgery setting, radiologists used heterogeneous methods for diagnosis (21, 22). In the study from Jarvis et al. before post-operative radiosurgery, 12% of the patients presented a local recurrence at 1 month. The early local recurrence rate was 37.5% at 1 month in patients with a subtotal resection (23). In these studies, the median delay between surgery and radiotherapy was 4–7 weeks (11, 13, 18), but could range from 18 days (14, 24) to 4.5 months (25).

Distant Brain Control

In our series, DBC rates are comparable to those reported in the literature after SRT (12). The phase III studies from Mahajan et al. and de Kocher et al. reported similar distant brain control rates, 43% at 1 year and 58% at 2 years, respectively in the observation arms (4, 16).

In this study, leptomeningeal disease seems more frequent (5, 12, 26). In Keller et al. study 89.4% [95% CI, 85.0–93.8%] and 88.9% [82.2–91.9%] of patients did not developed leptomeningeal disease at 1 and 2 year, respectively (12). In Atalar's study, 161 brain metastasis resection cavities treated from 1998 to 2011 with post-operative SRS were retrospectively reviewed. One and 2 year rates of leptomeningeal disease were 13%, but until 34% at 1 year for breast cancer (26). In our study, the rate of leptomeningeal disease may have been overestimated as we also reported very moderate leptomeningeal disease on MRI.

Overall Survival

Median OS of patients in our study was 15.2 months [95% CI, 12.0–17.9 months] and it was comparable to that observed in other studies. In the meta-analysis by Gans et al. median OS was of 14 months; 12.2 and 17 months in the randomized studies by Brown et al. and Mahajan et al., respectively, and of 12.7 and 17.3 months in the large retrospective series by Ling et al. and Keller et al., respectively (8, 12, 16–18).

In our study, patients presenting a primary NSCLC had a lower risk of death, with an *HR* of 0.57 [95% CI, 0.38–0.86], ($p = 0.007$), with respect to patients presenting other primary tumors. The risk of death increased also with the number of extra-cerebral metastatic sites at the time of diagnosis ($HR = 1.26$ [95% CI, 1.08–1.48], $p = 0.003$) and with larger PTV ($HR = 1.15$ [95% CI, 1.03–1.28], $p = 0.012$).

In the meta-analysis by Gans et al. a higher prevalence of single metastases in the cohort was the only factor associated with higher OS ($p < 0.02$) (17). The study by Keller et al. reported in multivariate analysis, that a RPA score of 3 ($p = 0.02$), piecemeal resection ($p = 0.017$) and an increased number of BMs ($p < 0.001$) were independent prognostic factors for a lower OS. Patients with multiple BMs had a risk of death 2.4 times greater than patients with a solitary BM ($p < 0.001$) (12). Kocher et al. randomized phase III

study evaluating the interest of adjuvant WBRT found in a multivariate analysis that the only factors with a significant impact on survival with Performance Status (PS) ≤ 2 were the initial PS (0 vs. 2, $p = 0.004$) and the presence of macroscopic tumor outside the brain (absent vs. present $p = 0.001$) (4).

Based on 7 randomized studies of the RTOG and 2,350 patients treated for BMs, Barnholtz-Sloan et al. developed a nomogram to estimate OS in patients with BM (27). The model revealed that the primary site was predictive of OS, with breast cancer and lung adenocarcinoma being associated with improved survival. Contrary to previous studies, in our series, the survival of patients with NSCLC could be improved with treatments including immunotherapy, targeted therapy and third generation tyrosine kinase inhibitors (28).

Safety and Radiation Necrosis

The tolerance was acceptable with 2.7 and 0.7% of patients presenting acute grade 2 and grade 3 toxicities, and 7.2 and 2.7% late grade 2 and 3 toxicities, respectively. These results are in line with the 10% toxicity rate after HFSRT revealed by the meta-analysis by Gans et al. (17). Risk of radiation necrosis has been shown to decrease with lower doses, greater number of fractions and smaller volume of the treated surgical cavity (29, 30). Eaton et al. demonstrated that for cavities bigger than 3 cm, treatment by radiosurgery was associated with a greater rate of radiation necrosis, with a $HR = 3.81$ [95% CI, 1.04–13.93], ($p = 0.043$) compared to treatment by HFSRT (29). The risk of radiation necrosis at 1 year was of 10.3% with HFSRT and of 19.2% after radiosurgery. In our study, 8.9% of patients presented a radiation necrosis during follow up and only re-irradiation was found to be predictive of radiation necrosis, possibly due to a lack of statistical power related to a low number of events. Median volumes of brain that received doses of 10 Gy ($V_{10\,Gy}$), 12 Gy ($V_{12\,Gy}$), and 21 Gy ($V_{21\,Gy}$) were not found to influence radiation necrosis. In Minniti et al.'s study using a schema of 3 × 9 Gy, the rate of radiation necrosis was 7% at 1 year and 16% at 2 years (31). This study showed that $V_{24\,Gy}$ was the only factor associated with radiation necrosis with a 16.8 mL threshold ($p = 0.03$).

In order to standardize practice, Soliman et al. recently published CTV contouring guidelines for SRS of completely resected cavity BM defined by 10 experts based on 10 clinical cases (32). Our delineation practices are in line with these guidelines. Improvements in local control can be achieved by adding a 2 mm margin around the resection cavity (33). The choice of 1 mm to define PTV is arguable. In our study, this PTV allowed to compensate for repositioning errors. In other studies a margin between 0 and 4 mm was more frequently used. However, in Gans et al.'s meta-analysis the use of a margin to define PTV did not allow to improve local control or OS (17).

Limitations

This is a retrospective study and several irradiation schemas were used. Nevertheless, the prescription regimen at the 80% isodose was homogeneous. For 55% of patients a dose of 8, 9 or 10 Gy in 3 fractions was prescribed.

CONCLUSION

This large retrospective multi-center study shows that, in our population of patients operated for BM, adjuvant treatment by HFSRT allows for good local control in the surgical cavity. This non-invasive technique was well-tolerated by patients. HFSRT is an efficient treatment option for patients with operated BM. The rate of distant recurrence and in particular leptomeningeal disease seems higher than the rate observed after WBRT. A close follow-up by MRI is necessary in patients with a high risk of intra-cerebral recurrence.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of local ethics committee and conducted in accordance with the Helsinki declaration with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Centre O. Lambret ethics committee.

AUTHOR CONTRIBUTIONS

DP and GM contributed to the conception, design, and manuscript preparation. GM performed data acquisition. GM, JG, DS, EB, ER, NR, EE, SM-M, RM-A, LB, XM, EL, and DP performed data analysis and interpretation. EB carried out statistical analysis.

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REVIEW
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Role of Radiosurgery/Stereotactic Radiotherapy in Oligometastatic Disease: Brain Oligometastases

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During the natural history of oncologic diseases, approximately 20–40% of patients affected by cancer will develop brain metastases. Non-small lung cancer, breast cancer, and melanoma are the primaries that are most likely to metastasize into the brain. To date, the role of Radiosurgery/Stereotactic Radiotherapy (SRS/SRT) without Whole brain irradiation (WBRT) is a well-recognized treatment option for patients with limited intracranial disease (1–4 BMs) and a life-expectancy of more than 3–6 months. In the current review, we focused on randomized studies that evaluate the potential benefit of radiosurgery/stereotactic radiotherapy for brain oligometastases. To date, no difference in overall survival has been observed between SRS/SRT alone compared to WBRT plus SRS. Notably, SRS alone achieved higher local control rates compared to WBRT. A possible strength of SRS adoption is the potential decreased neurocognitive impairment.

Keywords: oligometastases, radiosurgery, stereotactic radiotherapy, brain metastases, radiotherapy

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INTRODUCTION

During the natural history of oncologic diseases, approximately 20–40% of patients affected by cancer will develop brain metastases (BMs) (1). Non-small lung cancer, breast cancer and melanoma are the primaries that are most likely to metastasize into the brain (2, 3).

Recently, the concept of oligometastatic disease was introduced to define a metastatic disease with a low tumor burden, usually represented by 1–5 metastatic sites. Patients with a limited number of brain metastases and controlled extracranial disease are frequently observed in daily clinical practice. In this last subgroup of patients, local-ablative therapies in combination with new molecular agents aim to achieve a longer overall survival (OS) compared to whole brain palliative irradiation (4, 5).

Biological Aspects of Brain Metastases

Regarding the pathogenesis of metastasis, the oncologic community has generated several hypotheses. A commonly accepted hypothesis is the "seed and soil" hypothesis of Paget, first invoked in 1889 (6). He suggested that the successful growth of metastases and the specific metastatic site preference of certain types of tumors depends on the interactions and properties of cancer cells (the "seeds") and their specific affinity for the milieu of potential target organs (the "soil"). Metastases result only if the seed and soil are compatible. To date, several studies have confirmed the contemporary relevance of this historic hypothesis. In order to understand the theory, we are briefly going to highlight the process of cancer metastasis, which is sequential

and highly selective. First, tumor cells at the primary tumor site must proliferate and initiate angiogenesis. Secondly, tumor cells must invade host stroma and gain entrance into the lymphatics or blood stream to circulate and reach distant organs. Finally, circulating tumor cells must survive the journey through the blood stream and immune and non-immune defenses of the host to extravasate through the microvasculature of target organs ("niche") to deposit, survive, and grow in a foreign tissue environment (7, 8).

We have to keep in mind that the primary tumors are biologically highly heterogeneous and that metastases can derive from different clonal subpopulations of the primary tumor. For cancer metastasis, cancer stem cells must pass through all stages of the above-mentioned process, including proliferative, angiogenic, invasive, and metastatic steps. Only few cancer cells survive this series of sequential, interrelated steps, as it is highly dependent on the interplay of tumor cells with host factors and organ microenvironment. It has been shown, that cancer cells survive traveling in the circulation and the process of arrest in microcirculatory vessels and extravasion with high efficiency, with >80% of cells successfully completing this process in an experimental setting. Nevertheless, cancer metastasis is known to be complex, and once cells have completed extravasation, they appear much less efficient and more variable at completing subsequent steps in the metastatic process to form macroscopic metastases (9).

The blood-brain barrier of the brain has a specific anatomical and molecular constitution to prevent extravasation of circulating cell types into the brain parenchyma. However, since the brain has no classical lymphatics, hematogeneous metastasis is the only way for tumor cells to get access. Metastasizing cancer cells that arrest in brain microvessels are confronted with a highly alien organ microenvironment. The extracellular matrix, resident parenchymal cells and paracrine signaling molecules, such as cytokines and growth factors differ substantially from other sites of the body (10). Recently, whole-exome sequencing of matched brain metastases and primary tumors first proved the branched evolution of metastases, where all metastatic and primary sites shared common ancestral clones which continued to evolve independently (11–13). Moreover, in >50% of cases, clinically relevant and targetable alterations were found in brain metastases, which were not detected in the primary tumor or extracranial metastases (14). This new evidence is of great importance, especially in the present era of individualized and targeted therapies.

Nevertheless, it seems that there are different patterns of metastatic dissemination. An analysis of clear-cell renal cell carcinomas in a prospective multi-center study (TRACERx Renal) provided a comprehensive picture of the genetic principles and the evolutionary patterns of metastasis. The authors observed distinct models of metastatic dissemination. In cases of rapid progression to multiple sites, metastatic competence is acquired within the most recent common ancestor seeded by primary tumors of monoclonal structure. Usually, this leads to rapid local failure, poor response to systemic therapy and early cancer-related death. In contrast, attenuated progression is characterized by high primary tumor heterogeneity, with metastatic competence acquired gradually and limited to certain subpopulations in the primary tumor. This type of cancer metastasis usually results in initial progression to solitary metastasis, also known as oligometastatic disease, and is characterized by increasing metastatic capacity over time, resulting in more efficient and widespread metastases. This fact underlines the need for aggressive cytoreductive local therapies, in order to minimize the risk of future metastatic seeding from evolving tumors, harboring clones of variable metastatic potential (11, 15, 16).

Prognostic Factors of Brain Metastases

Several prognostic scores for BMs patients were designed to guide the clinicians' decision-making strategy. In clinical practice, the recursive partitioning analysis classes (RPA), the graded prognostic assessment index (GPA) and the Diagnosis-Specific GPA (DS-GPA) scores (17–21) are routinely used. Gaspar et al. (17) recommended the prognostic index scoring model RPA, which has been developed after evaluating 1,200 patients affected by BMs. Patients were stratified into 3 classes: (i) class I included patients aged up to an age of 65 years with a Karnofsky Performance Status (KPS) >70 and a controlled primary tumor without extracranial metastasis; (ii) class III included patients with a KPS score <70; and (iii) class II included all other cases. RPA classes were associated with different median OS rates: 7.1, 4.2, and 2.3 months for class I, II, and III, respectively (14, 22–24). Recently, Sperduto et al. proposed another prognostic index (GPA), which takes into account 4 clinical criteria (age, KPS, number of BMs, and presence/absence of extracranial metastases) based on data from 5 randomized RTOG trials, including a total of 1,960 patients. A higher GPA score correlated to a better prognosis with a median OS of 11 months, while for GPA scores of 0–1, the OS was 2.6 months (19). Based on an additional analysis, a specific prognostic tool, taking into account the primary histology, was developed (25). The DS-GPA score was correlated to clinical outcome, after stratification by means of diagnosis and treatment. The trial emphasized the heterogeneity in terms of patients' selection, but the usefulness of DS-GPA in clinical practice remains undisputed (20).

Starting from this background, a narrative review of literature was performed evaluating the role of radiosurgery/stereotactic radiotherapy (SRS/SRT) in the treatment of brain oligometastases.

METHODS

We searched PubMed, EMBASE, and Cochrane library for articles published in English language between 1 January 1990 and 1 January 2019. Only randomized studies concerning the irradiation of brain oligometastases were selected.

Inclusion criteria were: randomized studies comparing whole brain radiotherapy (WBRT) vs. SRS/SRT, WBRT vs. WBRT plus

Abbreviations: BMs, brain metastases; OS, overall survival; RPA, recursive partitioning analysis classes; GPA, graded prognostic assessment index; DS-GPA, diagnosis-specific GPA; KPS, karnofsky performance status; WBRT, whole brain radiotherapy; SRS, radiosurgery; SRT, stereotactic radiotherapy.

SRS/SRT, clinical trials exploring the role of SRS/SRT for 1–5 brain metastases. Exclusion criteria were: articles with no detailed information regarding clinical outcomes, review articles, editorials, articles not written in English language.

CLINICAL DATA

To assess the role of SRS, several randomized trials have been published in the last decades. In the randomized trial by Kondziolka et al. (26), 27 patients with 2–4 BMs were enrolled and received WBRT alone vs. WBRT and an additional SRS boost. The size of BMs was 2.5 cm or less. WBRT was given up to a total dose of 30 Gy in 12 fractions and the SRS dose was 1 × 16 Gy. Local control rates in patients receiving WBRT alone were 0%, compared to 92% in those receiving a SRS boost, suggesting high local failure with WBRT alone. Median time to local failure was 6 months with WBRT alone compared to 36 months with WBRT and SRS ($p = 0.0005$). In this study, the neurocognitive function was not assessed. In the WBRT plus SRS boost arm, the OS was 11 months, while in the WBRT alone arm the OS was 7.5 months. The Radiation Therapy Oncology Group (RTOG) conducted a similar study (27) from 1995 to 2008. In this trial, 333 patients with 1–3 BMs were randomized to receive WBRT vs. WBRT and SRS. Overall, there was no significant difference in OS between two groups, but a statistically significant advantage for patients with a single lesion. For these cases, the OS increased from 4.9 to 6.5 months with the addition of SRS ($p = 0.039$). It was also observed that in RPA class I patients, survival improved from 9.6 to 11.6 months with the addition of SRS ($p = 0.045$). The results of a follow-up analysis of the RTOG95-08 study were recently published (28). In this study, the RTOG95-08 patients were retrospectively evaluated according to the GPA score (29). The analysis confirmed that there was no OS benefit for patients with 1 to 3 BMs; however, there was a benefit for a subset of patients with a GPA score of 3.5–4.0 (median survival time for WBRT+SRS vs. WBRT alone was 21.0 vs. 10.3 months, $p = 0.05$) regardless of the number of metastases. This result strengthens the observations that SRS, when delivered with WBRT, improves LC and OS in patients with optimal prognostic factors and controlled primary tumors.

At the same time, with the arising of these results, the idea of omitting upfront WBRT in the scenario of oligometastatic BM in favor of SRS/SRT alone evolved, in order to reduce the risk of the neurocognitive deterioration. In this setting, 4 phase III randomized trials (29–32) evaluated the use of SRS alone compared to SRS plus WBRT in patients with 1–4 BMs.

In the Japanese Radiation Oncology Study Group (JROSG 99-1) (30) trial, 132 patients were randomized from 1999 to 2003 to receive SRS with WBRT vs. SRS alone. The inclusion criteria were 1–4 BMs, each with a maximum diameter of 3 cm and a KPS score of ≥70. The primary endpoint was intracranial recurrence rate the secondary points were OS, preservation of neurocognitive function and radiation toxicity. At 12 months follow-up, intracranial recurrence was 76% without WBRT compared to 47% with additional WBRT ($p < 0.001$). The 1 year freedom from new BMs was also improved for the group of patients treated with WBRT (64%) as compared to patients receiving SRS alone (41.5%; $p = 0.003$). Overall, more salvage treatments were required in patients treated with SRS. There were no significant differences in OS, radiation-associated toxicity or death from neurological causes.

Regarding the neurocognitive impact of radiotherapy, a phase III study from the MD Anderson (31) treated patients with 1–3 brain metastases comparing SRS plus WBRT vs. SRS alone. Eligibility requirements were: age ≥18 years, RPA class I or II, KPS ≥70 and 1–3 newly diagnosed BMs. The primary endpoint was neurocognitive function. This was measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) at 4 months. An early interim analysis showed a statistically significant decline in learning and memory function at 4 months of 96% for the SRS plus WBRT arm, resulting in an early closure of the trial. Overall, in-brain recurrences were more frequent in the group of patients treated with SRS alone. Within 1 year of follow-up, 73% of patients treated with SRS plus WBRT did not develop new BMs as compared to 27% of patients treated with SRS alone ($p = 0.0003$). In contrast to the JRSOG study (30), the median OS was 15.2 months for SRS alone vs. 5.7 months for SRS plus WBRT ($p = 0.02$). Taken together, the authors concluded that SRS alone with close follow-up is the preferred treatment strategy in patients with newly diagnosed BMs, as improved neurocognitive outcomes and potentially improved OS were reported. In 2010, the European Organization for Research and Treatment of Cancer (EORTC) (20) published the results of a phase III trial, which included patients with 1–3 BMs and a WHO performance status [PS] of 0–2 with a stable systemic disease or asymptomatic synchronous primary tumor. The study compared adjuvant WBRT with observation after SRS or surgery. The primary end-point was time to WHO PS deterioration of more than 2 points. Of 359 enrolled patients, 199 underwent SRS, and 160 underwent surgery. The patients were randomized to observation or WBRT. The median time to WHO PS deterioration of more than 2 was 10.0 months in the observation group and 9.5 months in the WBRT arm ($p = 0.71$). OS was not statistically influenced whether patients received upfront WBRT or not. In patients receiving WBRT, radiotherapy did not improve the duration of functional independence, while it reduced the risk of in-brain recurrence. A secondary analysis of the same study (33) targeted on the health-related quality of life (HRQoL) and showed better HRQoL scores for global health at 9 months in the observation arm as compared to WBRT ($p = 0.0148$). Physical function at 8 weeks, cognitive functioning at 12 months, and fatigue at 8 weeks were improved for patients of the observation group. Recently, the results of the North Coast Cancer Treatment Group (NCCTG-Alliance) N0574 phase III study (21) comparing SRS alone vs. SRS+WBRT in patients with 1–3 BMs (<3 cm) were published. Overall, 208 patients were randomized and the primary endpoint was neurocognitive outcome. The cognitive deterioration was defined as a decline of >1 standard deviation from baseline on at least 1 cognitive test at 3 months. Cognitive deterioration was higher after WBRT with SRS (91.7%) as compared to SRS alone (63.5%, $p < 0.001$). In long-term survivors (≥12 months), cognitive deterioration was

TABLE 1 | Results by randomized controlled trials (RCT) for 1–4 BMs.

RCT/Patient number	Primary tumor site: %	Median age (range)	Technique dose	Number brain metastases: %		Local Control (SRS vs. WBRT+SRS)	Distant Control (SRS vs. WBRT+SRS)	Overall survival (SRS vs. WBRT+SRS)	Neurocognitive Quality of life (SRS vs. WBRT+SRS)	Radionecrosis (SRS vs. WBRT+SRS)
Aoyama (30) SRS (*N* = 67) vs. WBRT + SRS (*N* = 65)	SRS Breast: 4 Lung: 67 Colorectal: 9 Other: 20	SRS: 62.1 y (33–86) WBRT+SRS: 62.5 y (36–78)	Technique: NA SRS alone: 22–25 Gy or 18–20 Gy in 1 fx WBRT: 30 Gy in 10 fx + SRS dose reduced 30%	SRS 1: 49 2–4: 51	WBRT+SRS 1: 48 2–4: 52	72.5% vs. 88.7% 1 y (*P* = 0.002)	36.3% vs. 58.5% 1 y (*P* = 0.003)	28.4% vs. 38.5% 1 y (*P* = 0.42)	MMSE same in both arms	Grade 4: SRS alone 1 cases and SRS+WBRT 2 cases
	WBRT+SRS Breast: 9 Lung: 66 Colorectal: 8 Other:17									
Chang (31) SRS (*N* = 30) vs. WBRT+SRS (*N* = 28)	SRS Breast: 13 Lung: 53 Melanoma: 13 Other: 21	SRS: 63 y (35–82) WBRT+SRS: 64 y (40–78)	PRIMART linear accelerator SRS: 20–24 Gy or 18 or 15 Gy in 1 fx WBRT: 30 Gy in 12 fx	SRS 1: 60 2: 23 3: 17	WBRT+SRS 1: 54 2: 28 3: 18	67% vs. 100% 1 y (*P* = 0.012)	45% vs. 73% 1 y (P =.02)	63% vs. 21% 1 y (P =.003)	Statistically significant decline in learning and memory function in WBRT arm	2 cases of grade 4 in SRS alone arm
	WBRT+SRS Breast: 14 Lung: 57 Melanoma: 11 Other: 18									
Kocher (32) SRS (*N* = 90) vs. WBRT+SRS (*N* = 95)	Observation* Breast: 11 Lung: 52 Colorectal: 9 Other: 28	Observation* 61 y (37–80) WBRT* 60 y (26–81)	Linear accelerator and Gamma-knife SRS: 20–25 Gy in 1 fx WBRT: 30 Gy in 10 fx	SRS 1: 68 2: 22 3:10	WBRT+SRS 1: 66 2: 24 3: 10	69% vs. 81% 2 y (*P* = 0.04)	52% vs. 67% 2 y (*P* = 0.023)	Median OS*: 10.9 months vs. 10.7 months (*P* = 0.89)	Decreased HRQoL at 9 months with WBRT arm	SRS alone: 8% SRS and WBRT: 13%
	WBRT* Breast: 12 Lung: 54 Colorectal: 8 Other: 26									
Brown (38) SRS (*N* = 111) vs. WBRT+SRS (*N* = 102)	SRS Breast: 9.9 Lung: 72.1 Colorectal: 6.3 Other: 11.7	SRS: 59.8 ± 10.4 y WBRT+SRS: 61.4 ± 10.6 y	Linear accelerator and Gamma-knife SRS alone: 24–20 Gy in 1 fx WBRT: 30 Gy in 12 fx + SRS 22–18 Gy in 1 fx	SRS 1: 49.5 2: 35.1 3: 15.3	WBRT+SRS 1: 54.9 2: 35.3 3:9.8	72.8% vs. 90.1% 1 y (*P* =0.003)	69.9% vs. 92.3% 1 y (*P* < 0.001)	Median OS: 10.7 months vs. 7.5 months (*P* = 0.92)	More decline in immediate recall, delayed recall, and verbal fluency in WBRT arm	NA
	WBRT+SRS Breast: 6.9 Lung: 65.3 Colorectal: 4.0 Other: 23.8									

Including surgical patients. SRS, radiosurgery; WBRT, whole brain radiotherapy; y, year/years; fx, fraction; MMSE, mini-mental state examination; HRQoL, health-related quality of life; NA, not available.

more frequent in patients receiving the combined treatment of SRS plus WBRT. The 1 year intracranial control rate was 84.6% with SRS+WBRT and 50.5% with SRS alone. Median OS was 10.4 months for SRS alone vs. 7.4 months with addition of WBRT ($p = 0.92$), but the study was not powered for this endpoint. These results are summarized in **Table 1**.

DISCUSSION

SRS/SRT without WBRT is an evolving paradigm in the management of patients with limited intracranial disease (1–4 metastases) (34). Historically, the definition of SRS was introduced by Leksell in the 1950s (35), as "a single high-dose irradiation per fraction, stereotactically directed to an intracranial region of interest" to treat BM in a non-invasive way. SRS/SRT procedures have certain characteristics: a well-defined target delineation by means of magnetic resonance imaging, a highly conformal target dose distribution, a steep dose gradient, accurate patient setup and delivery of a high dose of irradiation per fraction. The objectives of these SRS/SRT characteristics are mainly represented by the possibility to decrease the radiotherapy-related intracranial toxicity (through avoidance of WBRT) and to improve tumor control (36, 37).

Concerning the first clinical aspect, Brown et al. published the results of a phase III trial in which patients with 1–3 BMs were randomized to receive SRS or SRS plus WBRT (38). The authors showed that SRS alone resulted in less cognitive impairment compared to SRS plus WBRT. On the other hand, Yamamoto et al. analyzed the role of SRS using Gamma-Knife in 1–10 BMs patients, suggesting that SRS without WBRT in patients with five to ten BMs is non-inferior to the outcome in patients with two to four BMs (39).

The role of WBRT in the management of BMs was recently discussed in two other settings: (i) in the case of resected BMs and (ii) in the BMs from Non-Small Cell Lung Cancer unsuitable for resection or SRS/SRT. In the first clinical scenario, the randomized phase III- NCCTG N107C/CEC3 trial showed that patients who underwent SRS of the surgical cavity had less adverse events and neurocognitive decline compared patients treated with WBRT, without any differences in OS (40). On the other hand, the randomized phase III QUARTZ comparing dexamethasone plus WBRT or dexamethasone alone in case of multiple BMs from Non-Small Cell Lung Cancer unsuitable for resection or SRS/SRT, showed no difference in OS between the two groups (41).

Several other trials tested the impact of SRS/SFRT in case of multiple BMs, reporting no correlation between the number of BMs and OS (42, 43). Thus, the possibility to propose SRS in the setting of BMs is expanding over the numerical well-defined limits of "oligometastases." As confirmed in the recent NCCN guidelines, SRS could be indicated irrespectively to the number of BMs (not specifically specified) while other aspects, including a good performance status, the overall tumor volume and/or the presence of radioresistant histology are elements which need to be taken into account (44).

In the current review, we focused our search items looking at randomized studies evaluating the potential benefit of SRS/SFRT for brain oligometastases. To date, no difference is observed in terms of OS between SRS/SRT alone compared to WBRT plus SRS. Notably, SRS alone achieves higher rates of LC compared to WBRT. A possible strength of SRS adoption is the potential decreased neurocognitive impairment. In fact, the risk of neurocognitive decline seems to be negligible with SRS alone compared to WBRT, although hippocampal avoidance during WBRT represents a possible technical solution to improve the tolerability of WBRT (45). The upfront SRS approach does not preclude the possibility of performing salvage treatment for new BMs using WBRT or another SRS course. Notably, the upfront omission of WBRT increases the rate of intracranial relapse, in terms of out-of-field appearance of new BMs.

Obviously, this last failure could be related to several factors: (i) the different aggressive biological behavior and genetic heterogeneity of the tumors, (ii) the selective resistance to anti-tumoral drugs, (iii) the poor or non-penetration of drugs across the blood-brain barrier. New systemic therapies are showing promising CNS activity. For this reason, in case of brain oligometastases, the new systemic therapies could act as a "whole brain irradiation" surrogate to control for brain micrometastatic disease, while SRS/SRT can control the macroscopic foci.

In a cost-effectiveness analysis of SRS/SRT alone compared to SRS/SRT with upfront WBRT for BMs, it seems that SRS alone was found to be more cost-effective for patients with 1–3 BMs compared to upfront WBRT plus SRS/SRT (46). The emerging interest to treat patients affected by more than four BMs allowed to introduce a new technology of linac-based SRS/SRT for multiple BMs in daily clinical practice. The main intent of this new technology is to reduce the overall treatment time and the costs for the health systems due to the ability of delivering SRS/SRT for multiple BMs within a single session (47).

In conclusion, the role of SRS/SRT for brain metastases seems to be definitively assessed as a crucial part on the management of BMs patients. SRS/SRT has shown to be a safe and effective treatment procedure, able to pursuit a high level of local control.

AUTHOR CONTRIBUTIONS

FA and RM provided the largest writing contribution to the manuscript and edited all sections of the manuscript. AF, SC, FG, and VF performed literature review and wrote multiple sections of the manuscript.

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REVIEW
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Stereotactic Body Radiotherapy (SBRT) for Oligometastatic Spine Metastases: An Overview

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The oligometastatic state is hypothesized to represent an intermediary state of cancer between widely metastatic disease and curable, localized disease. Advancements in radiotherapy have allowed for delivery of high precision, dose escalated treatment known as stereotactic body radiotherapy (SBRT) to targets throughout the body with excellent rates of local control. Recently, the first phase II randomized trial comparing conventional radiotherapy to comprehensive SBRT of oligometastatic disease demonstrated an overall survival and progression free survival advantage. The spine is a common site of metastasis, and a complex site for SBRT given the adjacent spinal cord and the tumor embedded within the bone tissue putting the patient at risk of fracture. Although there are expert spine SBRT guidelines for practice, there are as yet no reported randomized trials that proves superiority as compared to conventional radiation. The use of SBRT in patients with oligometastatic disease and spinal metastases is the focus of this review.

Keywords: stereotactic body radiotherapy (SBRT), oligometastases, spine metastases, response assessment, outcomes, toxicities

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OLIGOMETASTASES AND SBRT

Hellman and Weichselbaum first proposed the clinical *oligometastatic* state in 1995 to reflect a subset of patients with limited metastatic disease (1). From the spectrum theory, this is suggested to represent an intermediary cancer state where the biological profile of a cancer may not progress to widespread metastases (2). Within this group, an opportunity arises where targeted treatment toward limited metastases may confer disease and even possibly survival advantages. Advancements in imaging techniques (i.e., MRI, PET), and development of cancer specific imaging strategies (i.e., PSMA-PET), have allowed for greater ability to identify those with oligometastatic cancer.

Select patients with oligometastatic disease to the lung and liver are considered for surgical metastectomy and within this highly selected group, observed outcomes in a non-randomized setting were promising. The International Registry of Lung Metastases included 5,206 patients over five decades, and demonstrated 5-year overall survival (OS) of 36% after resection of limited lung metastases from mostly epithelial cancers or sarcomas (3). In colorectal patients, hepatic resection is considered for limited liver metastases with survival nearing 50% at 5 years (4).

Advancements in radiotherapy over the past decade, specifically in image-guided linear accelerator technology, treatment planning, and better understanding of normal tissue constraints with hypofractionated radiation, has led to increased interest in safe delivery of ablative doses of radiation with stereotactic body radiotherapy (SBRT). Advantages of SBRT in comparison to

metastectomy includes the lack of surgical recovery time, side effect profile, and ability to safely target multiple metastatic lesions. SBRT may be secondarily advantageous in inducing an abscopal effect especially in malignancies strongly associated with an immune response (5).

High quality evidence supporting the role of SBRT to oligometastases with traditional endpoints such as overall survival (OS) and progression free survival (PFS) are lacking, but a significant volume of researchers are attempting to answer this question. The SABR-COMET study was presented at the 2018 American Society for Radiation Oncology annual scientific meeting and represents the first Phase 2 randomized study to report improved outcomes in targeting oligometastatic disease with SBRT (6). This study included 99 patients randomized 1:2 to palliative standard of care (SOC) treatments vs. standard of care plus SBRT to all metastatic lesions (to a maximum of 5 lesions). Median overall survival was 28 months in the SOC arm compared to 41 months in the SBRT arm ($p = 0.09$) and PFS was significantly improved (6 months in the SOC arm vs. 12 months in the SBRT arm, $p = 0.001$). The results of confirmatory Phase 3 randomized studies such as CORE, SARON, and NRG-BR002 are eagerly awaited. A case demonstration of a patient treated under this approach is described in **Figure 1**. In the non-small cell lung cancer population specifically, two trials have assessed consolidative local therapy in oligometastatic disease (7, 8) with both noting significant improvements in progression free survival compared to maintenance therapy alone.

SPINE METASTASES AND SBRT

The spine is a common location for metastases and confers significant morbidity and mortality. The classical treatment approach for patients with symptomatic spine metastases is conventional palliative radiotherapy delivered with two parallel opposed beams with common fractionation regimens such as 8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions. Though effective in improving symptomatology, there is poor local control (LC) (9). With the availability of more lines of systemic therapy improving patient survival, there is a desire in select patients to improve durable LC and prevent neurologic compromise. Delivery of high biological effective doses (BED) of radiotherapy with SBRT precisely to the spine yields prolonged local control along with pain relief (**Table 1**). For those with oligometastatic disease, SBRT of known disease can prolong progression-free survival and potentially delay entry to next line of systemic therapy (29). In the post-operative setting, neurologic status is maintained through improvements in local control after SBRT. Further, following prior spine radiotherapy, it is a method of safely retreating the same or adjacent segments while minimizing dose to critical neurological structures.

Specific to spine oligometastases, Barzilai et al. reported results from the AO Spine multicenter prospective cohort Epidemiology, Process, and Outcomes of Spine Oncology (EPOSO) study (30). Patients with oligometastatic disease (defined as <5 metastases) showed evidence of better survival compared to those with polymetastatic disease (>5 metastases). Of note, improved local control at 6 and 12 months were identified in the solitary/single spine metastasis subgroup, reflective of increased utilization of aggressive surgical and/or radiosurgery approaches.

Spine SBRT pertains unique considerations due to the balance of risk of neurologic compromise related to tumor progression and toxicities such as vertebral body fracture and myelopathy. Advancements in radiation planning and delivery, image guidance, robotic patient positioning, and understanding of dose tolerances to critical structures have made spine SBRT possible. With greater clinical experience, guidelines have been developed to direct safe practice (31–33) though supporting high-quality Phase 3 randomized data are pending. Delivery of spine SBRT requires careful patient selection, familiarity with the technique and an understanding of potential toxicities.

PATIENT SELECTION

Compared to conventional external beam radiotherapy, spine SBRT is significantly more resource intensive from both a patient and systems perspective. Multidisciplinary discussion with specialized spine surgeons, radiologists, radiation, and medical oncologists is essential for careful selection of patients to avoid treatment of those that may not benefit. Practical considerations such as funding for novel techniques must also be considered, where "payers," either that of public systems or private health insurance, may be reluctant to reimburse costly treatment modalities with limited prospective, high quality evidence justifying their use.

A number of schemes have been proposed to assist in identification of patients that benefit most from spine SBRT (34–36). Laufer et al. developed a four-point framework in the treatment of spine metastases (35). The Neurologic, Oncologic, Mechanics, and Systemic (NOMS) assessments assist in determining the optimal therapy for patients. The International Spine Oncology Consortium Report similarly proposes a multidisciplinary algorithm for the management of spine metastases given the recent advances in spine SBRT, and utilizes similar principles to guide management (34).

Prognosis

Patients with spine metastases, despite being generally thought to be incurable, represent a heterogenous population (37) where some may live many years (i.e., a patient with oligometastatic hormone responsive prostate cancer) whilst others a significantly shorter time interval (i.e., one who has failed second line systemic therapy for widely metastatic pancreatic cancer). In the former case, one may consider more aggressive techniques such as SBRT, favoring long-term local control as this patient would derive most benefit, whereas the latter patient may benefit most from conventional palliative radiotherapy (38), or possibly best supportive care alone. One should identify patients with favorable prognoses who may derive benefit from spine SBRT. Age, performance status, comorbidities, and functional capacity can assist in determination of such. The prognosis of patients as predicted by physicians is often generous, however, specific to spine

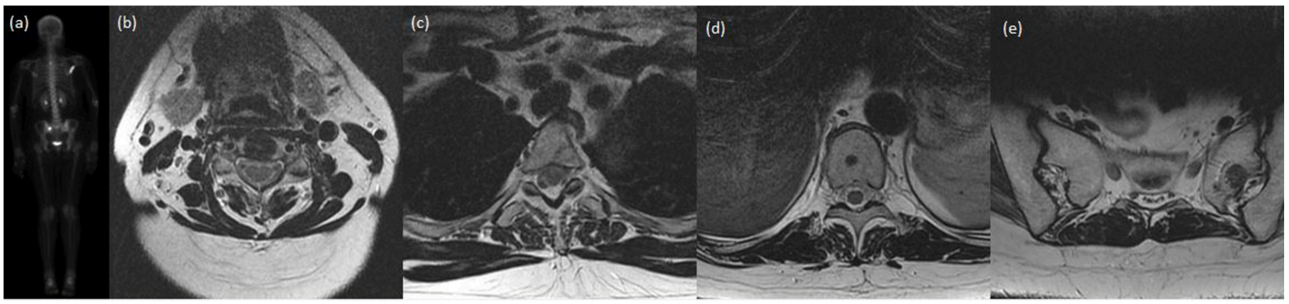

FIGURE 1 | A case presentation of a lady with invasive ductal carcinoma of the breast who was treated definitively with lumpectomy, adjuvant chemotherapy, and adjuvant radiotherapy. Shortly after completion of therapy, on re-staging investigations, she was found to have oligometastatic disease in the bones, specifically at C4, T3, T10, the left sacral ala, and right scapula. She received SBRT to each site and was started on hormonal therapy. At most recent follow-up 20 months later, she has not had progression of known disease nor interval development on new metastatic disease. **(a)** Posterior-anterior projection of pre-treatment bone scan demonstrating increased uptake within the right scapula, T3 and the right sacral ala. Subsequent images of axial slice of T2-weighted MRI demonstrating near complete marrow replacement of C4 **(b)**, focal marrow abnormality in posterior T3 body **(c)**, rounded focus centrally of the T10 vertebral body **(d)**, and 13 mm lesion of left sacral ala **(e)**.

metastases, Jensen et al. propose a Prognostic Index for Spine Metastases (PRISM) which can assist in determining the most appropriate method of treating spine metastases (39). Briefly, scoring accounts for gender, performance status, previous therapy at the intended treatment site, number of organ systems involved, time elapsed between diagnosis and metastasis, and number of spine metastasis. The scoring system categorizes patients into groups 1 (best prognosis) through 4 (worst prognosis), with median overall survivals not reached in subgroup 1, and 24.1, 13.1, and 6.5 months in groups 2, 3, and 4, respectively.

Histology

Histologies traditionally felt to be radioresistant (renal cell carcinoma, melanoma, sarcoma) demonstrate poor tumor control rates with conventional radiotherapy techniques (40, 41). Spine SBRT may overcome this radioresistance. In renal cell carcinoma specifically, local control at 1-year has been reported to be >80% (18, 42). As such, there is preference toward SBRT for patients with radioresistant histologies where local control is desired. In contrast, highly sensitive histologies, such as hematologic malignancies or small cell lung cancer may warrant upfront systemic therapy or derive similar benefit with conventional radiotherapy.

Systemic Disease and Systemic Treatment Options

Assessment of systemic burden of disease and the availability and response to systemic therapies can influence patients' goals of care. In patients with widely metastatic disease, there may be an urgency to proceed with systemic therapy over focal treatment of minimally symptomatic spinal disease. Further, the availability of further lines of systemic treatment options is intimately related to prognosis, and clinicians may favor conventional techniques in those with high visceral burden of disease with limited further options or prognosis.

Stability and Epidural Spinal Cord Compression

Mechanical spinal instability and presence of high-grade epidural spinal cord compression (ESCC) are independent indications for potential surgical intervention; radiotherapy, either with SBRT or conventional techniques may not be the most appropriate upfront in patients with reasonable prognoses.

Mechanical instability is usually not corrected with radiotherapy alone. As a method of grading instability, the Spinal Instability Neoplastic Score (SINS; **Table 2**) is a validated assessment tool of spine disease which may warrant surgical intervention (43–45). This score considers location, presence of mechanical pain, type of bony lesion, spinal alignment, vertebral body collapse, and posterolateral involvement and generates a score ranging from 0 to 18, with stable segment scores between 0 and 6, potentially unstable segments scoring between 7 and 12, and unstable lesions between 13 and 18. Potentially unstable and unstable lesions may warrant surgical evaluation.

In the case of epidural disease, the degree of ESCC and its potential consequences such as myelopathy or radiculopathy must be evaluated. Grading the severity of ESCC is commonly done via the Bilsky score, which facilitates communication between health-care providers (46). SBRT may be a more appropriate treatment option for those patients with appropriately graded low volume epidural disease. However, in the setting of acute clinical changes and/or high grade ESCC (Bilsky 2 or 3, and possibly 1c) patients warrant surgical evaluation. Consideration can be made to separation surgery, in which surgery to establish the epidural space is performed, followed by SBRT (47).

Post-operative SBRT

High grade ESCC and/or mechanical instability often warrants surgical intervention in the appropriate patient population. In this setting, significant rates of local recurrence (up to 69.3% at 1-year) (48) justifies adjunctive therapies. Post-operative radiotherapy has traditionally been delivered with conventional techniques (49), although recently SBRT in this setting has

TABLE 1 | Outcomes after spine SBRT for *de novo* metastases.

References	Patients/spinal segments (n/n)	Histology	Dose fractionation [dose (Gy)/fractions]	Follow-up duration (median, months)	Local control (time, if available)	Pain response
Tseng et al. (10)	145/279	Mixed	24/2	15	90.3% (1-year) 82.4% (2-years)	NR
Azad et al. (11)	25/25	Mixed	15–25.5/1–5	18	84%	2/3 had pain relief
Anand et al. (12)	52/76	Mixed	24–27/1–3	8.5	94% (1-year) 83% (2-years)	90–94% complete pain relief
Bishop et al. (13)	285/332	Mixed	Median tumor dose 43 Gy (BED, a/b = 10)	19	88% (1-year) 82% (3-years)	NR
Sellin et al. (14)	37/40	RCC	24–30/1–5	49.0	57%	41% report pain improvement
Bate et al. (15)	24/24*	Mixed	16–30/1–5	9.8	96% (1-year)	NR
Sohn et al. (16)	13/13	RCC	38/4 (median)	NR	86% (1-year)	77% overall (23% complete pain response)
Guckenberger et al. (17)	301/387	Mixed	10–60/1–20	11.8	90% (1-year) 84% (2-years)	44% with severe pre-treatment pain, pain free. 56% with mild/moderate pre-treatment pain, pain free.
Thibault et al. (18)	51/51*	RCC	18–30/1–5	12.3	83% (1-year) 66% (2-years)	NR
Garg et al. (19)	47/47	Mixed	16–24/1	17.8	88% (18 months)	18 patients pain-free post-treatment compared to 13 patients pre-treatment
Chang et al. (20)	93/131	Mixed	NR	23.7	89% (1-year)	NR
Gill et al. (21)	14/14*	Mixed	30–35/5	34	80% (1-year) 73% (2-years)	NR
Wang et al. (22)	149/166	Mixed	27–30/3	15.9	81% (1-year) 72% (2-years)	54% pain free at 6-months, compared to 26% at baseline
Staehler et al. (23)	55/105	RCC	19–20/1	33.4	94% (1-year) 90% (2-years)	Median pre-treatment score 5, median post-treatment score 0 1 week after
Sahgal et al. (24)	14/18	Mixed	24/3 (median)	9	72%	NR
Yamada et al. (25)	93/103	Mixed	18–24/1	15	93% (2-years)	NR
Chang et al. (26)	17/22	Mixed	27–30/3–5	NR	68%	Narcotic usage fell from 60% at baseline to 36% at 6 months
Gerszten et al. (27)	8/8*	Breast	15–22.5/1	16	100%	Long-term axial and radicular pain improvement occurred in 96% who were treated primarily for pain
Ryu et al. (28)	49/61	Mixed	10–16/1	NR	96% (9-months)	Overall response 85%

*NR, not reported; *Assuming one segment per patient.*

been explored (50). Overall, post-operative SBRT was well tolerated [no grade 3 or 4 toxicities, 3.8% rate of grade 1/2 gastrointestinal and genitourinary toxicities, 9% rate of pain flare and vertebral compression fracture (VCF)] with excellent one-year local control between 84 and 88% reported (47, 51).

SPINE SBRT TECHNIQUE

Safe delivery of high doses of radiation to the spine is imperative to avoid potentially catastrophic neurologic sequelae. Recent advances in treatment planning, immobilization, treatment delivery and a better understanding of toxicities associated with SBRT have allowed for advancements within this field (**Figure 2**). Near rigid patient immobilization, consensus treatment volume definitions, and image-guidance are key for delivery of spine SBRT (52).

Near rigid patient immobilization is required to allow for inter-fraction reproducibility and minimize planning target volumes, to sculpt dose to intended targets and avoid neurologic toxicities. Many methods of immobilization have been explored which must consider patient comfort during relatively long

TABLE 2 | Spinal instability neoplastic score (SINS).

Category	Description	Score
Location	Junctional (occiput-T2, C7-T2, T11-L1, L5-S1)	3
	Mobile (C3-C6, L2-4)	2
	Semirigid (T3-T10)	1
	Rigid (S2-S5)	0
Pain	Yes	3
	Occasional non-mechanical pain	1
	No	0
Bone lesion	Lytic	2
	Mixed lytic/blastic	1
	Blastic	0
Alignment	Subluxation/translation	4
	De novo deformity	2
	Normal	0
Vertebral body	>50% collapse	3
	<50% collapse	2
	No collapse but >50% involvement by tumor	1
	None of the above	0
Posterolateral involvement	Bilateral	3
	Unilateral	1
	None	0

**The SINS score adapted from Fisher et al. (39).*

simulation and treatment times. The physiologic motion of the spinal cord is <0.5 mm in all directions (53), which is relatively insignificant compared to potential gross patient motion. Our practice is acquisition of a treatment scanning CT scan with patients secured using a BodyFIX device (Elekta AB, Stockholm, Sweden) which has demonstrated reproducibility within 1.2 mm and 0.9° with 95% confidence (52). Other immobilization devise include custom cradles (25) and stereotactic body frames (54).

Intra-fraction motion is a further consideration due to potentially long treatment times and patient comfort. Using either an evacuated cushion, vacuum body fixation or thermoplastic S-frame mask for lesions treated above T3, Li et al. performed pre-treatment verification cone beam (CBCT) as well as mid-fraction and post-treatment CBCT. The authors found margins required to encompass residual setup errors to be within 2 mm with vacuum body fixation and 3 mm with the other systems (55). Another study found a 3 mm planning margin to be sufficient to account for both intra-fraction and inter-fraction motion, with greatest intra-fraction motion in the x-plane of 0.7 mm (95% confidence interval 0.5–1.0 mm) (56).

After acquisition of planning CT scan, axial T1 and T2 weighted volumetric MRI sequences are fused to aid in target and critical neural structure delineation. In those cases where MRI is contraindicated or uninformative, CT myelogram may be an alternative.

The International Spine Radiosurgery Consortium has published consensus guidelines for target delineation in spine SBRT based on expert opinion with 10 representative cases (57). In general, gross tumor volume (GTV) should utilize all available imaging modalities and include epidural and paraspinal disease extension. The clinical target volume (CTV) should include areas of potential microscopic extension. In general, if GTV were present within the vertebral body, pedicle, transverse process, lamina, spinous process, the entire region should be included. In addition, as a rule of thumb, the adjacent potential bony region should be included. For example, GTV involving the vertebral body and right pedicle should correspondingly expand to a CTV encompassing the entire vertebral body, right pedicle, right transverse process and right lamina. With bone only disease, extraosseous expansion of CTV volumes should not be necessary, specifically into the epidural space or paraspinal soft tissue spaces. The planning target volume (PTV) was suggested to be a uniform expansion of $\leq$3 mm, depending on immobilization and image guidance technique.

In a separate study of post-operative epidural progression following SBRT, Chan et al. found that post-operative epidural disease extent underestimated treatment volumes and that consideration of pre-operative disease is crucial to prevent subsequent progression (58). An international group of experts led by Redmond et al. generated consensus contouring guidelines for post-operative spine SBRT (59). Recommendations were to include the entire pre-operative extent of both bony and epidural disease and immediately adjacent bony structures as part of the CTV. With circumferential epidural disease specifically, a "donut" shaped CTV was applied regardless of the post-operative epidural disease extent. Surgical instrumentation was suggested to be excluded from the CTV.

Optimal dose fractionation for spine SBRT is unknown. Common fractionation schemes include 16–24 Gy/1 fraction, 24 Gy/2 fractions, 24–30 Gy/3 fractions, 30 Gy/4 fractions, and 30–40 Gy/5 fractions. Considerations includes risk of vertebral compression fracture [up to 39% risk with single fractions (60)] and treatment volume, where very large tumors may warrant 4–5 fraction courses. Single fractions of 15 Gy are effective, however, may be related to increased toxicities such as VCF, pain flare and myelopathy, and fractionation may reduce this (61). Our standard practice is a course of 24–28 Gy in 2 fractions or 30 Gy in 4 fractions for larger tumors, to maintain an acceptable fracture risk of 10%.

There are differences in SBRT treatment planning compared to conventional techniques and Task Group 101 of The American Association of Physicists in Medicine outlines best practices (62). Perhaps the greatest change is allowing hotspots within treatment targets and the requirement for sharp drop-offs especially near organs at risk. As such, CTV and PTV margins are significantly smaller, whilst delivery with non-overlapping and possibly co-planer beams allow for sharp dropoff. Relating to spine SBRT specifically, there is an absolute requirement to not violate the thecal sac and spinal cord PRV dose limits for the sake of preventing catastrophic neurologic sequelae (63, 64). As such, it is acceptable for PTV coverage to be compromised.

Once a treatment plan has been generated, assessment of patient positioning on the treatment unit should be conducted. Image verification is completed with cone-beam CT after patient set-up. A Hexapod robotic couch (Medical Intelligence, Schwabmuenchen, Germany) facilitates set-up correction with

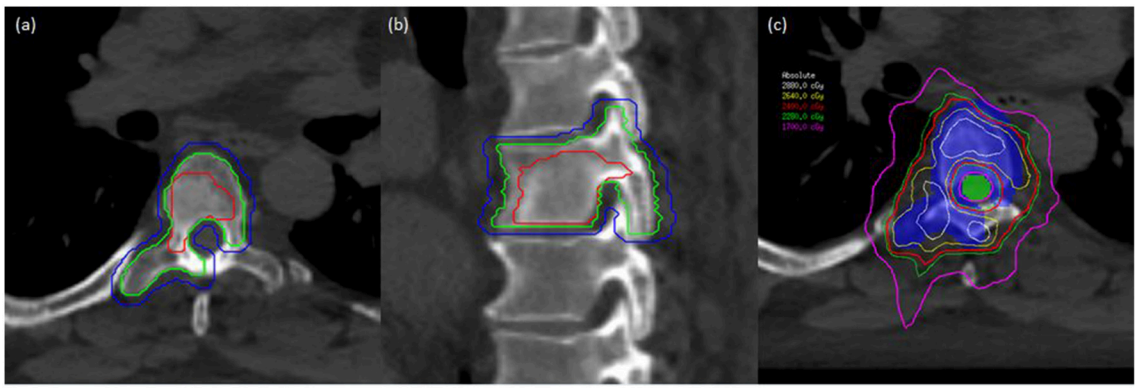

FIGURE 2 | A man with oligometastatic castrate-resistant prostate cancer with painful spine metastases. This man was treated to 24 Gy in 2 fractions. **(a)** Axial planning CT scan demonstrating T6 vertebral level with gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) delineated with red, green, and blue lines, respectively. **(b)** Sagittal planning CT demonstrating T6 vertebral level with GTV, CTV, and PTV in red, green, and blue, respectively. **(c)** Dose distribution at the level of T6 with PTV (colorwash blue) and spinal cord planning organ at risk volume (PRV) in colorwash green. Demonstration of sharp-dose fall-off to respect critical structures while allowing coverage of the target volumes.

six degrees of freedom. Subsequent CBCT can then be acquired for assessment of residual setup error, and intrafraction and post-treatment periods to ensure geometric stability. Other image verification techniques include CT-on-rails (65) and Cyberknife tracking (66).

OUTCOMES

Response Assessment

Assessment of response post-spine SBRT is challenging as criteria such as RECIST 1.1 are difficult to apply, and tumor specific phenomena exist whereby imaging must be interpreted with caution and with familiarity of expected changes after treatment. MRI signal changes creating a pseudoprogression phenomenon, as first seen following treatment of brain tumors, can occur after spine SBRT. Rather than true progression which demonstrates consistent growth over time, the radiographical appearance of pseudoprogression subsequently subsides on serial imaging. The incidence of pseudoprogression has been reported in the range of 14–37% and risk factors include lytic tumors, earlier volume enlargement, greater GTV to reference non-irradiated vertebral body T2 intensity ratio, and growth confined to 80% of the prescription isodose line (67–69).

In response to the need for common criteria assessing response post-spine SBRT, a group of international experts devised the SPIne response assessment in Neuro-Oncology (SPINO) guidelines as a method of standardized reporting (70). Recommendations of imaging response include spine MRI every 2–3 months for the first 12–18 months then every 3–6 months thereafter, interpreted by a radiologist and radiation oncologist jointly treating patients with this technique. Progression is defined as gross increases in tumor volume, new tumors in epidural space, and neurologic deterioration due to known epidural disease. Where progression is questionable, serial imaging and consideration of tissue biopsy should be made to rule out pseudoprogression. Assessment of pain response should be conducted with the Brief Pain Inventory at 3 months post-treatment adopting the consensus guidelines published by the International Bone Metastases Consensus Working Party (71).

Local Control

Treatment of *de-novo* metastases with spine SBRT yields favorable local control, in the range of 80–95% in a heterogenous patient population, treated with a number of dose/fractionation regiments ranging from a single 15 Gy fraction to 30 Gy in 3 fractions (19, 22, 72). In a review of nearly 1,400 patients following SBRT, Hall et al. report overall local control of ∼90% at 15 months (73). The largest single institutional experience utilizing 24 Gy in 2 fractions as standard for *de novo* metastases included 279 spinal segments from 145 consecutive patients (10). Local control at 1- and 2-years was 90.3 and 82.4% with excellent reported safety. There is a relative reduction in 2-year compared to 1-year LC ranging from 66 to 93% (**Table 1**). This may reflect the heterogenous nature of the mentioned studies, however merits further investigation. Though control rates at 2-years are still higher than with conventional palliative radiotherapy, in patients with limited metastatic disease and relatively excellent clinical status, durable LC is the treatment goal and endpoints beyond 1-year may be of further interest. In patients who do have local progression at this time point, retreatment with spine SBRT is safe and does offer excellent outcomes, though patients should be discussed in the multidisciplinary setting.

Retrospective studies have explored local control with a specific interest in traditionally radioresistant histologies that typically exhibit poor control with conventional external mean radiotherapy. One-year local control of 83% was reported after treatment of renal cell carcinoma (RCC) spine metastases treated with most common dose of 24 Gy in 2 fractions (18). Ghia et al. also report similar 1-year LC of 82% in RCC, and found that multi-fraction courses yielded inferior outcomes compared to single-fraction (sub-hazard ratio 6.57) which may suggest that BED escalation may be advantageous in radioresistant histologies

(74). The high rates of local control are replicated in patients with sarcoma (75) and melanoma (76).

In the post-operative setting, inclusion of spine SBRT yields excellent local control, similar to *de-novo* metastases. Following vertebrectomy or laminectomy, 1-year LC in has been reported to be >80% in multiple studies (47, 77). In those where downgrading of epidural disease is surgically possible, local control is further improved (51). The considerations and treatment techniques are summarized in a critical review of post-operative spine SBRT by Redmond et al. (78).

Palliation of spine metastases with conventional techniques is limited by cumulative doses tolerated by the spinal cord. Despite high probability of pain response after conventional retreatment (79), local control remains poor which may become problematic for those with favorable prognoses. Especially in the modern setting of additional lines of systemic therapies that are potentially more efficacious, there is an increasing need to safely deliver retreatment to spine metastases. In a systematic review, local control after SBRT in this setting ranged from 66 to 90% at 1-year and improvement in pain scores post treatment ranged from 65 to 81% (80). Importantly, reirradiation was safe; vertebral fracture rate was 12% and treatment related myelopathy was 1.2%. Hashmi et al. pooled outcomes after retreatment with SBRT in 7 institutions (81). The median initial conventional radiotherapy delivered was 30 Gy in 10 fractions and 60% were re-treated with a single fraction SBRT. Local control remained excellent at 83% and importantly, there were no cases of radiation myelopathy after treatment of 247 spinal segments.

Pain Response and Quality of Life

Overall pain response after conventional palliative radiotherapy is ∼62% regardless of fractionation schedule, with complete response rates of 24% (38). The duration of response can be for months, with retreatment considered after 4 weeks, which may be effective despite initial non-response (82). In spine SBRT, complete pain response ranging between 46 and 92% have been reported (42, 83).

It is hypothesized that delivery of higher BED of radiotherapy to the spine may yield improved pain response. It is unclear the optimal dose fractionation for pain response specifically, and whether this technique offers improvements in pain response compared to conventional radiotherapy. Recently, Sprave et al. conducted a randomized phase II trial with the endpoint of pain-control, enrolling 55 patients treated with either SBRT (24 Gy in a single fraction) vs. 3D conformal radiotherapy to a dose of 30 Gy in 10 fractions (84). The authors assessed response using the parameters as established by the International Bone Consensus Working Party (71). There was a trend toward improved complete response at 3 months (43 vs. 17%, $p = 0.0568$) and at 6 months, rates of complete response were significantly higher in the SBRT group (53 vs. 10%, $p = 0.0034$). Responses were also more durable after SBRT. The vertebral compression fracture risk was 8.7% at 3 months and 27.8% at 6 months. There were no grade ≥ 3 adverse events reported. This continues to be assessed in the randomized phase II/III setting with the ongoing NCIC CTG SC.24 trial comparing conventional palliative radiotherapy to a standardized spine SBRT dose of 24 Gy in 2 fractions and RTOG 0631 comparing a single fraction of 16 Gy vs. conventional 8 Gy in 1 fraction (85, 86).

In a multi-institutional, international analysis of 387 spine segments treated with a median dose of 28 Gy in 3 fractions, over 40% of patients with severe pretreatment pain were pain free (definitionally a complete response assuming no increase in analgesic intake) at last follow-up with a median follow-up duration of 11.5 months (87). Pain improvement after retreatment with SBRT has similarly reported to be high (66).

Quality of life (QOL) is an important endpoint which is frequently assessed in addition to physical symptom outcomes and radiographic disease status. Sprave et al. assessed QOL using validated instruments including the EORTC QLQ-BM22, QLQ-FL13, and QSC-R10 and found that QOL was not worse after SBRT for spine metastases compared to conventional palliative radiotherapy (88). This endpoint will also be assessed in the ongoing NCIC CTG.SC24 phase II/III clinical trial.

Predictors of Failure

Progression after spine SBRT is most common within the epidural space and may reflect the relative underdosing of tumor when intimate with thecal sac, or inherent biological aggressiveness of spine metastases with epidural components (51, 89). Al-Omair et al. found that surgical downgrading epidural disease extent resulted in improved local control prior to spine SBRT (51). Methods of mitigating this influence on local control include considering escalating the allowable dose to the spinal cord, or interventional surgical techniques to target epidural disease extension.

TOXICITIES

Spine SBRT is generally well-tolerated, and typically a threshold of <5% is accepted as risk of serious adverse events such as myelopathy. VCF rates have been relatively well-studied after spine SBRT, and a greater understanding of pretreatment assessment and radiotherapy technique has mitigated this risk.

Pain Flare

Defined as a transient increase in pain shortly after commencing or completing radiotherapy, pain flare is common in approximately a third of patients after conventional palliative radiotherapy (90). The range of patients developing pain flare after spine SBRT is significant, from 14 to 68% (91–93). Dexamethasone has been prospectively evaluated in the prevention of pain flare and reduced its rate from 68 to 19% (94).

Vertebral Compression Fracture

Delivery of a high BED of radiotherapy generates an intense acute inflammatory effect that is hypothesized to weaken the bony matrix and place patients at risk of VCF (60). The rate of VCF in the range of 11–39% with a crude risk of 13.9% in a review (60, 95, 96), compared to 3% for conventional radiotherapy (97). Regardless of the mechanism of VCF, both pre-treatment characteristics and treatment related parameters influence the rate of VCF that can result in further pain, and requirement for surgical stabilization. Median time to development of VCF

was 2.5 months in a multi-institutional study including 57 fractures (98).

In retrospective analyses, the aforementioned SINS score includes several elements predictive of VCF including baseline fracture, lytic disease, spine malalignment, >50% vertebral involvement and the overall high SINS score was similarly predictive (60). Lee et al. assessed the capability of SINS in predicting fracture, and found that those in the high SINS group to have a 66.3% risk of fracture at 24 months compared to 21.3% for the low SINS group (99). Further, volume of lytic disease, a refinement of the SINS component, has independently been demonstrated to predict for SBRT-inducted VCF (100). These data support multidisciplinary assessment of patients with spinal metastases, especially in those with intermediate/high SINS scores who may benefit from surgical or minimally invasive procedures to stabilize the spine prior to radiotherapy.

High dose, single-fraction SBRT has been associated with a higher rate of VCF. Those receiving a single fraction of ≥24 Gy, compared to those receiving 20–23 Gy and those receiving ≤20 Gy had a 39% vs. 23% vs. 11% risk of fracture, respectively. In support of this, Rose et al. report a fracture rate of 39% after single doses ranging from 18 to 24 Gy (96). Our institution has observed an 8.5% 1-year VCF risk utilizing our standard 24 Gy in 2 fraction technique.

Sprave et al. assessed bone mineral density as a prespecified secondary endpoint in their study comparing conventional palliative radiotherapy to spine SBRT (101). Both conventional radiotherapy and SBRT increased bone mineral density at 3- and 6-months with one technique not being statistically significantly better. In osteolytic metastases specifically, SBRT increased bone density whereas conventional RT did not. These findings support the safety of spine SBRT, especially where vertebral body fracture is a consideration.

Myelopathy

Radiation myelopathy is a late complication of SBRT and most feared due to potential catastrophic outcomes. A review of nearly 1,400 patients reveal that rates of myelopathy to be 0.4% (73). Point max doses to the spinal cord categorized by number of fractions was reported in a study of nine cases of myelopathy compared to 66 cases without by Sahgal et al. (102). With two fractions, a point max dose of 12.5, 14.6, 15.7, 16.4, and 17.0 Gy yielded an estimated risk of 1, 2, 3, 4, and 5% of myelopathy, respectively. In the reirradiation setting, after conventional external beam radiotherapy, a cumulative thecal sac point maximum dose of 70 Gy in equivalent 2 Gy per fractions (utilizing an alpha-beta ratio of 2) was suggested as long as sufficient time had elapsed since initial treatment (≥5 months) and the point maximum for retreatment should not exceed 25 Gy in equivalent 2 Gy fractions (101).

CONCLUSIONS

The recent, first randomized clinical trial demonstrated overall and progression free survival benefits after SBRT to oligometastatic disease which supports prior retrospective case series (6). The spine is a common site of metastatic bone disease, and as high quality data continue to mature, along with completion of additional randomized clinical trials, it is expected that utility of SBRT to the spine will increase in the future.

Spine SBRT is unique due to the requirement of sharp dose falloff to prevent serious neurologic morbidity. With recent advances in radiotherapy planning, robotic patient positioning, image guidance and radiotherapy delivery, this has been made possible. Local control is excellent, and pain response is comparable to conventional radiotherapy. Patient selection is of utmost importance due to this resource intensive technique, and multidisciplinary consultation is warranted.

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KZ, AS, and SM were responsible for the conception of this review. KZ and SM were primarily involved in the abstraction and analysis of data. All authors contributed to the writing of this review, editing, and final approval prior to submission.

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Stereotactic Body Radiotherapy (SBRT) for Oligometastatic Lung Nodules: A Single Institution Series

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Aim: Lung metastases from an extra-pulmonary origin occasionally present with a limited metastatic disease burden. In cases where metastatectomy is not feasible, stereotactic body radiation therapy (SBRT) represents a non-invasive, efficacious option. We report the outcomes of patients treated with lung SBRT in cases of limited metastatic disease.

Methods: We retrospectively reviewed outcomes in 44 patients with 50 lung nodules from various extra-pulmonary malignancies treated with SBRT. Fifty percent of the patients were male and median age was 64. The median number of nodules was 1 and 90% of patients had oligometastatic disease. Thirty-four percent of patients had extra-thoracic disease.

Results: Fifty lung nodules were treated with SBRT in 44 patients. Median dose was 48 Gy in 5 fractions with a median biological effective dose (BED) of 100 Gy_{10}. Follow-up imaging was available for review in 96% of nodules. Median follow-up was 17.5 months. One year local control was 82%. BED >72 Gy_{10} predicted improved local control (90 vs. 57% at 1 year). One year overall survival following SBRT was 66%. There was no difference in overall survival if patients had extra-thoracic disease.

Conclusion: Lung SBRT is a safe, effective tool for treatment of limited lung metastases. Dose selection remains important for local control.

Keywords: SBRT, lung nodules, metastases, oligometastatic, SABR

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INTRODUCTION

Historically, lung metastases from an extrapulmonic origin signified widespread tumor dissemination and overall poor prognosis. However, a subset of patients will present with limited metastatic disease burden, with metastatic involvement of only a few anatomic sites (i.e. oliogmetastatic disease). Though systemic therapy remains the primary treatment modality in these cases, aggressive local therapy has been utilized with moderate success (1).

Surgical resection (i.e., metastatectomy) represents the preferred local treatment strategy when technically feasible (2, 3). Unfortunately, a subset of patients will not be operative candidates due to medical co-morbidities, anatomic limitations, or even patient refusal. In these cases of inoperable disease, alternative approaches are often utilized; with stereotactic body radiotherapy (SBRT) representing a non-invasive, efficacious option.

Lung SBRT emerged as a viable alternative to surgical resection for patients with medically inoperable non-small cell lung cancer (NSCLC) (4, 5). Results from early RTOG trials showed local control rates in the range of 90%, with limited toxicity when treating peripheral lesions < 5 cm in size (5). Given the favorable outcomes and toxicity profiles seen with lung SBRT in NSCLC, investigations assessing the role of SBRT in patients with limited metastatic disease burden confined to the lung were soon to follow (6–9). To that end, results of ongoing trials utilizing SBRT in the oligometastatic setting were recently presented showing improved overall and progression-free survival compared to standard of care, thus supporting the role of local ablative therapy in cases of limited systemic disease (10, 11). Herein, we present the results of a cohort with limited lung metastases treated with SBRT at our institution.

METHODS

We retrospectively reviewed the records of patients with known or suspected metastatic extra-pulmonary disease treated with SBRT between 2008 and 2017 in this institutional review board (IRB) approved study. All methods were carried out in accordance with relevant guidelines and regulations of the IRB affiliated with Allegheny Heath Network at Allegheny General Hospital. Patients having histologic confirmation of metastatic disease within the lung were included, as were, cases in which there was a high degree of clinical suspicion based upon previous clinical/pathological staging of the extra-pulmonary primary, history of metastatic disease, and/or radiographic enlargement of nodules over time. Patients were excluded if they presented with lung tumors exceeding 5 cm, or if they had a history of prior chest radiation. Patients were treated after review of their case and clinical characteristics in a multidisciplinary setting including medical oncology, thoracic surgery, diagnostic radiology, and radiation oncology. Patient characteristics are outlined in **Table 1**.

SBRT was delivered in the outpatient setting using dose and fractionation schemes determined by the treating radiation oncologist. All patients underwent a 4-dimensional non-contrast chest CT using 1.5-3 mm slices for treatment planning simulation to account for respiratory motion. A gross tumor volume (GTV) was delineated on a free breathing scan and expanded on four expiratory and four inspiratory phases to generate an internal target volume (ITV) to account for intra-fractional motion. The planning target volume (PTV) expansion was 5 mm in all directions. Linear accelerator-based radiotherapy (without fiducial placement) was delivered via 8-12 coplanar 3D conformal beams with 6 MV photons. The median dose covering 95% of the PTV was consistent with the prescribed dose and a primary goal of treatment planning. Doses to surrounding organs at risk were reviewed and all attempts were made to meet constraints as outlined in the NCCN guidelines based on number of fractions (12). Daily megavoltage cone beam CT was used for image guidance to account for inter-fractional motion. **Figure 1** shows a representative treatment plan.

TABLE 1 | Patient, disease, and treatment-related characteristics.

Patient characteristics	
Age	64 years (38–86)
Males	22 (50%)
Females	22 (50%)
ECOG	
0	15 (34%)
1	24 (55%)
2	5 (11%)
Disease characteristics	
Number of lung nodules	50
Size	1.3 cm (0.4–3.8)
Pre-SBRT SUV	3.7 (0.6–12.2)
Extra-thoracic disease	14 (34%)
Oligometastasis (<5 sites)	39 (89%)
Primary Site	
Colorectal	22 (50%)
Breast	6 (13.5%)
Head and neck	6 (13.5%)
Endometrial	3 (7%)
Other*	7 (16%)
Location	
Upper	26 (59%)
Middle	2 (4.5%)
Lower	22 (50%)
Treatment characteristics	
Dose	48 Gy in 5 Fx (36–54 Gy in 3–8 Fx)
Planning target volume	12.92 cc (3.3–103 cc)
Chemotherapy prior to lung SBRT	33 (75%)

*ECOG, Eastern Cooperative Oncology Group; SBRT, Stereotactic Body Radiotherapy; SUV, Standard uptake volume; Gy, Gray; Fx, Fractions; cc, cubic centimeter. *Includes renal (n = 2), thyroid (n = 1), bladder (n = 1), Ewing's (n = 1), cholangiocarcinoma (n = 1).*

After treatment, patients were typically followed with surveillance non-contrast chest CT or PET/CT at 3–6 month intervals for 1 year and every 6 months thereafter. PET/CT was obtained at the discretion of the treating medical or radiation oncologist, typically to determine response to prior therapy or restage the patient's disease. Response to treatment and local/distant control was assessed via RECIST criteria. Local failure was defined as an increase in the sum of the longest diameter of the target lesion by $\geq$ 20% from baseline. Distant failure was defined as any failure outside the treatment volume (including mediastinum, opposite lung, same lung). Patient and disease characteristics were reported (if available) and correlated with disease progression using univariate and multivariate analysis via Cox regression models (13). Survival, local control, distant control, and freedom from progression were all determined via Kaplan-Meier methodology using time from SBRT as the timeframe (14). All statistics were conducted via MedCalc Version 18.0 (Ostend, Belgium).

RESULTS

Cohort

A total of 44 patients (22 males and 22 females) with 50 treated lung lesions from an extra-pulmonary primary were included in this study (**Table 1**). The median age was 65 years (range

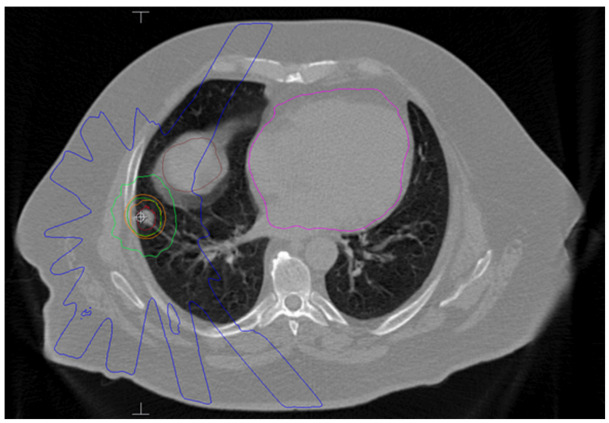

FIGURE 1 | Axial slice of an SBRT plan for a patient with a single lung metastasis from a colonic adenocarcinoma. He received 50 Gy in 5 fractions. The red contour is the internal target volume (ITV) and the orange contour is the planning target volume (PTV). The dark green line is the 50 Gy isodose line. The light green line represents the 25 Gy isodose line and the blue line represents 10 Gy. The brown structure is the liver and the magenta structure is the heart.

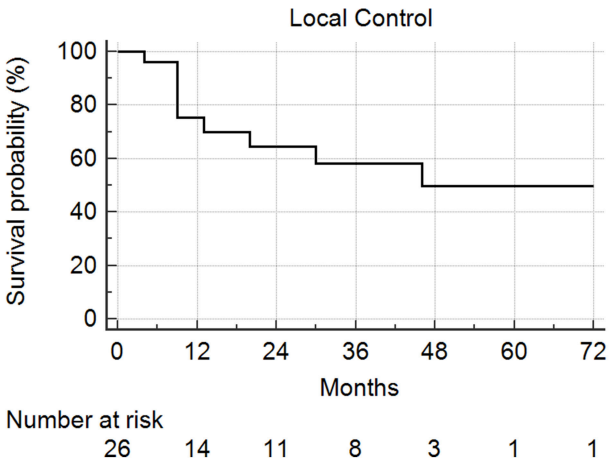

FIGURE 2 | Local control following SBRT for lung metastases. Local control at 1 and 2 years was 82 and 74%, respectively.

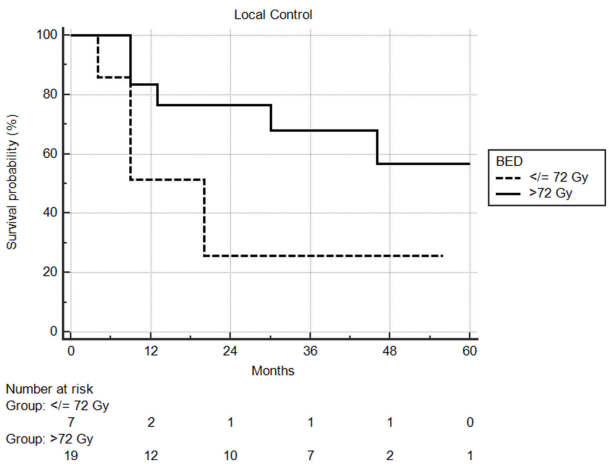

FIGURE 3 | Local control by BED using a cutoff of 72 Gy. One year local control was 90% compared to 57%, in favor of higher biologic dose.

38–86) with a median Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range: 0–2). Thirteen patients (30%) had pathologic confirmation of the lung metastasis, with the remaining thirty-seven patients (70%) carrying a clinical diagnosis. Of note, 50% ($n = 22$) of patients had lung metastases from a colorectal origin. The median time from diagnosis of primary cancer to lung metastases was 26 months (range: 0–376). The median time to lung SBRT from primary diagnosis was 39.5 months (range: 4–377). Fifteen (34%) patients had extra-thoracic disease (metastatic disease to another organ outside the lungs/mediastinum) at time of SBRT and almost all (89%) patients had oligometastatic disease (defined here as 5 or fewer sites of metastasis). Seventy-five percent of patients had systemic therapy, typically chemotherapy, prior to receipt of lung SBRT. No patients had concurrent systemic therapy with SBRT. Ninety-three percent of patients went on to additional systemic therapy after SBRT. Twenty-seven (61%) patients had a pretreatment PET/CT, with median SUV in the treated nodule of 3.7 (0.6–12.2). The median number of nodules treated was 1 (range: 1–3). The median SBRT dose was 48 Gy in 5 fractions, ranging from 36 Gy to 54 Gy in 3 to 8 fractions with corresponding biologic equivalent dose (BED) range of 60 Gy_{10}-105.6 Gy_{10}. The median PTV volume was 12.92 cc (range: 3.3–103 cc). Of note, one single lesion received 8 fractions due to central location.

Local Control

Median follow-up from SBRT was 17.5 months (range: 1–68) and median follow-up from primary diagnosis was 56.5 months (range: 9–409). Follow-up imaging was available for 48 of 50 nodules (96%), with a median number of follow-up scans of 4 (range: 1–14). Median local control was not reached; however 1 and 2 year local control rates were 82 and 74%, respectively (**Figure 2**). Notably, local control was not influenced by PTV volume, histology, or anatomic location likely due to the small sample size and heterogeneity of the cohort. However, BED $\geq$72 Gy_{10} did show a benefit in terms of local control (1 year local control rate: 90%) compared to those with a BED $<$ 72 Gy_{10} (1 year local control rate: 57%) (**Figure 3**). For the 27 patients having a follow-up PET/CT, lesions with SUV $>$ 4.0 were more likely to have a local failure (33% at 1 year) compared to lesions with SUV $\leq$ 4.0 (8% at 1 year) (**Figure 4**).

Survival

Median overall survival following SBRT was 29 months, with 1 and 2year overall survival rates of 66 and 63%, respectively (**Figure 5**). From the time of initial diagnosis, the median overall survival was 85 months. There was no difference in overall survival by extra-thoracic disease or oligometastatic status. PTV

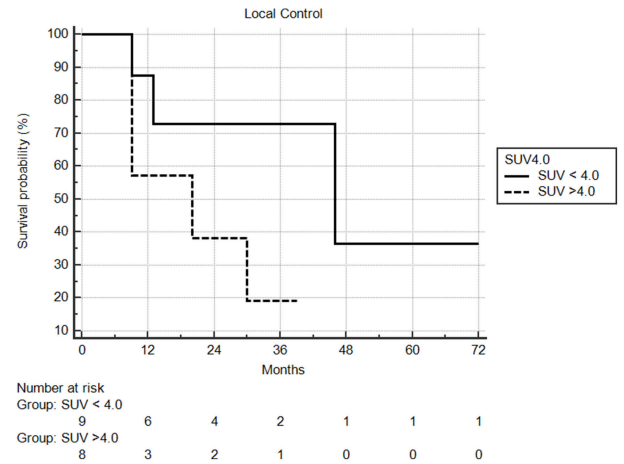

FIGURE 4 | Local control based on pretreatment SUV. Local control at one year was 92% compared to 67%, in favor of lesions with less avidity.

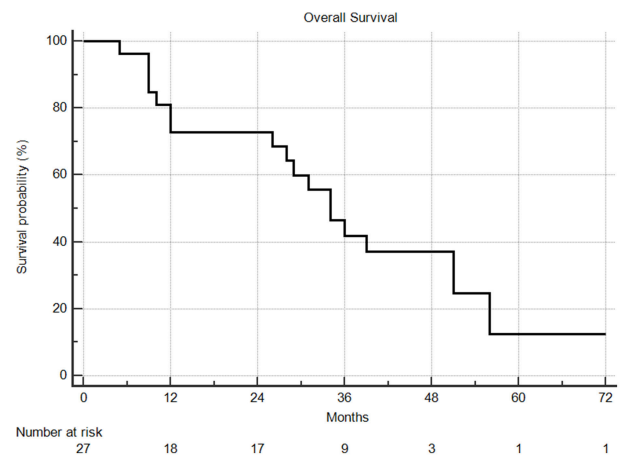

FIGURE 5 | Overall survival from time of SBRT. Two and 5 year overall survival were 63% and 9%, respectively.

volume, dose, age, ECOG, tumor size, and fractionation did not predict for any differences in overall survival.

Patterns of Failure

The median time to distant failure was 7 months, with a distant failure rate of 46 and 61% at 6 months and 1 year, respectively. No predictors were identified for distant failure. There was no acute or late grade 3 or higher toxicity noted in this patient population.

DISCUSSION

Lung metastases are relatively common and occur in 30–55% of cancer patients (1). Oftentimes, lung metastases are a harbinger of widely disseminated and essentially incurable disease. There are instances, however, where disease is truly limited, contemporarily referred to as oligometastasis (15). According to the concept, first described by Hellman and colleagues in 1995, the goal therein is to provide aggressive local therapy potentially rendering patients disease-free for a protracted interval. Criteria for defining oligometastatic disease varies by institution, protocol, and publication, keeping in mind additional factors such as total disease volume, genetics, histology, and location may also impact the outcome (16).

In terms of oligometastatic disease involving the lung, surgical resection is the current standard treatment. A group at Memorial Sloan Kettering reviewed outcomes from their institutional database including over 700 metastatectomies for lung metastases from sarcoma treated over a 25 year period (17). The median disease-free survival was relatively short at 6.8 months, but at 10 and 15 years 26% and 22% of patients were still alive, respectively. Another study from Denmark reviewed outcomes from various malignancies with limited pulmonary metastases treated surgically (18). This study included 178 patients with 256 surgical resections. At 5 years, survival for those with renal cell and colorectal cancers was 50%, while those with sarcoma and melanoma were 20–25% (15).

As previously stated, surgery is not always feasible for a variety of reasons. Generally, the accepted criteria for surgical resection include: adequate cardiopulmonary reserve, technical feasibility, control of primary tumor, and absence of extra-pulmonary disease (2, 3, 19). In situations where any or all of those criteria cannot be met, a slightly less invasive approach may be favored.

In those situations, SBRT represents a viable treatment option. A phase I/II trial from the University of Colorado enrolled 38 patients with 1–3 lung metastases from various primary sites. A 3 fraction SBRT regimen was utilized, with escalation of dose from 48 Gy to 60 Gy (20). With a median follow-up of 15 months, local control at 1 and 2 years was 100 and 96%, respectively. Toxicity was minimal with a single episode of symptomatic pneumonitis. A group from Rochester also has successfully demonstrated the efficacy of SBRT in treatment of oligometastatic disease (8). Results of this study were derived from a combination of two pilot studies which included all oligometastatic sites. Dose-fractionation was variable and dependent on anatomic location. The 2 year local control rate was 77%, with worse rates for larger tumors. In this particular study, lesions from gastrointestinal primaries tended to fair worse overall.

A group from Germany reported outcomes from a large multi-institutional series of 700 patients with medically inoperable lung metastases treated with SBRT (9). Patients in this study were treated using SBRT with a median fractional dose of 12.5 Gy (noting that they did include patients treated with >5 fractions). Median follow-up was over 1 year and local control at 2 years was 81%, with survival rate of 54%. They did note a 6.5% rate of pneumonitis, which was predicted by BED.

Within the past year, a few trials have presented exciting data showing improved outcomes utilizing SRS and SBRT in the oligometastatic patient. The first trial, SABR-COMET, was presented at ASTRO 2018 and enrolled close to 100 patients with various malignancies, defining oligometastatic state as up to 5 sites of metastatic disease (11). Therapeutic arms in that study were either standard of care or standard of care plus SBRT/SRS to sites of metastasis. The median overall survival was 41 months

in the experimental arm compared to 28 months in the standard of care arm. Similarly, progression free survival was improved from 6 months to 12 months in favor of SBRT. A similar study, also presented in 2018, enrolled 49 patients all with metastatic NSCLC with no evidence of progression after initial systemic therapy. In this study patients were required to have 3 or less sites of metastasis (10). Another key difference was that consolidative therapy in this study was either surgery or SRS/SBRT, which was compared to ongoing standard maintenance therapy. With a median follow up of over 3 years the median overall survival was 41 months compared to 17 months in favor of local consolidative therapy ($p = 0.017$). Progression free survival was likewise improved from 4.4 months to 14.2 months ($p = 0.014$).The results of these two studies are exciting, showing meaningful improvement in important outcomes for this patient population.

Comparing the results of the current study, our results mirror those mentioned above with excellent local control of over 80% at one year. In addition, based on the various dose schemes employed we were able to show improved local control for doses with a $BED_{10} > 72$. This finding is concordant with previous reports in patients with NSCLC, in which, increased BED (i.e., >100 Gy_{10}) was associated with improved local control and survival (21). This difference in local control emphasizes the importance of dose selection, even in the metastatic setting. Interestingly, our results showed inferior local control for lesions with an SUV >4.0, perhaps indicating radioresistance and a role for dose escalation. However, caution is advised when interpreting this result, as we did not have pretreatment PET/CT scans in all patients (61%). Additionally, of those with a pre-treatment PET, only 10 patients had an SUV>4.0. Another noteworthy finding relates to the disproportionate number of patients (i.e., 50%) in our cohort having pulmonary metastases from a colorectal primary. A previous meta-analysis suggested poorer local control in cases of pulmonary oligometastases from colorectal primaries possibility due to greater radioresistance (22). Nevertheless, 5 year overall survival in our series was similar to those mentioned above, with a rate of 64%, showing that excellent outcomes are attainable in appropriately selected patients. Furthermore, most of our patients (75%) had prior treatment with chemotherapy, which still remains the cornerstone of treatment in the metastatic setting. Comparable to previous investigations, SBRT was well tolerated in our patient population, with no reports of serious toxicity (Grade 3+).

The limitations of our study are those inherent to any retrospective series including selection bias. In addition, when dealing with patients with metastatic disease, distant failure and death from non-pulmonary causes are significant competing factors, which can perhaps skew local control results. This factor must be taken into consideration when considering results of studies completed using a similar patient population.

CONCLUSION

Lung SBRT remains a viable treatment option for patients with limited metastatic disease in the lungs from extra-pulmonary primaries, with high rates of local control and minimal toxicity. Dose selection is important, with increased local control with higher BED_{10}.

ETHICS STATEMENT

All methods were carried out in accordance with relevant guidelines and regulations of the Allegheny Health Network Institutional Review Board (IRB) at Allegheny General Hospital and all subjects completed an informed consent document prior to treatment initiation.

AUTHOR CONTRIBUTIONS

RW: project conception, data collection, manuscript construction. SA: manuscript editing, manuscript submission. SH: manuscript editing, data collection, statistical analysis. LS and AC: project conception, manuscript editing.

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Linac-Based Radiosurgery for Patients With Brain Oligometastases From a Breast Primary, in the Trastuzumab Era-Impact of Tumor Phenotype and Prescribed SRS Dose

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Background: The role of stereotactic radiosurgery (SRS) in the treatment of limited numbers of brain metastases in selected breast cancer patients is well-established.

Aims: To analyse outcome from a single institutional experience with SRS, to identify any significant prognostic factors and to assess the influence of Her-2, estrogen receptor status, and prescribed dose on outcome.

Methods: The medical records of 56 patients treated at in a single institution between 2009 and 2014 were reviewed. Demographic, treatment related and outcome data were analyzed to identify prognostic factors in this patient population. The primary endpoints were overall survival and local control. Secondary endpoint was distant intra-cranial progression-free survival.

Results: The median follow- up time for the entire cohort was 10.33 months (1.25–97.28). The overall median survival was 12.5months (95%CI= 5.8–19.2), with 53.3%, and 35.8% surviving at 1- and 2- years post-SRS. After adjustment for the effect of Her 2 status, uncontrolled extra-cranial disease at the time of SRS predicted for shorter survival (HR for death = 3.1, 95% CI= 1.4–6.9, $p = 0.006$). At the time of death, 75% of the patients had active, uncontrolled intra-cranial disease, with 56% these patients presenting intra-cranial disease only. Sustained local control was observed in 56 (59.6%) of 94 treated metastases. In univariate analysis, Her2 status, ERHer2 group status?, and prescribed SRS dose were highly significant for local progression free-survival (LPFS). After adjustment for the effect of Her 2 status, patients receiving 12–16 Gy can expect shorter LPFS than those receiving 18–20 Gy (HR = 1.7, 95% CI = 1.0–2.8, $p = 0.043$). After adjustment for the effect of dose group, patients with Her 2 negative cancer can expect shorter LPFS than those with Her 2 positive cancer (HR = 2.6, 95% CI = 1.5–4.4, $p < 0.0005$). Use of prior WBRT did not impact survival, local or distant intra-cranial progression-free survival.

Conclusions: Survival outcome is similar to the published literature. Improved outcomes are observed in patients with Her 2-positive, controlled extracranial disease at the time of SRS and higher SRS dose delivered. Achieving intra-cranial control appears to be an important factor for the survival of the breast cancer patients in the era of targeted therapies.

Keywords: brain metastases, SRS, Her 2 status, breast cancer, dose

INTRODUCTION

Brain Metastases occur in 20–40% of patients with metastatic cancer (1). Whole brain radiotherapy (WBRT) and steroid therapy have historically been used as the standard management. However, outcome is poor with this approach (2). Corticosteroid treatment has a modest impact, extending median survival by as little as 1–2 months and has significant toxicities. WBRT has a greater impact, but median survival is still measured in months (3). The biggest disadvantage with WBRT is that it doesn't result in a high prolonged local control rate, which contributes to overall low survival. Due to this limitation of WBRT investigators explored the use of surgical removal of oligometastatic (limited number) brain metastases in selected patients. In a randomized trial, Patchell et al. reported a median survival of 19 months in patients treated for solitary brain metastases, with surgical resection and WBRT compared to 9 months in those treated with WBRT alone (4). This trial which included patients with breast and other primary sites demonstrated the potential value of aggressive local intervention for oligometastatic brain tumors in patients with good performance status and controlled extracranial disease.

Historically stereotactic radiosurgery (SRS) was pioneered by Leksell for managing intracranial conditions such as arteriovenous malformations (5, 6) Following its successful use for benign brain conditions the technology was applied to brain metastases with results similar to those reported for surgery (7). SRS offers a non-invasive treatment alternative, which is performed as an outpatient procedure and generally well-tolerated.

As the systemic treatment of metastatic breast cancer has evolved and improved the prospect of achieving durable control of extracranial disease has increased dramatically. This has created a greater demand for the successful treatment of brain metastases of breast cancer patients for two reasons. Firstly, more patients fulfill the selection criteria by virtue of the control of extracranial disease and the fact that their performance status is higher systemic therapies are increasingly better tolerated. The second main reason is the identification of Her-2-Neu positive breast cancer. Up to 30% of breast cancer patients overexpress the Her-2-Neu receptor (8). This overexpression is associated with an aggressive phenotype. However, with the discovery of Trastuzumab, a monoclonal antibody against Her-2-Neu the prognosis has dramatically improved. In the metastatic setting, up to 30 to 40% of such patients will ultimately develop brain metastasis. The reason for the high incidence of brain metastasis in Trastuzumab treated patients is assumed to be because Trastuzumab (which is a large monoclonal antibody) may not cross the blood-brain barrier. As more patients achieve control of their Her-2-Neu positive extracranial disease they may develop brain metastases in a setting where SRS is clinically appropriate. It is therefore important to assess which prognostic factors will affect the outcome of this therapy and to define an optimal dose range.

MATERIALS AND METHODS

The study was approved by the local Institutional Review Board.

Cohort

A retrospective analysis was performed on 56 patients with metastatic breast cancer with metastases to the brain. All of the patients were treated with Stereotactic Radiosurgery (SRS) or intensity modulated radiosurgery (IMRS) between 2009 and 2014. All patients had a fine resolution 3DMRI of the brain (confirming diagnosis of brain metastases) within the 14 days preceding the treatment.

An Excel database was generated which included the patients demographics (age, date of diagnosis, treatment, pathology, brain progression details), treatment related and outcome related data. The Disease-specific graded prognostic assessment score (DS-GPA) was retrospectively calculated in all patients. DS-GPA score is a prognostic scoring system specifically designed for brain metastases. It takes account of performance status, age, number of brain metastases, and status of extracranial disease to assign a class ranging from I-IV. Class I has the best prognosis. Information was gathered on these patients using the hospital's electronic (ARIA) and paper charts.

Planning Technique

For all patients a dedicated contrast-enhanced planning brain CT was acquired, with slice thickness of 1.25 mm, using the frame or frameless systems for localization of the lesions. Of the 56 patients receiving SRS, 37 had a frameless mouth-bite coordinate system applied to minimize patient discomfort; 19 patients had a frame-based coordinate system attached under local anesthesia due to inadequate dentition required for the frameless system.

The planning CT was co-registered with fine resolution brain MRIs (T1, T2, SPGR, FLAIR sequences with and without contrast). The use of contrast for the planning CT can help to identify small structures such as blood vessels which can be cross referenced on the planning CT and the fused MRI to assess the accuracy of image fusion. This is particularly relevant when the metastasis is not visible on the CT and

target volume definition is reliant on the fused MRI. The gross tumor volume (GTV) was defined as the enhancing lesion on the CT and/or MRI T1 SPGR contrast enhanced sequence. The planning target volume (PTV) was defined as the GTV with a 1 mm circumferential margin. Varian Eclipse treatment planning system (Varian, Palo Alto, CA) was used to generate cone-based SRS or intensity modulated radiosurgery (IMRS) plans. For tumors <3 cm maximum dimension in any plan, a single fraction of 14–24 Gy was delivered, generally using the RTOG guidelines (9). The variation in the doses prescribed, not conforming with these ranges, was due to individual physician choice, particularly when lower doses were used. For larger tumors, IMRS was used to deliver either 30 Gy/5 fx or 24 Gy/3 fx. The dose was prescribed at the 80% isodose line for cone-based SRS, while a minimum isodose of 95% prescription dose covered the target for the IMRS plans. Treatment characteristics for the 56 patient included in this study are depicted in **Table 1**.

The SRS/IMRS was delivered using a Varian Trilogy Tx linear accelerator, using a cone-based or MLC based technique. Stereotactic localization was provided using the Varian SonArray infra-red localization or Vision RT surface guidance (from 2014 onwards) systems.

Steroids were not routinely recommended, however patient on steroids at the time of SRS (22 patients) were kept on the same dose (no modifications) during treatment.

Follow-Up

Follow-up data were collected from institutional records, records from referring facilities and family physicians. After SRS, patients generally underwent routine follow-up clinical examination and imaging. MRI brain (as described above) was performed at 2 months' post SRS, then every 3 months for the first 2 years. In case of suspicion of pseudoprogression, a short-interval (6–8 weeks) MRI brain was done. For patients unable to attend our institution for follow-up, the data was retrieved from other institutional or family physician records. The data was reviewed and the response and reported toxicity were scored retrospectively. MRI images were routinely reviewed by a neurosurgeon with expertise in imaging neuroanatomy.

TABLE 1 | Treatment characteristics for 94 treated brain metastases in 56 patients with primary breast cancer.

Parameter		
Number of brain metastases treated/patient	1	33 pts (58.9%)
	2–3	18 pts (32.2%)
	4–5	5 pts (8.9 %)
Tumor size (mm)		
	Mean ± STDEV	17.6 ± 8.5 mm
	Median (Range)	16 (3–40)
Dose fractionation	21–24 Gy/1 fx	12 lesions (12.8%)
	18–20 Gy/1 fx	38 lesions (40.4%)
	14–16 Gy/1 fx	37 lesions (39.4%)
	<14 Gy/1 fx	2 lesions (2.1%)
	30 Gy/5 fx or 24 Gy/3 fx	5 lesions (5.3%)

pts, patients; fx, fraction.

Statistical Analysis

The primary endpoints were local control and overall survival. The secondary endpoint was distant intra-cranial progression-free survival.

Local control was defined as stability or reduction in size of the treated lesion(s) on serial MRIs. MRI response was analyzed by a neurosurgeon with expertise in brain MRI response assessment. Distant intracranial progression was defined as development of new lesion(s) outside the treated metastasis.

Patient, tumor and treatment characteristics were summarized. The following factors were analyzed for impact on local, and distant intra-cranial progression-free survival: age, clinical presentation (symptomatic vs. incidental), GPA, status of the extracranial disease at the time of SRS (controlled yes vs. no), ER status (positive vs. negative), Her 2 status (positive vs. negative), location of brain metastases (supra vs. infratentorial), number of brain metastases (targets: 1 vs. 2–3 vs. 4–5), lesion size (as a continuous variable), dose prescribed (12–16 vs. 18–20 vs. 20–24 vs. IMRS), time to development of brain metastases from the initial diagnosis (<1 year or >1 year), and WBRT (yes vs. no).

Categorical variables were analyzed using chi-square tests. The Kaplan-Meier method was used to estimate survival times, and the log -rank tests to compare differences in survival. Survival was calculated from the date of SRS/IMRS to the date last follow-up/ death (overall survival, OS), to the date of first local progression/ death (local progression-free survival, LPFS) or to the date of first distant progression/ death (distant progression-free survival, DPFS). Overall and distant intra-cranial progression-free survival were analyzed by individual patient, while the local progression-free survival was analyzed by individual metastasis. The Cox proportional hazards model was used to assess the effects of co-variates (statistically significant in univariate analysis) on survival. All statistical tests were two-sided and assessed for a significance at 0.05 level. Statistical analyses were carried out using IMB SPSS statistical program version 24.

RESULTS

Cohort

The cohort included 56 females with brain metastases from a breast cancer primary, with a median age of 52.8 years (30.8–82.5). Patient, tumor and treatment characteristics are detailed in **Table 2**. The majority of the patients ($n = 54$, 96.4%) had a Karnofsky performance status score (KPS) >70 and GPA of at least 2 was recorded for 68% of the patient Most patients ($n = 35$, 62.5%) had either no or controlled extra-cranial disease at the time of SRS, 70% of them received prior chemotherapy and 50% received systemic concurrent treatments (Herceptin or Taxanes).

The average age at the time of development of brain metastases was 52 years old (30–82). The median time from initial diagnosis to development of brain metastases (BM) was 44.04 months (2.82–220.8) and the median time from initial diagnosis to the SRS was 51.6 months (3.15–221.7). The average time to development of BM was significantly longer in patients with ER+ disease (ER+ vs. ER– = 76.7 vs. 32.2 months, $p = 0.0001$). Her 2

TABLE 2 | Demographics, treatment and target characteristics in 56 patients with brain metastases from a breast cancer primary, who received stereotactic radiosurgery between 2009 and 2015.

		Number (%)
Age	Mean ± STDEV	53.1yo ± 12.0
	Median (Range)	52.8 (30.8–82.5)
Gender	Males	0 (0%)
	Females	56 (100%)
KPS	60	2 (4%)
	70	11 (20%)
	80	27 (48%)
	90	16 (29%)
GPA	1	12 (21%)
	2	24 (43%)
	3	14 (25%)
	Unknown	6 (11%)
Extracranial disease controlled at the time of SRS	No	16 (29%)
	Yes	35 (62%)
	Unknown	5 (9%)
Her 2 status	Positive	33 (59%)
	Negative	20 (36%)
	Unknown	3 (5%)
ER status	Positive	29 (52%)
	Negative	24 (43%)
	unknown	3 (5%)
Prior chemotherapy	Yes	40 (71%)
	No	16 (29%)
Concurrent systemic treatments (herceptine, hormones)	Yes	28 (50%)
	No	26 (46%)
	Unknown	2 (4%)
Time interval between initial diagnosis and BM(months)	Mean ± STDEV	57.4 ± 43.6
	Median (Range)	44.0 (2.8–220.8)
Presentation	Incidental finding	22 (39%)
	Seizures	2 (4%)
	Headaches	12 (21%)
	Other neurological symptoms	20 (36%)
SRS intent	At progression after WBRT	24 (43%)
	Boost after WBRT	10 (18%)
	Boost after resection	2 (4%)
	Alone	20 (36%)
No intracranial metastases at the time of SRS	1	33 (59%)
	2	16 (29%)
	3	2 (4%)
	4	3 (5%)
	5	2 (4%)

negative status was associated with longer time to development of BM, but it did not reach significance (Her 2– vs. Her 2+ = 69.6 vs. 47.7, $p = 0.07$).

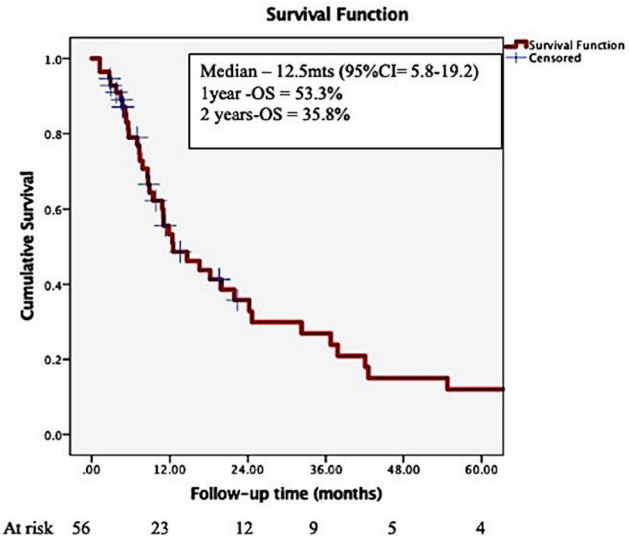

FIGURE 1 | Overall survival in patients with brain metastases from a breast primary, treated by stereotactic radiosurgery.

Most of the patients (n =33, 58.9%) were treated for a single brain metastasis. The median tumor size was 16 mm (3–40). However, there were five patients with more than five brain metastases at the time of SRS (one patient with six lesions, one with seven, and three patients with eight); for these patients only the progressing lesions (after prior WBRT) received SRS.

Survival

The median follow- up time for the entire cohort was 10.33 months (1.25–97.28). At the time of the last known follow-up, 17 patients (30.4%) were alive, and 39 (69.6%) have died. Among the 39 patients who died, 29 (74.35%) had uncontrolled intra-cranial disease at the time of death (13 both intra and extracranial disease uncontrolled and 16 intracranial disease only).

The overall median survival was 12.5 months (95% CI = 5.8–19.2), with 53.3%, and 35.8% surviving at 1- and 2- years post-SRS (**Figure 1**), with a small proportion (5–20%) surviving more than 5 years after the initial SRS.

In Cox multivariate analysis (MVA), after adjustment for the effect of Her 2 status, controlled extra-cranial disease at the time of SRS (HR for death if uncontrolled ECD = 2.9, 95% CI= 1.3–6.3, $p = 0.009$) was significantly associated with OS. The Her 2 status presented a trend toward significance (HR for death for Her 2 negative cancer = 2.1, 95% CI= 0.97–4.9, $p = 0.057$) after adjustment for the effect of extra-cranial disease. Addition of whole brain RT (WBRT) was not associated with increased OS. **Figures 2**, **3** depict the OS function of the Her 2 status and the status of extracranial disease.

Local Control

During follow-up, 35 lesions (37%) have progressed, after a median of 7.3 months (1.25–97.28). Six lesions were salvaged by further local treatments (1-surgery, 2-IMRS, 3-SRS). Therefore, at the last known follow-up, of the 94 treated lesions, 61 (64.9%)

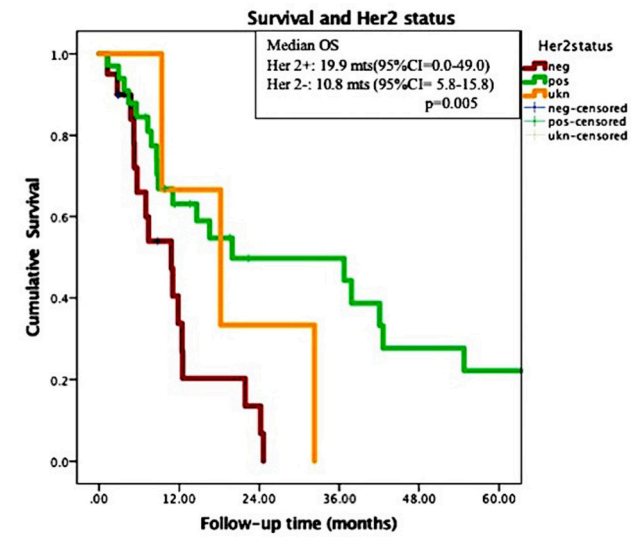

FIGURE 2 | Overall survival and Her 2 status in 56 patients with brain metastases treated by SRS.

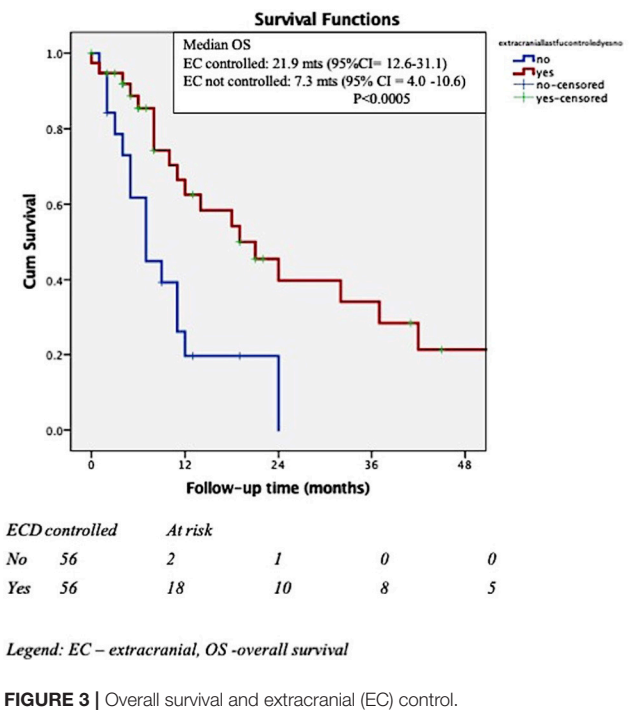

FIGURE 3 | Overall survival and extracranial (EC) control.

were controlled locally, 29 progressed (30.9%) and we were unable to assess the response for 4 lesions (4.5%).

The median LPFS was 8.6 months (7.0–10.2), with 1- and 2 years-LPFS of 33 and 15%, respectively. LPFS is depicted in

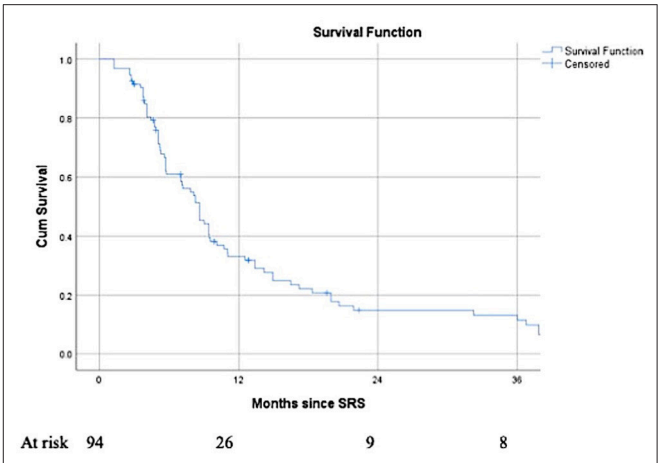

FIGURE 4 | Local Progression-free survival for 94 brain metastases from a breast primary, treated by SRS.

Figure 4. In univariate analysis, Her 2 status, ERHer2 group, and dose group were highly significant for LPFS (**Table 3**). After adjustment for the effect of Her 2 status, patients receiving 12–16 Gy can expect shorter LPFS than those receiving 18–20 Gy (HR = 1.7, 95% CI = 1.0–2.8, $p = 0.043$). After adjustment for the effect of dose group, patients with Her 2 negative cancer can expect shorter LPFS than those with Her 2 positive cancer (HR = 2.6, 95% CI = 1.5–4.4, $p < 0.0005$). Use of WBRT did not impact LC. **Table 4** presents the local recurrence rates for small lesions (<2cm) function of tumor size and dose received. **Table 5** presents the local recurrence rates for all treated lesions, function of the dose received.

Distant Intra-cranial Progression-Free Survival

During follow-up, 23 patients (41%) developed distant intra-cranial progression. The median DPFS was 9.85 months (7.6–12.1), with actuarial 1-, 2-years DPFS of 40.1 and 11.8%, respectively. None of the variables analyzed was significantly associated with DPFS. Particularly, WBRT either prior to, at the time to SRS or at progression, did not affect DPFS.

Toxicity

There was no G3 or more acute or late toxicity identified for this cohort. The most commonly identified side effect was fatigue grade 1-2, in 10 patients (17.8%).

DISCUSSION

This experience from a single institution confirms some of the findings reported from other series. The median survival of 12 months is in keeping with other publications. In this series, survival was 53.3% at 1 year after SRS and 35.8% at 2 years. Kondziolka et al. from UPMC reported the outcome for 350 breast cancer patients with 1535 brain metastases (10). Overall survival was 49% at 1 year, 26% at 2 years with a median survival of 11.2 months.

TABLE 3 | Univariate analysis variables significant for local progression free survival in a cohort of 56 breast cancer patients with 94 brain metastases, treated by SRS.

		Estimated median LPFS (mts)	95% CI		*p*-value (log-rank)
			Lower bound	Upper bound	
Her 2	**Positive**	**10.1**	7.4	12.8	<0.0005
	Negative	5.7	5.2	6.1	
ERHer2group	**ER+Her2+**	**10.7**	8.1	13.4	0.001
	ER−Her2+	9.528	7.7	11.3	
	ER+Her2−	5.1	4.7	5.4	
	ER−Her2−	5.7	5.4	6.0	
SRS dose prescribed	12–16 Gy/1 fx	7.1	3.8	10.4	0.006
	18–20 Gy/1 fx	8.6	7.6	9.6	
	21–24 Gy/1 fx	**9.4**	4.5	14.3	
	IMRS (24–30 Gy/3 fx)	3.9	1.9	5.9	

ER, estrogen receptor; fx, fraction; LPFS, local progression-free survival; mts, months.

TABLE 4 | Local progression rates for 64 small lesions (<2cm) according to the tumor size and SRS dose prescribed.

			Local progression		
			Yes	No	Total
Size-dose group	TS<1 cm 22–24 Gy/1 fx	Count	**1**	6	7
		% within group	**11.1%**	66.7%	100.0%
	TS<1 cm 18–20 Gy/1 fx	Count	**4**	13	17
		% within group	**23.5%**	76.5%	100.0%
	TS <1 cm 12–16 Gy/1 fx	Count	**3**	2	5
		% within group	**60.0%**	40.0%	100.0%
	TS 1.1–2 cm 22–24 Gy/1 fx	Count	**0**	3	3
		% within group	**0.0%**	100.0%	100.0%
	TS 1.1–2 cm 18–20 Gy/1 fx	Count	**3**	12	15
		% within group	**18.8%**	75.0%	100.0%
	TS 1.1–2 cm 12–16 Gy/1 fx	Count	**9**	8	17
		% within group	**52.9%**	47.1%	100.0%
Total		Count	20	44	64
		% within group	29.9%	65.7%	100.0%

Lesions for which the response was not known were excluded.
TS, tumor size (diameter). Chi-square test not valid because of small numbers in some cells.

TABLE 5 | Local progression rates for 90 treated lesions, according to the SRS dose prescribed.

Dose group		Local Progression		Total
		No	Yes	
12–16 Gy/1 fx	Count	17	**21**	38
	% within dose group	44.7%	55.3%	100.0%
18–20 Gy/1 fx	Count	27	**10**	37
	% within dose group	73.0%	27.0%	100.0%
22 Gy/1 fx	Count	9	**1**	10
	% within dose group	90%	10%	100.0%
24–30/3–5 fx	Count	2	**3**	5
	% within dose group	40.0%	60.0%	100.0%
Total	Count	55	35	**90**
	% within dose group	61%	39%	100.0%

Lesions for which the response was not known were excluded.
Chi-square test not valid because of small numbers in some cells.

In multiple series reporting SRS for brain metastases, the primary site of origin is an important predictor of outcome (11–13). Breast cancer origin appears to be associated with improved overall survival compared to other histologies (12). It may also predict a higher prospects of achieving local control of the treated metastases. Results of several retrospective studies in patients with brain metastases from a breast primary, treated by SRS, are presented in **Table 6**. These series (10, 14–28) identified several factors which impact on the outcomes of these patients, with longer survival reported for higher KPS, lower RPA class, single small metastasis (<1 cm), deep cerebral location, controlled extracranial disease and ER+ or Her2 + the biological subtypes. In this series we focused on outcome for breast cancer patients only. We observed that patients with Her-2+ brain metastases developed the metastases sooner after diagnosis than other phenotypes, in line with prior publications. This may reflect the more aggressive natural history of this subtype and its particular predilection for brain spread. Similarly, estrogen negative patients developed their brain metastases after diagnosis sooner than estrogen positive patients. However, on MVA, after controlling for other variables, the only factor associated with improved OS was controlled extra-cranial disease at the time of SRS. After adjustment for the effect of Her 2 status, LPFS was significantly correlated with the SRS dose group. After adjustment for the effect of dose group, Her 2 status was highly predictive for LPFS patients (with Her 2–status is associated with shorter LPFS with Her 2 +, HR = 2.6, 95% CI = 1.5–4.4, $p < 0.0005$). None of the other factors analyzed had predictive value for the studied outcomes.

Patients with Her 2 disease treated by Trastuzumab are at particular risk of developing brain metastasis. In the metastatic setting, up to 30–40% of such patients ultimately develop brain metastasis: three of the five adjuvant trails of Trastuzumab reported brain metastasis following the treatment. 1.6% of these

TABLE 6 | Selected studies of brain SRS in patients with brain metastases from a breast primar.

Study	No patients/no lesions/dose	Survival	Local and intra-cranial control	Observations
Shenker et al. (14)	128 pts 1-2BM/pt 20Gy/fx (10-24Gy)	- medOS-16.3 mts OS-1y = 56% OS-2y = 18% OS-2y = 10%	- IC failure−6 m = 24% - IC failure−12 m = 41% - IC failure−24 m = 51%	- ER,PR ± trend toward decreased neurological death - Factors associated with non-neurological death: status extracranial disease, dose, Her 2 status
Wolf et al. (15)	200 pts 1237 BM (diff histology) Med 18Gy/fx		LC1y = 97% LC2y = 93% LC = 100% for TS<1 cm	Increased survival for lesions<1 cm
Pessina et al. (16)	66 pts Surgery–SRS/WBRT	Med OS = 30.7 mts OS-1y = 78.5% OS-2y = 57.4% OS-3y = 43.3%	LRR-24.2% LC-1y = 87.5% LC-2y = 71.2% LC-3y = 63%	- Factors associated with survival: KPS, number of BM, local treatment performed, status of EC disease at the time of dg of BM, treat with Herceptine
Mix et al. (17)	214 pts 23% GK SRS 46% SRS-WBRT 31% WBRT	Med OS 21 mts SRS vs. 3 mts WBRT	NR	- WBRT prior or as salvage did not impact survival - Tumor volume and Her 2 status significantly associated with OS - ER status did not impact on OS
Roehrig et al. (18)	111 pts	Med OS = 16.8mts OS-1y = 59.5% OS-2y = 38.4%	NR	KPS – strongest predictor for survival in MVA No impact of number lesions, WBRT
Mohammadi et al. (19)	896 pts- 3034BM (<2 cm in size) 166 breast cancer	Med OS = 14.9 mts	- New IC lesions rate-45% after a median of 10.2 mts - 10% rate of local progression	- Factors associated with local/IC control: tumor diameter (< or >1cm), tumor volume, conformality index, prescribed dose (24Gy vs. <24)
Nieder et al. (20)	25 pts brain -only mets WBRT+/-SRS	MedOS−11.7 mts OS-1y = 48% OS- 2y = 28%	Brain PFS - Med = 6.2 mts - @1y = 22% Med time to brain progression−10.8mts Freedom of brain progression @1y−36%	- Predictors for OS: KPS, TNBC, coordination deficits, lack of upfront surgery, lack of hormone therapy/herceptine - Predictors for brain PFS: KPS, location (cerebellar worse), cognitive or coordination deficits, systemic treatments after SRS
Cho et al. (21)	131 pts Med−3 lesions/pt (1-22)	- Med time SRS to death = 15.7 mts - Med OS = 7 mts for TNBC		- ER+Her2- and Her 2 + - longest survival - TNBC poor prognostic - Prior WBRT, age – no impact - Cerebellar lesions TNBC – worse survival
Yang et al. (22)	136 pts 186 BM	Med Sv- 17.6 mts OS-1y = 65% OS-2y = 45%	LF-1y = 10% Regional failure @12mts = 45%	- In MVA – predictors for Sv: >1lesion, TNBC, active EC disease - EC disease associated with regional failure - Tumor size – associated with risk of LF
Tam et al. (23)	57pts 28pts Her2+	Her 2+ vs. Her 2- Med OS = 22 vs. 12 mts	Her2+ vs. Her 2- - medTTP- 7 vs. 11mts - Salvage tt: 50% vs. 21%	- Her 2+ appears to show higher rates of intra-cranial relapse, despite better OS rates
Yomo et al. (24)	80 pts 40 pts Her 2+	Lapatinib vs. non-lapatinib tt: -OS-1y = 50% vs. -OS−2 y = 26%	LC−1y = 84% LC−2yc = 70% Lapatinib vs. non-lapatinib LC-1y = 86 vs. 69%	- Factors associated with survival: Her 2 status, RPA class, total PTV at initial SRS - Factors associated with local control: tumor volume, peripheral dose
Xu et al. (25)	103 pts – 24 with TNBC	TNBC vs. non-TNBC - OS (after dg): 43 vs. 82 mts - Neurological Sv: 13 vs. 25 mts - Radiosurgical Sv: 6 vs. 16 mts		- TNBC – adverse prognostic factor

(Continued)

TABLE 6 | Continued

Study	No patients/no lesions/dose	Survival	Local and intra-cranial control	Observations
Kelly et al. (26)	79 pts Had salvage SRS>3mts after initial treatment 76 of them - WBRT	Med OS = 9.8 mts	Brain PFS Median = 5.7 mts post-SRS	- Her 2+ status and stable EC disease have improved clinical course and survival - 82% of these patients would require further systemic treatment
Caballero et al. (27)	310 pts salvage SRS 90 pts – breast cancer	Med OS −8.4 mts		Favorable fact for survival in breast cancer patients: single brain met, age<50, longer time interval WBRT-SRS
Kondziola et al. (10)	350 pts 1535BM SRS at dg or at recurrence Srs dose -RTOG criteria	OS 6mts-69% 12mts−49% 24 mts−26%		- Longer OS if controlled EC disease, lower RPA, higher KPS, smaller number of metastases, smaller tumor volume, deep metastases, Her 2+
Karam et al. (28)	441 pts 40% Her 2+	Med OS (from brain treat)-4.5 mts Med OS RPA 1vs. 2 vs. 3 = 14.5 vs. 6.4 vs. 1.8 mts		- RPA class significantly associated with survival

patients ultimately develop brain metastasis (29). The reason for the high incidence of brain metastasis in Trastuzumab treated patients has been assumed to be due to the fact that Trastuzumab with 185 kDa molecular weight may not be able to cross the blood-brain barrier (BBB). Therefore, the brain might be a sanctuary site for malignant cells. Dijkers et al. (30) have performed Her2neu staining whole body scintigraphy and have demonstrated that Trastuzumab can partially penetrate the BBB. Additionally, Stemmler et al. (31) measured Trastuzumab levels in CSF of Her2neu positive brain metastasis patients and found that these levels were increased if meningeal carcinomatosis was present or if the patient had received WBRT. Analyzing these two sets of data one may postulate that BBB may be disrupted by tumor spread or by WBRT. However, it may not be disrupted by the presence of cells in the brain and this may allow brain metastasis to develop before the disruption of the BBB occurs. In other words, the cells may establish themselves as significant micro-metastatic deposits or small macroscopic deposits before the BBB is sufficiently disrupted to allow Trastuzumab to potentially treat the metastases.

The good outcome following the treatment of good prognosis limited brain metastases in Her2 positive disease may be primarily a manifestation of the overall favorable biology and efficacy of systemic therapy. However, Her 2 positive disease may be more radiosensitive than other cancer subtypes. Liang et al. (32) demonstrated *in vitro* Trastuzumab enhanced radiation-induced apoptosis in breast cancer cells in a Her 2 level-dependent manner. They postulated that PI3/Akt pathway may be involved in this effect. In a metanalysis by Dahabreh et al. (29), the addition of adjuvant Trastuzumab to chemotherapy resulted in a lower risk for developing locoregional recurrence (data from 3 of the 5 trials, 6,752 patients: RR 0.58, 95% CI = 0.43–0.77, $p = 0.0002$). However, it is not clear if this is due to concurrent radiosensitization or independent Trastuzumab activity.

Neurological death is defined as death in the presence of active intracranial or leptomeningeal disease. In 2017, McTyre (33) reported that disease specific GPA, number of brain metastases, melanoma histology and SRS dose are predictive for neurological death. Targeted therapies appear to delay neurological death. Their results are based on the analysis of outcomes of 738 patients with brain metastases (different histologies) treated by upfront SRS; in 30.6% of them neurological death occurred, while 42% died of non-neurological causes. In 2018, Shenker (19) reported the outcomes of 128 breast cancer patients treated by SRS (median doze 20 Gy/1 fx) for 1-2 brain metastases. In their series, ER+PR+ status was associated with a trend toward decreased neurological death, while status of extra-cranial disease, SRS dose and Her 2 status were associated with the non-neurological death. In our series, 75% of the patients who died had active, uncontrolled intra-cranial disease, with 56% of these patients presenting intra-cranial disease only at the time of death. Therefore, achieving intra-cranial control appears to be an important factor for the survival of the breast cancer patients in the era of targeted therapies. Moreover, 10–20% of the patients included in this cohort survived more than 5 years (**Figure 1**), further emphasizing the importance of intra-cranial control for survival. We could not identify any statistically significant differences between the neurological and non-neurological death groups (results not shown); however, the number of patients having uncontrolled intracranial disease at the time of death was higher for lower SRS dose delivered: 51% if 12–16 Gy/1 fx vs. 27% if 18–20 Gy vs. 20% if 21–24 Gy/1 fx (p-0.21).

In addition to clinical factors, the UPMC series (10) suggest that higher tumor dose predicted progression free survival. In patients with brain metastases from a breast primary treated by SRS, the reported 1y-LC varies between 69 and 90% (**Table 5**), utilizing SRS doses between 15 and 24 Gy/1 fx. However, most of the reported studies included patients who received WBRT. Very few studies report the outcomes of the patients who received SRS alone. The impact of dose on the local control was reported by two other large studies published in 2018 and 2017 (24) on patients with brain metastases from different primaries (including breast). Our study is in agreement with these previously published data: lesions treated with 21–24 Gy

had a local progression rate of 8.3 %, those treated with 18–20 Gy had 21%, while 43 and 60% of those treated with 12–16 Gy and IMRS, (respectively) developed local recurrence.

Several randomized trials have assessed the value of adding whole brain radiotherapy (WBRT) to SRS for patients with limited number of brain metastases from a variety of primary sources (34). None of these trials have demonstrated an overall survival advantage to adding WBRT. It is not routinely added to SRS because it has also been demonstrated that adding WBRT to SRS increases the risk of cognitive deterioration. The use of WBRT added to SRS does however result in reduced occurrence of local progression at the treated lesions compared to SRS alone and reduces the occurrence of new brain metastases in other parts of the brain. In the trial conducted by the Alliance for Clinical Trials in Oncology local control of the treated metastases was 73% with SRS alone vs. 90% when WBRT was added to SRS (35). Patients treated with SRS alone received 24 Gy in a single fraction if lesions were <2.0 cm or 20 Gy if lesions were 2 to 2.9 cm in maximum diameter. The focus of debate surrounding the results of these trials has understandably been the implications for the use of WBRT. However, these trials demonstrate increased local control when WBRT is added to SRS. This raises the possibility that enhanced local control of metastases treated with SRS could be achieved if the dose of SRS was increased to an optimal level, rather than adding WBRT.

A systematic review of SRS for brain metastases (arising from various multiple primary sites) demonstrates the wide variety of fraction sizes in use (36). Across the series included in the review, the range was 10 to 30 Gy. The optimal dose for single fraction SRS has therefore clearly not been identified and adopted in clinical practice. RTOG 90-05 was a dose escalation trial of single fraction SRS dose (37). That trial identified the maximum tolerated doses to be 24, 18, and 15 Gy for tumors of ≤20 mm, 21–30 mm, and 31–40 mm maximum diameter. These doses have since been adopted in clinical practice for previously untreated lesions often without the addition of WBRT. However, in the RTOG trial, all patients had recurrent previously irradiated primary or metastatic brain tumors. Therefore, a dose escalation trial restricted to previously unirradiated lesions would likely identify higher maximum tolerated doses. Therefore, a need is identified to conduct trials to ascertain the optimal dose for SRS in previously unirradiated cases.

In January 2019, a search on clinicaltrials.gov identified two ongoing trial escalating the dose of single fraction SRS: NCT02390518 (38) clinical trial (run by University of Utah) includes patients with 1–5 brain metastases, for whom dose escalation is preview, based on the tumor diameter and volume: for tumors <1 cm, and <0.52 cc: dose will be escalated to 26 Gy/1 fx, then 28 Gy/1 fx and finally to 30 Gy/1 fx. For tumors with diameters of 11–20 mm and volume 0.52–4.1 cc, dose will be escalated to 26 Gy/1 fx, then 28 Gy/1 fx and 30 Gy/fx. For large metastases with a diameters 21–30 mm and a volume 4.18–14.3 cc the dose will be escalated to 20 Gy/1 fx, then 22 Gy/1 fx and 24 Gy/1 fx. A second trial run by University of Texas (NCT02645487) (39) will escalate dose by 3 Gy/step, based on the tumor diameter: for metastasis ≤1 cm dose will be escalated from 24 Gy to 30 Gy/fx, for 1–2 cm size dose will escalate from 21 Gy to 27 Gy/fx; for metastases between 2 and 3 cm dose escalation from 18 to 24 Gy, and for large metastases (size 3–4 cm) dose will be escalated from 15 Gy to 21 Gy/fx.

The rapid ongoing evolution of systemic therapies targeting the individual phenotypic subtypes of breast cancer has implications for analyzing outcome of breast cancer brain SRS. The high risk of brain metastases in patients treated with the monoclonal antibody Trastuzumab, provides an illustration of how new systemic therapy can alter the risk of developing brain metastases (29, 40). It has long been recognized that systemic therapies can positively influence local control within the breast itself when radiation is used in breast conservation (33). New systemic therapies may also influence the radiosensitivity of brain metastases.

The limitations of this study are its small sample size and its retrospective nature. This analysis demonstrates encouraging results. The prolonged median survival and the moderate number of patients surviving for 2 to 3 years may be a significant advance compared to the outcome of treatment of brain metastases before SRS was developed. Further advances for such patients may result from a better understanding of biology, improved tailored systemic therapy, appropriate surgery and further developments in stereotactic radiosurgery itself.

CONCLUSIONS

Survival outcome is similar to the published literature. Improved outcomes are observed in patients with Her 2-positive, controlled extracranial disease at the time of SRS and higher SRS dose delivered. Achieving intra-cranial control appears to be an important factor for the survival of the breast cancer patients in the era of targeted therapies.

ETHICS STATEMENT

This is a retrospective study carried out in accordance with the recommendations of Beacon Hospital Ethics Research Committee. At the time of their treatment, all patients included in this study consented that their information can be used for the retrospective analysis of their outcomes. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Beacon Hospital Ethics Research Committee.

AUTHOR CONTRIBUTIONS

KA and JWa contributed to database creation, drafting of the article and editing. MD contributed to statistical analysis and editing. LR contributed to drafting of the article and editing. JWe, PT, and CM contributed to review draft and editing. AM contributed to project development, data analysis, review and editing of all versions of the draft. All authors gave final acceptance of the manuscript.

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Hypofractionated Image-Guided Radiation Therapy With Simultaneous-Integrated Boost Technique for Limited Metastases: A Multi-Institutional Analysis

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Purpose: To perform a multi-institutional analysis following treatment of limited osseous and/or nodal metastases in patients using a novel hypofractionated image-guided radiotherapy with simultaneous-integrated boost (HIGRT-SIB) technique.

Methods: Consecutive patients treated with HIGRT-SIB for ≤5 active metastases at Duke University Medical Center or Durham Veterans' Affairs Medical Center between 2013 and 2018 were analyzed to determine toxicities and recurrence patterns following treatment. Most patients received 50 Gy to the PTV_{boost} and 30 Gy to the PTV_{elect} simultaneously in 10 fractions. High-dose treatment volume recurrence (HDTVR) and low-dose treatment volume recurrence (LDTVR) were defined as recurrences within PTV_{boost} and PTV_{elect}, respectively. Marginal recurrence (MR) was defined as recurrence outside PTV_{elect}, but within the adjacent bone or nodal chain. Distant recurrence (DR) was defined as recurrences not meeting HDTVR, LDTVR, or MR criteria. Freedom from pain recurrence (FFPR) was calculated in patients with painful osseous metastases prior to HIGRT-SIB. Outcome rates were estimated at 12 months using the Kaplan-Meier method.

Results: Forty-two patients met inclusion criteria with 59 sites treated with HIGRT-SIB (53% nodal and 47% osseous). Median time from diagnosis to first metastasis was 31 months and the median age at HIGRT-SIB was 69 years. The most common primary tumors were prostate (36%), gastrointestinal (24%), and lung (24%). Median follow-up was 11 months. One acute grade ≥3 toxicity (febrile neutropenia) occurred after docetaxel administration immediately following HIGRT-SIB. Four patients developed late grade ≥3 toxicities: two ipsilateral vocal cord paralyzes and two vertebral compression fractures. The overall pain response rate was 94% and the estimated FFPR at 12 months was 72%. The estimated 12 month rate of HDTVR, LDTVR, MR, and DR was 3.6, 6.2, 7.6, and 55.8%, respectively. DR preceded MR, HDTVR, or LDTVR in each instance. The estimated 12 month probability of in-field and marginal control was 90.0%.

Conclusion: Targeting areas at high-risk for occult disease with a lower radiation dose, while simultaneously boosting gross disease with HIGRT in patients with limited osseous and/or nodal metastases, has a high rate of treated metastasis control, a low rate of MR, acceptable toxicity, and high rate of pain palliation. Further investigation with prospective trials is warranted.

Keywords: simultaneous-integrated boost, oligometastasis, oligoprogression, radiotherapy, stereotactic, elective, occult, marginal recurrence

INTRODUCTION

Ever since Hellman and Weichselbaum proposed the existence of the oligometastatic state (1) as a corollary to the spectrum theory of cancer spread (2), there has been increasing interest in treating oligometastatic patients with high-dose precisely-targeted radiation (3). Recent randomized evidence demonstrates progression-free and overall survival improvements with the use of hypofractionated image-guided radiotherapy (HIGRT) to treat limited metastases (4–6). However, the optimal radiotherapy technique used to treat limited metastatic patients remains unknown.

Current radiotherapy techniques to treat oligometastases typically utilize stereotactic body radiotherapy principles including small margins and steep dose gradients (7, 8) to minimize potential toxicity of the high dose per treatment. Consistent with this approach is an avoidance of a clinical target volume (CTV) to treat nearby microscopic cancer spread. However, patterns of progression demonstrate that using this technique, recurrences typically occur in nearby structures beyond the treated target volume (9–13).

In an attempt to prevent marginal recurrence (MR) and avoid subjecting patients to another course of treatment, we investigated a simultaneous-integrated boost (SIB) technique when delivering HIGRT. We hypothesized that treating a larger elective volume (including areas at high-risk of harboring occult disease) with a lower dose considered to be well-tolerated by nearby organs at risk, while simultaneously boosting gross disease to a higher dose, would decrease MR with an acceptable toxicity profile.

MATERIALS AND METHODS

Patient Selection

Consecutively treated patients with lymph node and/or osseous metastases treated with the HIGRT-SIB technique in the Department of Radiation Oncology at Duke University Medical Center or the Durham Veterans' Affairs Medical Center prior to October 1, 2018 were identified. Patients >18 years of age with pathologically confirmed solid tumor malignancy of any primary site with five or fewer active metastatic sites at the time of HIGRT-SIB were included in this analysis. The combination of computed tomography (CT) and nuclear medicine imaging (i.e., bone scan and/or positron emission tomography [PET] as indicated by National Comprehensive Cancer Network guidelines) were used to quantify the number of active metastatic sites prior to HIGRT-SIB. All prostate cancer patients were staged with a combination of CT scans and technetium-99 m bone scans, while all other patients were staged with a combination of CT scans and ^{18}F-fluorodeoxyglucose-PET scans.

We extracted the following information from medical records: age at HIGRT-SIB, gender, primary tumor site, tumor histology, primary tumor treatment, systemic therapy, time to metastatic disease, number of active metastatic sites, largest diameter of metastasis (cm), biomarker level before and after HIGRT-SIB (i.e., prostate specific antigen [PSA], carcinoembryonic antigen [CEA], alpha-fetoprotein [AFP], carbohydrate antigen 19-9 [CA 19-9], and thyroglobulin), presence of painful metastasis prior to HIGRT-SIB, dose per fraction to PTV receiving boost dose (PTV_{boost}), dose per fraction to PTV receiving elective dose (PTV_{elect}), number of fractions, gross tumor volume (GTV, cm^3), PTV_{boost} (cm^3), PTV_{elect} (cm^3), and date of death or last follow-Up.

Treatment Technique

Patients were typically simulated supine with raised arms in a customized immobilization device, with respiratory management and intravenous contrast as indicated with 2–3 mm CT slices. The GTV was contoured on each axial slice. An elective CTV was contoured encompassing the gross disease and areas at high-risk of occult spread, including the surrounding nodal chain or contiguous bone. Typically, in the case of bony spine metastases, the entire vertebrae was included in the CTV as well as the spinal cord and canal at that level. The CTV was expanded by 5–7 mm in each direction to generate the PTV_{elect}. The GTV was expanded by 0–5 mm in each direction to generate the PTV_{boost}. Metastases with overlapping PTV_{boost} were considered as a single site, unless they involved different organs (e.g., obturator lymph node and pelvic bone).

The most frequently prescribed dose-fractionation was 50 Gy to the PTV_{boost} and 30 Gy to PTV_{elect} over 10 fractions. Organs at risk were contoured and assigned dose constraints compiled from published prospective and retrospective analyses (14–16). The PTV_{boost} could be selectively under-dosed to meet constraints of dose-limiting organs at risk such as the spinal cord, cauda equina, brachial plexus, and hollow viscera. Treatment was delivered on a linear accelerator with volumetric modulated arc therapy (VMAT) or intensity-modulated radiotherapy (IMRT) with cone beam computed tomography (CBCT) alignment approved by the physician prior to each fraction. Patients were seen once weekly during HIGRT-SIB for assessment of acute toxicity, 4–6 weeks

after treatment, and then follow-up and imaging performed as clinically indicated.

Outcomes

The primary outcome was the probability of in-field and marginal control. Events that contributed to this primary outcome include high-dose treatment volume recurrence (HDTVR), low-dose treatment volume recurrence (LDTVR), and MR. HDTVR was defined as clinical and/or radiographic progression or recurrence within the PTV_{boost}. LDTVR was defined as clinical and/or radiographic recurrence within the PTV_{elect}. MR was defined as clinical or radiographic recurrence outside the PTV_{elect} but within the same bone or nearby lymph node chain. Distant recurrence (DR) was defined as clinical or radiographic recurrence at a new site outside the PTV_{elect} that did not meet criteria for MR. Three authors (CJ, JS, MM) independently reviewed each clinical and radiographic recurrence, and a consensus categorization was reached in every case.

For metastases from prostate, thyroid, or gastrointestinal primaries with elevated biomarkers prior to treatment, biochemical recurrence (BR) was defined as biomarker elevation above the pre-HIGRT-SIB level. Overall survival (OS) was defined as the time from HIGRT-SIB start to death or last follow-up date. Disease-free survival (DFS) was defined as the time from HIGRT-SIB start to first recurrence (HDTVR, LDTVR, MR, DR, or BR), death, or last follow-up date, whichever was sooner.

Acute and late toxicities were measured using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Improvement in pain was defined as any decrease in severity on a 10-point scale after HIGRT-SIB. Pain recurrence was defined as equating or exceeding the metastasis pain severity from the pre-HIGRT-SIB level on a 10-point scale. Freedom from pain recurrence (FFPR) was calculated from the time of HIGRT-SIB start to pain recurrence in patients with painful osseous metastases prior to treatment.

Statistical Analysis

Demographic, tumor, and treatment characteristics were summarized with N (%) for categorical variables and median (interquartile range) for continuous variables for all metastases or patients, where applicable. Median length of follow-up was calculated from the start of HIGRT-SIB until death or last contact date for all patients. Crude event rates for each of the previously defined clinical endpoints were calculated out of the applicable populations (i.e., varying denominators). For HDTVR, LDTVR, MR, and probability of in-field and marginal control rates were calculated out of the total number of metastatic sites. Probability of in-field and marginal recurrence was also stratified by whether the metastasis was nodal or osseous and groups were compared with a log-rank test. For DR, OS, and DFS, rates were calculated out of the total number of patients. For BR, the rate was calculated for the total number of patients with pre-HIBRT-SIB elevated biomarkers. For FFPR, the rate was calculated out of the total number of patients with painful osseous sites of disease. Estimates and 95% confidence intervals (CI) of 1- and 2 year rates and median time to event for clinical endpoints were estimated using the Kaplan-Meier (K-M) method. Additionally, K-M

TABLE 1 | Demographic, tumor, and treatment characteristics.

Patient-specific variable ($n = 42$)	**N (%) or median (IQR)**
Age at HIGRT-SIB	69 (60–72)
Gender	
Female	8 (19)
Male	34 (81)
Primary tumor site	
Gastrointestinal*	10 (24)
Kidney	1 (2)
Head and neck°	2 (5)
Lung†	10 (24)
Prostate	15 (36)
Skin	3 (7)
Testicle‡	1 (2)
Histology	
Adenocarcinoma	27 (64)
Follicular dendritic cell sarcoma	1 (2)
Hepatocellular carcinoma	2 (5)
Melanoma	2 (5)
Merkel cell carcinoma	1 (2)
Mesothelioma‡	1 (2)
Papillary thyroid with follicular features	1 (2)
Renal cell carcinoma	1 (2)
Small cell carcinoma	2 (5)
Squamous cell carcinoma	4 (10)
Time from diagnosis to first metastasis (months)	31 (5–103)
Number of active metastases at time of HIGRT-SIB	
1	22 (52)
2	13 (31)
3	5 (12)
4	0 (0)
5	2 (5)
Biomarker level prior to HIGRT-SIB ($n = 23$)	
AFP (ng/mL)	29 (5–53)
CA19-9 (U/mL)	26**
CEA (ng/mL)	8.8 (5.9–11.0)
PSA (ng/mL)	8.9 (2.5–12.0)
Thyroglobulin (μg/L)	216**
Treated metastasis-specific variable ($n = 59$)	**N (%) or median (IQR)**
HIGRT-SIB target	
Lymph node metastasis	31 (53)
Painful osseous metastasis	16 (27)
Non-painful osseous metastasis	12 (20)
HIGRT-SIB anatomic location	
Abdominopelvic	27 (46)
Spine	14 (24)
Sternum or rib	8 (14)
Supraclavicular fossa, mediastinum, or axilla	10 (17)

(Continued)

TABLE 1 | Continued

Treated metastasis-specific variable ($n = 59$)	N (%) or median (IQR)
Greatest diameter of largest metastasis (cm)	3.0 (2.1–3.7)
GTV (cm^3)	12.4 (4.9–20.9)
PTV_{boost} (cm^3)	30.0 (15.5–49.7)
PTV_{elect} (cm^3)	182.7 (108.2–315.7)
Dose to PTV_{elect}	30 (30–30)
Fractions	10 (10–10)
HIGRT-SIB duration, days	13 (11–14)

**The distribution among gastrointestinal primary tumors was one anal canal, three colorectal, three esophagus, two liver, and one periampullary.*
◦One patient had papillary thyroid cancer with follicular features and another had p16-negative squamous cell carcinoma of the tonsil.
†One patient had medically inoperable oligometastatic extrapulmonary small cell carcinoma and comorbid contraindications to systemic therapy. After HIGRT-SIB, this patient remains disease-free for over 30 months. One patient had follicular dendritic cell sarcoma and received HIGRT-SIB to five sites per multidisciplinary consensus recommendations in lieu of systemic therapy.
‡One patient had oligometastatic testicular mesothelioma.
***Single measurement.*
AFP, Alpha-fetoprotein; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GTV, gross tumor volume; HIGRT-SIB, hypofractionated image-guided radiotherapy with simultaneous-integrated boost; IQR, interquartile range; PTV, planning target volume; PSA, prostate specific antigen.

TABLE 2 | Acute and late toxicities per treated site of HIGRT-SIB ($n = 59$).

Toxicity	Acute grade 1–2 *N* (%)	Acute grade ≥3 *N* (%)	Late grade 1–2 *N* (%)	Late grade ≥3 *N* (%)
Fatigue*	26 (55)	0 (0)	0 (0)	0 (0)
Gastrointestinal	25 (42)	0 (0)	6 (10)	0 (0)
Genitourinary	3 (5)	0 (0)	0 (0)	0 (0)
Hematologic*	2 (4)	1 (2)†	0 (0)	0 (0)
Musculoskeletal	0 (0)	0 (0)	2 (3)	2 (3)‡
Neurologic	6 (10)	0 (0)	0 (0)	2 (3)◦
Respiratory	2 (3)	0 (0)	0 (0)	0 (0)
Skin	5 (8)	0 (0)	0 (0)	0 (0)

**Rates were reported per course of HIGRT-SIB (n = 47).*
† Febrile neutropenia 5 weeks after completing HIGRT-SIB in a single patient with prostate cancer treated with HIGRT-SIB to two pelvic sites immediately followed by a cycle of docetaxel.
‡ Two patients developed ipsilateral vocal cord paralysis.
◦One patient required kyphoplasty for compression fracture and one patient required long-term narcotics for vertebral compression fracture limiting activities of daily living.
HIGRT-SIB, hypofractionated image-guided radiotherapy with simultaneous-integrated boost.

estimates of the primary endpoint were calculated for nodal vs. osseous metastases, and K-M estimates of DFS were calculated by number of active metastases at time of HIGRT-SIB. Differences in in-field or marginal recurrence or DFS by metastasis location and number, respectively, were compared between the groups using a log-rank test. Statistical analysis was performed using R version 3.4.3 (17), with Kaplan-Meier estimates obtained from the survival package (18).

RESULTS

Baseline Characteristics

Between July 2013 and October 2018, 42 patients met the inclusion criteria and 59 sites were treated with HIGRT-SIB. Demographic, disease, and treatment characteristics are summarized in **Table 1**. Median time from diagnosis to first metastasis was 31 months, and the median age at HIGRT-SIB was 69 years. The majority of patients had a single (52%) or two (31%) active metastatic sites at the time of HIGRT-SIB. The most common primary tumor was prostatic adenocarcinoma (36%), followed by gastrointestinal (24%), and lung (24%).

Among the 59 sites treated with HIGRT-SIB, 53% were nodal and 47% were osseous. Nearly one-half (46%) of all nodal or osseous metastases were in an abdominopelvic site, and nearly one-quarter (24%) were in the cervical, thoracic, or lumbar spine. The median GTV and PTV_{boost} were 12.4 and 30.0 cm^3, respectively. The median net PTV enlargement to generate the PTV_{elect} was 164 cm^3 with respect to PTV_{boost}. All but four patients received a prescribed dose of 50 and 30 Gy in 10 fractions to the PTV_{boost} and PTV_{elect}, respectively. Three patients were selectively underdosed to meet spinal cord or brachial plexus constraints, and one patient received 30 and 20 Gy in five fractions to the PTV_{boost} and PTV_{elect}, respectively.

Toxicity and Pain Analysis

Table 2 summarizes the acute and late toxicities per treated site or course of HIGRT-SIB. The most common acute toxicities were grade 1–2 fatigue (55%) and grade 1–2 gastrointestinal (42%). An acute pain flare occurred in four osseous sites (14%) and no nodal sites. Patients requiring a short course of steroids or non-steroidal anti-inflammatory drugs to facilitate laying comfortably on the treatment table during HIGRT were considered acute grade 1–2 neurologic toxicities (10%). The incidence of all other acute grade 1–2 toxicities was <10%, including dermatitis (8%). One acute grade ≥3 toxicity was noted in a patient who received docetaxel immediately following HIGRT-SIB and was subsequently hospitalized for febrile neutropenia. No other acute grade ≥3 toxicities were noted.

Late grade ≥3 toxicity following HIGRT-SIB was noted in four patients. Two of these were vertebral compression fractures; one requiring kyphoplasty and another treated with long-term narcotics for pain that limited the patient's activities of daily living. The two other grade ≥3 toxicities occurred in patients with esophageal cancer treated to the supraclavicular fossa and/or upper mediastinum who developed ipsilateral vocal cord paralysis. One of these patients had hoarseness prior to HIGRT-SIB, and underwent multiple esophageal dilations for grade 2 dysphagia. The other patient manifested hoarseness 32 months after completing HIGRT-SIB that did not improve with vocal cord injection. Of note, both of these patients had received prior thoracic chemoradiation therapy for their primary disease and one of the two patients underwent subsequent esophagectomy.

There were 12 patients with painful bony metastases in the study and 11 of them reported pain relief following treatment. The estimated 12 month FFPR was 72%. In total, there were 16

TABLE 3 | Crude and estimated rates of clinical endpoints.

Variable	HDTVR	LDTVR	MR	BR	DR	Any recurrence	Death
Crude events, *n* (%)	2/59 (3%)	1/59 (2%)	2/59 (3%)	11/23 (48%)	21/42 (50%)	26/42 (62%)	8/42 (19%)
Estimated rate at 12 months (95% CI)	3.6% (0.0–10.2%)	6.2% (0.0–17.4%)	7.6% (0.0–18.1%)	43.4% (18.1–60.9%)	55.8% (31.3–71.5%)	60.1% (38.5–74.2%)	11.9% (0.0–22.5%)

BR, Biochemical recurrence; CI, confidence interval; DR, distant recurrence; HDTVR, high dose treatment volume recurrence; LDTVR, low dose treatment volume recurrence; MR, marginal recurrence.

painful osseous metastatic sites treated, with 15 (94%) noted as having a decrease in severity following treatment.

Patterns of Recurrence

After a median follow-up of 11 months (interquartile range 6–24 months), there were five marginal or in-field recurrences (**Table 3**). The estimated probability of in-field and marginal control at 12 months was 90.0% (95% CI 80.9-100.0%, **Figure 1A**). When stratified by whether a nodal or osseous metastasis was treated with HIGRT-SIB, the estimated probability of in-field and marginal control at 12 months was 86.2% (95% CI 72.5-100.0%) for nodal metastases and 94.7% (95% CI 85.2-100.0%) for osseous metastases ($p = 0.33$, **Figure 1B**).

After review of individual isodose lines, daily CBCT, and diagnostic surveillance imaging, the crude number of events for HDTVR, LDTVR, MR, and DR were 2, 1, 2, and 21, respectively (**Table 3**). The estimated rates of HDTVR, LDTVR, MR, and DR at 12 months were 3.6% (95% CI 0.0-10.2%, **Figure 2A**), 6.2% (95% CI 0.0-17.4%, **Figure 2B**), 7.6% (95% CI 0.0-18.1%, **Figure 2C**), and 55.8% (95% CI 31.3-71.5%), respectively. The median time to DR was 11 months, and DR preceded HDTVR, LDTVR, or MR in each instance.

Further exploring MR, one occurred in a patient with lower extremity melanoma initially treated with wide local excision and inguinal nodal dissection who later received HIGRT-SIB for ipsilateral external and common iliac lymph node oligometastases. A biopsy-proven recurrence developed in the surgically dissected inguinal region, which was not included in the PTV_{elect}.

Additionally, a lung cancer patient developed both MR and LDTVR following two separate courses of HIGRT-SIB. This patient initially received 60 Gy to the primary lung tumor and mediastinal lymph nodes with concurrent carboplatin and paclitaxel. The first course of HIGRT-SIB targeted an isolated left upper mediastinal nodal recurrence while attempting to avoid overlap with the initial fields. As depicted in **Figure 3**, the MR occurred just outside of the PTV_{elect}, right between the junctions of the radiotherapy fields. The second HIGRT-SIB course treated the right supraclavicular fossa, where a LDTVR likely occurred due to an insufficiently treated subcentimeter oligometastasis that was visible on CT, but not avid on pre-treatment positron emission tomography (PET).

Both HDTVRs occurred in patients with prostate cancer. One patient with castrate-resistance developed widespread osseous metastases on the initial surveillance scan and shortly thereafter demonstrated disease progression within the PTV_{boost} 6 months after HIGRT-SIB. The second HDTVR occurred 25 months following HIGRT-SIB in one of five treated para-aortic lymph nodes in the setting of chronic immunosuppression and a new primary bladder malignancy.

Of the 23 patients with biochemically-detectable malignancies, 11 met our definition of BR. The median time to BR was 18 months. Among those with BR, the elevated laboratory value preceded any clinical or radiographic recurrence in 73% of patients.

Survival Analysis

Eight deaths occurred during the follow-up period (**Table 3**). The median OS was 36.6 months and the estimated 12 month OS was 88.1% (95% CI 77.5-100.0%). Any recurrence occurred in 26 (62%) patients during the follow-up period. The median DFS was 8.3 months and the estimated 12 month DFS was 38.8% (95% CI 25.1-60.1%). When stratified by number of active metastatic sites, the median DFS for patients with 1, 2, 3, and 5 active metastatic sites prior to HIGRT-SIB was 11.3, 7.7, 3.7, and 5.4 months, respectively.

DISCUSSION

Despite increasing enthusiasm for and growing evidence supporting the treatment of limited or "oligo" metastases with radiation, the optimal radiotherapy technique is unknown. Most of the evidence supporting the use of radiation for limited metastases has been accomplished using small fields directed at gross disease with a minimal margin to decrease the likelihood for toxicity. However, as progression near treated tumors occurs at a significant rate, we sought to decrease the likelihood of such by including an elective, lower-dose volume including adjacent areas at high-risk of harboring occult disease. With this technique, we found high treated tumor control rates, consistent with prior reports using HIGRT (11, 13, 19–37). Additionally, we found that the HIGRT-SIB technique altered previously reported patterns of progression, as we saw few in-field or marginal recurrences (10% combined at 12 months). Furthermore, treatment was well-tolerated with low rates of acute and late grade $\geq$3 toxicity, and pain responses following HIGRT-SIB were higher than historical rates observed following standard, palliative radiation doses.

The high rate of treated tumor control (96% at 12 months) seen in our patients treated with this HIGRT-SIB technique was promising. Our results are comparable with reported 12 month local control rates in other studies of HIGRT in oligometastastic patients with spinal (>80%) (20, 28, 33, 36, 38, 39), non-spine

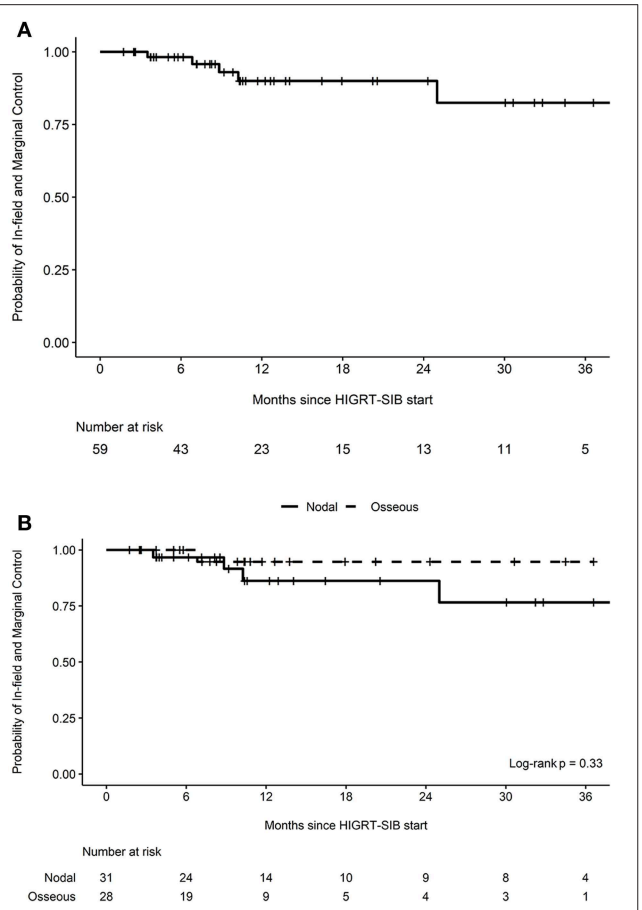

FIGURE 1 | Probability of in-field and marginal control. Kaplan-Meier curves depicting the probability of in-field and marginal control **(A)** for all treated metastatic sites ($n = 59$) as well as **(B)** stratified by nodal vs. osseous metastases treated with HIGRT-SIB.

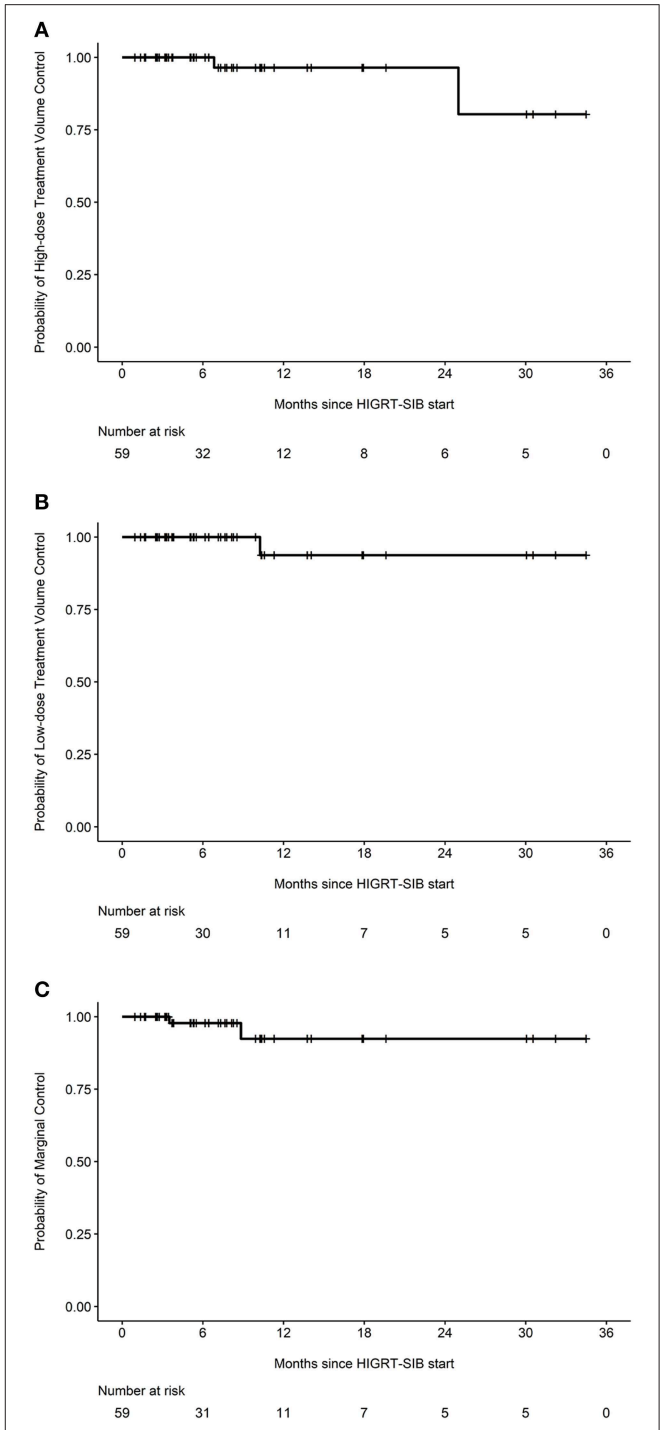

FIGURE 2 | Specific probabilities of in-field and marginal control. Kaplan-Meier curves depicting the probabilities of **(A)** high-dose treatment volume control, **(B)** low-dose treatment volume control, or **(C)** marginal control among all treated metastatic sites ($n = 59$).

bony (>91%) (19, 22, 25, 26, 34), and lymph node metastases (>77%) (11, 13, 21, 23, 24, 29–32, 35, 37), treated to visible tumor only. Additionally, it appears that the inclusion of a low dose PTV_{elect} may have reduced nearby progression. Prior studies describing patterns of progression following HIGRT to nodal metastases report 26–55% recurrence rates in adjacent lymph nodes (11, 13, 25). For patients with spinal metastases treated with HIGRT, prior studies have described the patterns of progression occurring primarily in the epidural space and/or in adjacent bony elements that have either not been included in the treatment volumes or purposely underdosed in order to meet spinal cord constraints (9, 33, 38, 39). Of the limited studies specifically investigating MR in radiation treated spinal metastases, one reported a crude MR rate of 12.5% and a cumulative incidence at 12 months of 9.5% (10). We noted only two MRs and a single LDTVR, corresponding to a combined estimated rate of 5% at 12 months. Comparison of these rates with prior studies investigating the use of HIGRT for patients with non-spine bony metastases is difficult, as the rates and patterns of progression immediately outside of the treated field are not commonly reported in the existing, limited literature for these patients.

This HIGRT-SIB technique was well-tolerated, as both acute and late grade ≥3 toxicity rates were low (≤10%). Importantly,

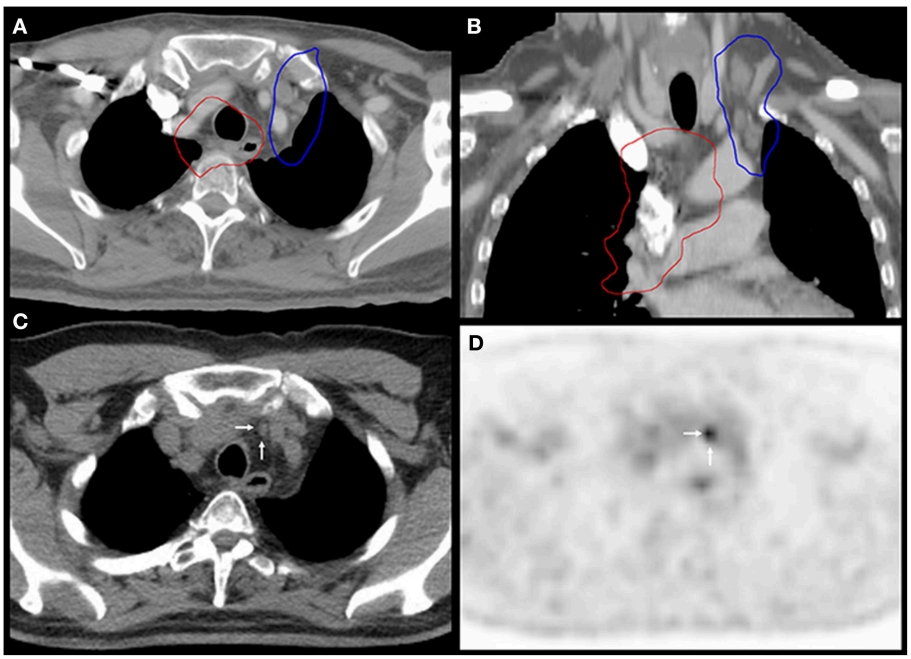

FIGURE 3 | Marginal recurrence between the junctions of radiation fields. Images **(A,B)** show the 60 Gy isodose lines (red) from the first course of chemoradiation and the 30 Gy isodose lines (blue) from the PTV_{elect} of HIGRT-SIB on fused axial and coronal planning CT images. Images **(C,D)** correspond to the axial slices of the surveillance PET-CT scan that identified the marginal recurrence (white arrows) in an undertreated lymph node between the junctions of the radiation fields.

we did not observe any bowel obstruction, bowel perforation, gastrointestinal hemorrhage, myelopathy, or death due to HIGRT treatment. Comparison of our observed toxicity rate is difficult due to the heterogeneity of treatment sites included in this analysis. However, our results compare favorably with existing reports, including a recently reported prospective randomized trial of standard of care (SOC) treatment with HIGRT vs. SOC alone in patients with 1–5 metastatic sites that found 29% experienced acute grade $\geq$2 toxicity with three treatment-related grade 5 events (6). Another recent randomized trial of HIGRT vs. maintenance chemotherapy in oligometastatic NSCLC patients reported a 20% grade three treatment-related toxicity rate in the radiation arm (4).

We found that HIGRT-SIB resulted in a high subjective pain response (>90%) that was also durable, with 72% of patients reporting continued pain improvement at 12 months. The pain response rate seen in our study was higher than the rate of 66% reported for all patients treated on the multi-fraction palliative radiotherapy arm of RTOG 97-14 (40) as well as the rate of 62% in patients with spine metastases in that trial (41). Our results also compare favorably to reported pain response rates following stereotactic body radiotherapy (SBRT) for spinal metastases (41–98%) (38, 42–44) and non-spine bony metastases receiving SBRT (77–88%) (34, 45).

While others have used a SIB technique to treat limited metastases, our technique is novel in several ways. First, patients in this study were most commonly received 10 fractions, delivering an established oligometastatic treatment dose of 50 Gy along with an elective dose of 30 Gy, the latter of which is commonly utilized to treat metastatic disease in multiple anatomic sites. Additionally, for osseous spinal metastases we included the entire involved vertebrae, including the posterior elements and spinal canal, in the PTV_{elect}. For non-spine osseous metastases a generous elective volume could be included and for patients with limited lymph node metastases, we targeted occult spread throughout the contiguous lymph node chain and not just the immediate vicinity around the involved node. We were able to treat large volume oligometastases with this technique. Finally, we were able to deliver treatments using commonly available CBCT image-guidance and without more advanced spine SBRT techniques, indicating that many centers may be able to adopt our HIGRT-SIB technique as a tool to treat oligometastatic, oligorecurrent, or oligoprogressive patients in their clinic.

Prior reports of a SIB technique for spinal metastases have utilized a CTV that included the vertebral body and selected, but not all, posterior elements in order to meet spinal cord constraints delivering one fraction of 21–24 Gy to the GTV and 18 Gy electively, or alternatively three fractions delivering 30 Gy to the GTV and 24 Gy electively (20). For lymph node metastases, HIGRT with a SIB technique utilizing 1–5 fractions with a much smaller low-dose CTV as a 5-mm expansion from gross disease with anatomic modifications has been used (46). Recently, a spinal simultaneous integrated boost (SSIB) technique for patients with spinal metastases considered to be "radiation-resistant" and unsuitable for treatment with standard spine SBRT approaches has been described (47). The study involved 12 patients with 15 treated sites extending between 3 and 5 vertebral body levels that were treated using a 10-fraction

SSIB technique. Gross disease was prescribed 40 Gy whereas a CTV including the involved vertebral bodies, at-risk paraspinal space, and spinal canal was prescribed 30 Gy. The 1 year local control rate was 93%, which was similar to our analysis. While only 78% of patients in this study reported any improvement in metastasis-related pain, 94% of the treated sites in our analysis resulted in any improvement in pain, potentially reflecting a dose-response relationship. Although the HIGRT-SIB technique and SSIB techniques have many similarities, there are several distinct differences. First, we used a higher dose per fraction to treat our GTV, which may have accounted for the improved pain response. Second, our CTV only included para-spinal areas if there was evidence of extraosseous extension on diagnostic imaging. Lastly, the SSIB technique was specifically utilized in patients with spinal metastases unfit for standard HIGRT, while this study described HIGRT-SIB use for patients with non-spine bony and lymph node metastases.

There are several limitations to our retrospective analysis. First, it is subject to effects from unidentified, potentially confounding variables in this very heterogeneous population. Second, the number of patients is small and the duration of follow-up is short, and therefore may not adequately capture all late toxicities and recurrences. Finally, a major limitation is the lack of a control arm (e.g., HIGRT without SIB and an elective treatment volume) to compare the rates of marginal and treated site recurrence with the experimental HIGRT-SIB technique; however, efforts are currently underway to identify patients treated with standard HIGRT at our centers and further analyses will be forthcoming.

In conclusion, targeting areas at high-risk of occult disease by treating a larger elective volume while simultaneously boosting gross disease with HIGRT in patients with limited osseous and/or nodal metastases has acceptable rates of acute and late toxicity with low rates of marginal or in-field recurrence. HIGRT-SIB showed a high rate of overall pain response that was durable. Further investigation with a prospective trial is warranted to determine if HIGRT-SIB with a PTV_{elect} has similar rates of local control, decreases MR, improves DFS, lengthens systemic therapy-free intervals or delays switching systemic therapies, and/or results in a similar or better toxicity profile compared to standard HIGRT. Importantly, prospective trials are indicated to determine if the described HIGRT-SIB technique increases the overall palliative pain response rate and/or provides more durable pain relief in patients with osseous metastases compared to traditional palliative external beam radiotherapy.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The retrospective research was completed under a protocol approved by the Duke University Medical Center Institutional Review Board (Pro00101071) and a protocol approved by the Durham VA Health Care System Institutional Review Board (MIRB #1740). Research was conducted under waivers of consent, HIPAA authorization, and decedent notification at both institutions.

AUTHOR CONTRIBUTIONS

CJ, JS, and MM contributed conception and design of the study and organized the database. CJ and HW performed the statistical analysis. CJ wrote the first draft of the manuscript. MM, JS, HW, BC, JP, and MP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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MINI REVIEW
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A Review of Ongoing Trials of Stereotactic Ablative Radiotherapy for Oligometastatic Cancers: Where Will the Evidence Lead?

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Purpose: The oligometastatic state is a proposed entity between localized cancer and widely metastatic disease, comprising an intermediate subset of metastatic cancer patients. Most data to support locally-directed treatment, such as stereotactic ablative radiotherapy (SABR), for oligometastases are from retrospective institutional reports. Following the success of a recently completed and reported phase II trial demonstrating important clinical outcomes, herein we review the current landscape of ongoing clinical trials in this context.

Materials and methods: A review of currently activated and registered clinical trials was performed using the clinicaltrials.gov database from inception to February 2019. A search of actively recruiting trials, using the key words oligometastases, SABR, and various related terms was performed. Search results were independently reviewed by two investigators, with discrepancies settled by a third. Data abstracted from identified studies included study type, primary disease site, oncologic endpoints, and inclusion/exclusion criteria.

Results: Of the initial 216 entries identified, 64 met our review eligibility criteria after full-text review. The most common study type was a phase II clinical trial (n = 35, 55%) with other study designs ranging from observational registry trials to phase III randomized controlled trials (RCTs). A minority of trials were randomized in design (n = 17, 27%). While most studies allowed for metastases from multiple primary disease sites (n = 22, 34%), the most common was prostate (n = 13, 15%), followed by breast, gastrointestinal, non-small cell lung cancer (NSCLC), and renal (n = 6, 9% each). In studies with a solitary target site, the most common was liver (n = 6, 9%) followed by lung (n = 3, 5%). The most common primary endpoints were progression-free survival (PFS) (n = 20, 31%) and toxicity (n = 10, 16%). A combined strategy of systemic therapy and SABR was an emerging theme (n = 23, 36%), with more recent studies specifically evaluating SABR and immunotherapy (n = 9, 14%).

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Conclusion: The safety and efficacy of SABR as oligometastasis-directed treatment is increasingly being evaluated within prospective clinical trials. These data are awaited to compliment the abundance of existing observational studies and to guide clinical decision-making.

Keywords: stereotactic, radiotherapy, SBRT, SABR, oligometastasis

INTRODUCTION

Metastatic cancer is a heterogeneous entity on a spectrum that ranges from a single metastasis to widely disseminated disease. Historically, patients with metastatic disease were generally considered incurable whereby palliative systemic therapy is the primary treatment and radiotherapy is reserved for palliation of symptoms (1). Today, the concept of oligometastases has diffused into the medical vernacular, and it represents an intermediate state between locoregionally confined cancer and widespread metastases whereby the number of metastases and organs are limited, typically between 1 and 5 lesions. By nature of having limited spread, it has been postulated that with aggressive metastasis-directed therapy, one can achieve better than expected survival, and in some scenarios, cure (2).

The oligometastatic state can also be further defined by its chronicity and evolvement. Synchronous oligometastatic disease is defined as *de novo* presentation of a primary cancer associated with limited metastases. In contrast, metachronous oligometastatic disease refers to the development of a few metastases after a primary cancer is detected. The term oligo-recurrence describes the development of metachronous oligometastases with a controlled primary site (3). Meanwhile, oligoprogression describes a state in which a limited number of metastatic lesions progress, while all other sites of disease remain stable, typically while on systemic therapy (4, 5). As each of these definitions represents a distinct scenario with a range of associated prognoses, classification of the appropriate type of oligometastasis is crucial both in the clinic and when appraising the growing outcomes-based literature.

The clinical implication of oligometastatic state is that cure or long-term survival can be achieved for this subset of patients with metastatic disease. Initially, reports on favorable survival outcomes in oligometastatic cancers largely involved surgery (6). In 1997, the International Registry of Lung Metastases reported a 5-year overall survival (OS) of 36% in patients with lung metastases treated by surgical resection (7). Moreover, a 5-year OS of 40% was reported following liver resection for metastatic colorectal cancer patients with a median survival of 46 months (8). A retrospective chart review from a single institution reported a 5-year OS of 70% among 12 patients with non-small cell lung cancer (NSCLC) after complete surgical resection of synchronous or metachronous brain metastases followed by whole brain irradiation (9). A review of 10 articles examining the outcomes of adrenalectomy for isolated synchronous and metachronous adrenal metastases in NSCLC reported a 5-year OS of 25% (10).

Currently, stereotactic radiosurgery (SRS) is generally considered to be the recommended treatment option for resected cavity and non-resected brain metastases (11). In a retrospective study involving 42 patients with synchronous solitary brain metastases from NSCLC, a 5-year OS of 21% was reported (12). Consequently, the use of metastases directed ablative therapy in the form of stereotactic ablative radiotherapy (SABR) has rapidly increased. SABR is a modern radiation technique that achieves highly accurate targeting, very conformal dose distributions and delivers highly ablative dose over a short overall treatment duration, usually in 1–5 treatments. A systematic review reported a 2-year local control rate of 77.9% and a 2-year OS of 53.7% for patients with lung oligometastases treated with SABR (13).

The clinical evidence to support SABR as a minimally invasive treatment for oligometastatic disease comprises of, in decreasing order of abundance, single-institution retrospective series, multi-institutional retrospective series, single-arm prospective trials, and randomized controlled trials (RCTs). Several RCTs have been published thus far.

The first was a phase II multicenter trial examined local consolidative therapy (LCT), including surgery or SABR, vs. maintenance therapy or observation for patients with oligometastatic NSCLC without progression after first-line systemic therapy (14). The study was closed early when interim analysis demonstrated a significantly longer median progression-free survival (PFS) in the LCT group vs. maintenance therapy group, 11.9 vs. 3.9 months, respectively (HR 0.35; 90% CI: 0.18–0.66; $p = 0.0054$). At final analysis, median OS was also significantly longer in patients in the LCT group than in the maintenance treatment group, 41.2 vs. 17.0 months, respectively ($p = 0.017$), with no additional grade III or higher toxicity. Similarly, a recent phase II single center RCT examined maintenance chemotherapy with or without LCT following partial or complete response on first-line platinum-based induction chemotherapy for NSCLC (15). This study was also closed early as PFS was nearly triple in the LCT arm vs. maintenance chemotherapy arm alone (9.7 vs. 3.5 months, respectively; $p = 0.01$). There was no difference in toxicity between the arms. Median OS was not reached in the SABR-maintenance chemotherapy arm, though the study was not powered to show a statistical difference in this measure.

The STOMP trial examined the effect of metastasis-directed therapy for oligometastatic prostate cancer (16). It was a phase II multicenter RCT that compared LCT vs. surveillance with oligometastatic prostate cancer detected on choline positron emission tomography–computed tomography. The authors found that androgen-deprivation therapy-free survival was higher in the LCT arm compared to the surveillance arm, 21 vs.

13 months, respectively (HR 0.60; 80% CI: 0.40–0.90; $p = 0.11$). No grade 2 or higher toxicity was observed.

Our group recently published the results from SABR-COMET, a phase II multicenter RCT for metachronous oligometastases of any origin (17). The study compared SABR vs. standard of care palliative treatment for up to 5 metastatic lesions among 99 patients. Median OS was 28 months for the standard of care treatment arm vs. 41 months in the standard of care treatment plus SABR arm (HR 0.57; 95% CI 0.30–1.10; $p = 0.090$). SABR was well-tolerated with no difference in overall quality of life at 6 months ($p = 0.99$). There were three (4.5%) treatment-related deaths in the SABR arm.

There is an increasing worldwide trend toward the use of SABR for oligometastatic cancers, despite a paucity of prospective data to support this strategy (18). Nonetheless, a number of clinical trials have been designed and are actively accruing. In this review, we aim to summarize the current state of registered oligometastatic clinical trials using SABR for oligometastasis-directed treatment.

MATERIALS AND METHODS

Clinicaltrials.gov is a database registry of privately and publicly funded clinical studies worldwide. A search was performed in the clinicaltrials.gov registry from inception to February 19, 2019. A combination of search terms was used to capture trials that reported on SABR ("stereotactic," "stereotaxis") for metastases ("oligo-, metastatic, metastasis, metastasize"). All trials underwent full text review by two independent reviewers. A third reviewer was available in case of a discrepancy between the two initial reviewers. Inclusion criteria included:

- Population: trials with inclusion criteria that limited the number of metastases throughout the whole body to any upper limit. This ranged from 3 to 10 metastases. Metastases were allowed from any primary disease site.
- Intervention: at least a proportion of the study population must undergo SABR. This can be combined with other local therapies (surgery, radiofrequency ablation), and/or systemic therapies.
- Recruitment status: actively recruiting.

Data abstracted from selected studies included study design, primary disease site(s), target site(s), population, outcomes, and inclusion/exclusion criteria.

RESULTS

The initial search identified 216 studies. The study description, recruitment status, and inclusion/exclusion criteria were reviewed for relevance. In total, 64 studies were selected for data collection. Of the 152 excluded studies, reasons for exclusion included not limiting the number of metastases ($n = 142$), and not having SABR as an intervention ($n = 10$). Notably, a large number of brain and spine SABR trials defined oligometastases in a solitary target site and did not limit the number of metastases elsewhere in the body, hence its exclusion from this review. The study selection process is summarized in **Figure 1**.

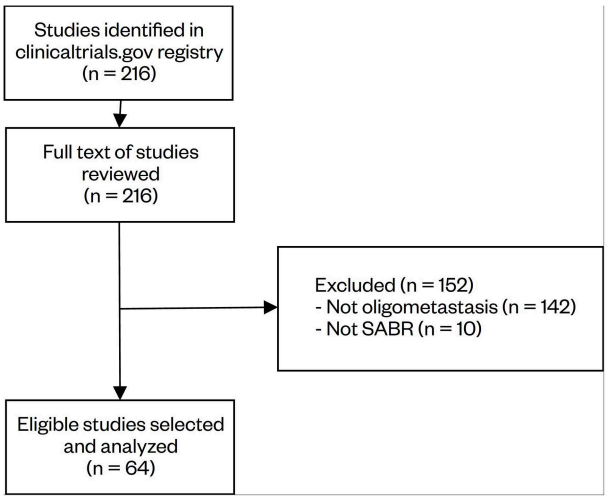

FIGURE 1 | Selection process of clinical trials regarding oligometastasis-directed SABR treatment. The initial search identified 216 studies, which were reviewed by two independent reviewers. Based on the eligibility criteria, 64 studies were selected for analysis.

Details of the reviewed studies are summarized in **Table 1**. The most common study type was a phase II clinical trial ($n = 35$, 55%) with other study designs ranging from observational registry trials to phase III RCTs. A minority of trials were randomized in design ($n = 17$, 27%). While most studies allowed for metastases from multiple primary disease sites ($n = 22$, 34%), the most common was prostate ($n = 13$, 15%), followed by breast, gastrointestinal, NSCLC and renal ($n = 6$, 9% each). In studies with a solitary target site, the most common was liver ($n = 6$, 9%) followed by lung ($n = 3$, 5%). Of note, there was 1 trial (2%) targeting the pediatric population. The most common primary endpoints were PFS ($n = 20$, 31%) and toxicity ($n = 10$, 16%). A combined strategy of systemic therapy and SABR was an emerging theme ($n = 23$, 36%), with more recent studies specifically evaluating SABR and immunotherapy ($n = 9$, 14%).

DISCUSSION

This review of active clinical trials evaluating the use of SABR in the setting of oligometastases illustrates that significant prospective efforts are underway to help inform decision-making in various scenarios. Although the number of trials identified is encouraging, there are a number of caveats. First, a lack of consistency in the definition of the type and number of oligometastases studied may limit the generalizability of these trials. Second, few were randomized in design, and many had non-definitive endpoints such as PFS or toxicity. Further, many trials combined SABR with other local treatments and/or systemic therapies, which presents challenges in measuring the direct risks and benefits of SABR. Finally, many trials employing brain and spine SABR in a solitary target site were

TABLE 1 | Summary statistics of the analyzed studies.

Study phase	
Phase I	4 (6%)
Phase I/II	7 (11%)
Phase II	35 (55%)
Phase II/III	5 (8%)
Phase III	5 (8%)
Observational studies	4 (6%)
Unspecified	4 (6%)
Primary disease site	
Breast	6 (9%)
Gastrointestinal	6 (9%)
Head and neck	2 (3%)
Non-small cell lung cancer	6 (9%)
Prostate	13 (20%)
Renal	6 (9%)
Multiple	22 (34%)
Target site	
Brain	2 (3%)
Liver	6 (9%)
Lung	3 (5%)
Spine	1 (2%)
Unspecified/multiple	52 (81%)
Population	
Pediatrics	1 (2%)
Primary endpoint	
Dose, planning	6 (9%)
Feasibility	3 (5%)
Overall survival	5 (8%)
Progression-free survival	20 (31%)
Toxicity	10 (16%)
Study design	
Non-randomized comparison	5 (8%)
Randomized	17 (27%)
Single treatment	38 (59%)
Disease state	
Metachronous metastases only	7 (11%)
Synchronous metastases only	5 (8%)
Oligoprogression only	6 (9%)
Oligorecurrence only	3 (5%)
Neither oligoprogression or oligorecurrence (*de novo* only)	5 (8%)
Systemic treatments	
Prior systemic treatments allowed	26 (41%)
Trial combines SABR with systemic treatment	23 (36%)
Trial combines SABR with immunotherapy	9 (14%)

excluded from analysis, as they included both oligometastatic and polymetastatic patients. Thus, this overview may not fully address the relative merits of SABR in central nervous system targets.

A recent literature review highlighted the importance of differentiating among the subtypes of oligometastatic states. An analysis of 17 publications comprising 869 patients who underwent SABR for lung oligometastases demonstrated that the cohort of patients with a disease-free interval of longer than 24 months conferred higher OS than those without (19). This supports the theory that there is a prognostic difference between those with synchronous and metachronous oligometastasis and raises the possibility of a difference between those with oligo-recurrence and oligoprogression.

In the absence of abundant prospective clinical trial data, there have been various epidemiological studies to help guide prognosis. For example, the METABANK score is a predictive nomogram for survival after stereotactic radiotherapy for oligometastatic disease based on a retrospective analysis of 403 patients who received SABR for 1–5 metastatic sites at a single institution (20). Three parameters had a high independent impact on survival: presence of brain metastases, non-adenocarcinoma histology, and low performance score.

A multi-institutional pooled analysis of 361 patients with extracranial oligometastatic disease who received ablative doses of radiotherapy found that prognostic factors associated with higher OS included age, number of metastases, primary tumor type, time to metastatic diagnosis, metastatic site, and a biological equivalent dose of $\geq$75 Gy (21). Another pooled analysis of 700 patients with lung metastases treated with SABR reported better outcomes for patients with good performance status, single vs. multiple pulmonary metastases, breast or colorectal primary vs. NSCLC and sarcoma, and a longer time interval between the initial primary tumor diagnosis and the SABR treatment (22). Further work is needed to further characterize the biological basis behind these prognostic indicators.

There is a growing interest in the role of SABR in anti-cancer immunity, as evidenced by the number of trials combining SABR and immunotherapy and using the abscopal effect as a secondary endpoint. The abscopal effect describes the theoretical ability of localized radiation inducing regression and response of non-irradiated metastatic sites due to a systemic anti-tumor immune response (23). Originally described in multiple case reports in the 1950s, this effect has renewed attention given the recent success of immunotherapies. For example, a subgroup analysis of the KEYNOTE-001 trial of 98 patients with advanced NSCLC treated with pembrolizumab reported that PFS and OS were higher in patients who were previously treated with radiation therapy compared to those without, suggesting a synergistic effect between radiation and immunotherapy (24). This was further suggested in a phase I study that evaluated the safety of pembrolizumab combined with SABR in patients with advanced solid tumors (25). Patients with metastatic disease and progressing on standard treatments received SABR to multiple sites followed by pembrolizumab within 7 days of completing radiation treatment. The authors reported comparable rates of toxicity of SABR or pembrolizumab monotherapy, and tumor control in 36 of 52 (69.2%) patients. In patients who had SABR to multiple but not all metastases, the authors observed a 26.9% response rate in non-irradiated sites.

Additionally, PEMBRO-RT is a phase II RCT examining the effects of pembrolizumab alone vs. SABR followed by pembrolizumab in patients with metastatic NSCLC (26). A recent interim analysis demonstrated a significant increase in median

PFS from 1.8 to 6.4 months in the monotherapy and combination therapy arms, respectively (HR 0.55; CI 0.31–0.98; $p = 0.04$). Further, the authors did not observe any significant differences in toxicity between the arms. Meanwhile, a phase II RCT examining the abscopal effect in patients with metastatic head and neck squamous cell cancer by comparing nivolumab alone vs. nivolumab with SABR to a single lesion did not demonstrate a difference in PFS or OS between the two arms (27). It is clear that more clinical trial data is needed to clarify the role of SABR and immunotherapy.

CONCLUSION

The safety and efficacy of SABR as oligometastasis-directed treatment is increasingly being evaluated within prospective clinical trials. Emerging themes include differentiating among the subtypes of oligometastatic states and combining SABR and systemic therapies. These data are awaited to compliment the abundance of existing observational studies to guide clinical decision-making. Enrolling in prospective trials evaluating SABR in various clinical scenarios has several benefits beyond the generation of higher quality evidence. Firstly, vigorous quality assurance within trials provides a mechanism to improve the framework of technical nuances within centers that are looking to expand the scope to organ systems not previously treated within the team in a controlled manner. Secondly, the implementation of protocols for trial patients inherently benefits patients who are treated off trial in the same institution by nature of these implementations. Finally, subset analyses of prospective trials for endpoints such as safety can be performed using dosimetric information, which will be invaluable to further refine organ at risk constraints. Ultimately, as the landscape of advanced cancer management rapidly evolves with the rise of immunotherapy, targeted therapies, and other novel agents, clarity on how SABR fits within the proven and purported benefits of these treatments will be a priority area of research moving forward.

AUTHOR CONTRIBUTIONS

AL and FA-S contributed to the conception and design of the study. AA organized the database. FA-S wrote the first draft of the manuscript. AA and AL wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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MINI REVIEW
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The Yin and Yang of Cytoreductive SBRT in Oligometastases and Beyond

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Background: Oligometastatic disease has emerged as a possibly distinct metastatic phenotype in numerous cancer histologies. With the advancement in treatment modalities including stereotactic body radiation therapy (SBRT), certain patients may derive benefits from local ablative therapy. SBRT alone has already shown to have potential benefits in certain oligometastatic disease types. However, more understanding of the immunologic modulation and microenvironment is needed to guide which patients may benefit from SBRT alone or with combination therapy, if at all.

Purpose: The purpose of this review is to offer an update on the emerging data testing SBRT combined with immunotherapy, review the pro-inflammatory and immunosuppressive effects of the tumor microenvironment, discuss novel molecular targets used to augment the immune response, and review potential methods used to decrease toxicity in order to improve the therapeutic ratio.

Keywords: SBRT, radiation, cytoreduction, immunotherapy, 4-1BB, CSF-1R, TGF-beta, oligometastases

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Stereotactic body radiation therapy (SBRT) has emerged as a prominent and safe modality for metastasis-directed therapy across histologies and appears to result in long-term disease control (1). Initial Phase 2 trials suggest that this long-term disease control translates into a progression-free survival as well as an overall survival benefit further increasing the excitement for definitive phase 3 trials (2, 3). Potential benefits of this approach are hypothesized to include delaying progression in known metastases, preventing further seeding of new metastases, as well as inhibiting progression of micrometastatic foci (4–6). In terms of the effectiveness of the SBRT on local control, increasing the biologically effective dose (or BED) of radiation correlates with the robustness of tumor control (7–10). These techniques have been shown to be effective even when targeting larger metastases (11), with treated metastasis control ranging from 70 to 90% (12). Ongoing phase III trials are investing whether this approach may lead to improve overall survival in a subset of patients with limited metastatic disease (NRG BR002, LU002, SABR-COMET-3, SABR-COMET-10, and SARON). Here, we will focus on the emerging role for SBRT combined with immunotherapy, the modulation of the tumor microenvironment through the utilization of novel molecular targets, and mechanisms used to decrease toxicity during multi-site SBRT.

Beyond radiation alone for oligometastases, there is great interest in enhancing the effects of both radiotherapy and immunotherapy with combined regimens. The goal of combined therapy is to improve both local control of irradiated metastases and un-irradiated responses outside the radiation field (abscopal effect) (13). This immune response may be further affected by the tumor microenvironment. For instance, an immune-excluded environment, which is characterized by a lack of T-cell infiltration, low TH1 cell activity, and reduced cytotoxic T cells, has been shown to predict for worse response to therapy (14).

Described mechanisms for the improvement in immune modulation include but are not limited to increased tumor antigen exposure, improved antigen presentation by dendritic cells, improved T-cell function, re-priming of T-cells, as well as modulation of immunosuppressive cell populations such as T regulatory cells and myeloid derived suppressor cells (15–17). In addition, direct tumor debulking by radiation may also improve systemic immunotherapy outcomes (18, 19). Moreover, ablating multiple areas of disease may also help to overcome PD-L1/CTLA-4 monoclonal antibody therapy resistance (20, 21). Thus, the pre-clinical data suggest that radiation, and in particular SBRT-like doses, may induce a CD8+ T cell mediated anti-tumor response leading to tumor control of the irradiated tumor and potentially to tumor control outside the radiation field.

However, the initial reports of clinical trials combining SBRT with immunotherapy are difficult to interpret with conflicting results. For example, a recent trial (ASCO 2018) in patients with advanced NSCLC treated with 8 Gy x 3 to a single metastatic site followed by Pembrolizumab demonstrated a doubling in overall response rate (ORR) in a randomized setting (22). In contrast, a similar trial design with Progression-Free Survival (PFS) as an endpoint conducted and recently presented in head and neck cancer patients (using 9 Gy x 3, to a single metastasis) failed to demonstrate a signal of efficacy (23). Given the higher doses of radiation in the head and neck trial compared with the NSCLC trial (BED_{10} of 51.3 vs. 43.2, respectively), and the type of immunotherapy were similar (both PD-1 monoclonal antibodies), the difference may lay in the timing of SBRT with immunotherapy. Since the NSCLC trial used sequential SBRT followed by Pembrolizumab and the head and neck trial used SBRT between doses of Nivolumab, the SBRT timing may serve a purpose to "prime" the immune system for optimal effect. However, this efficacy may be tempered by possibly increasing toxicity from a robust response from sequential administration.

As phase 3 trials continue with SBRT alone and many early phase trials continue combining radiation and immunotherapy, a fundamental question remains: which patients, if any, may benefit from SBRT directed at oligometastases? In order to begin to understand this issue, one must incorporate tumor biology into one's treatment paradigm since activation of various cellular pathways may identify potentially curable oligometastatic states (24). Radiation therapy may modulate the tumor microenvironment through pro-immunogenic and immunosuppressive signals (see **Figure 1**), and the balance of these signals may determine the effectiveness of local tumor cell killing and systemic antitumor immune response. Once we have a better understanding of the immunosuppressive and pro-immunogenic actions of radiation, we can begin to understand which patients may benefit from cytoreductive SBRT alone or in combination with molecular targets. Below we are going examine a few examples of current attempts to modulate the tumor microenvironment to be more favorable toward an SBRT and immunotherapy approach where early stage therapeutics exists for both pre-clinical and clinical testing.

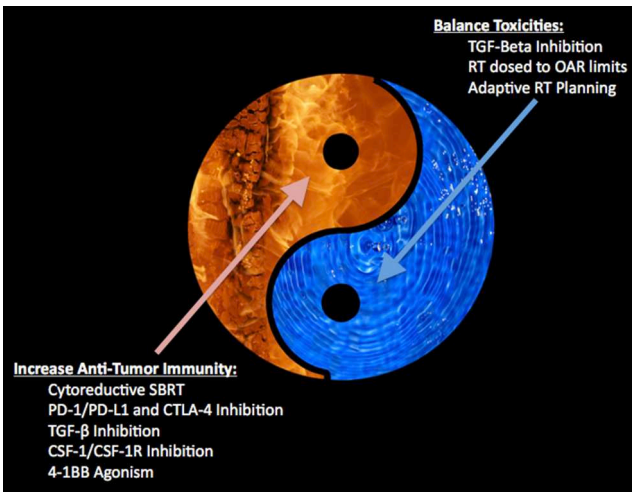

FIGURE 1 | Depicts the balance between increasing anti-tumor immunity with toxicity within the tumor microenvironment.

One method of modulating the microenvironment in favor of SBRT and immunotherapy may be achieved by augmenting pro-inflammatory effects. For example, 4-1BB (CD137) stimulation promotes survival and cell cycle progression of activated human CD8+ T cells while simultaneously inhibiting regulatory T cells (T-regs) (25). Due to these effects, there are numerous ongoing trials using 4-1BB ligands in combination with chemoradiation (NCT00461110), other targeted monocloncal antibody targets (NCT01775631, NCT02110082), and PD-1 inhibitors (NCT03792724, NCT02845323). As these trials examine the combination of 4-1BB ligands with one other modality, our institution is currently evaluating the safety of combining a 4-1BB ligand (Uralumab) with a PD-1 inhibitor (Nivolumab) and SBRT (NCT03431948). These clinical trials will gauge the safety of combination therapy, and may prove useful in identifying future directions for this molecular target.

Another method of improving the therapeutic ratio for SBRT and immunotherapy may come through inhibiting immunosuppressive signals. Activation of these signals result in increased infiltration by T-regs and myeloid-derived suppressor cells (MDSCs). One such pathway with a molecular target includes the macrophage colony-stimulating factor 1 receptor pathway (CSF-1R). CSF-1R signaling has specifically demonstrated a role in differentiation, maintenance, trafficking, functioning of the monocytic lineage, and serves as a prominent driver in resident tumor macrophages (26, 27). These tumor-associated macrophages (TAMs) have shown the ability to promote tumor regrowth (28). Although the relationship between TAMs is relatively plastic, the ratio of M1/M2 TAMs is prognostic of clinical outcome in multiple of human cancers including lung, breast, pancreas, and lymphoma (29, 30). There is evidence of a benefit in cancer therapies by targeting these trophic effects of TAMs through this CSF-1R pathway (31, 32). Moreover, further research targeting this receptor in combination with other therapies (i.e., PD-1/PD-L1 inhibitors) are currently underway. For example, preliminary phase 1a/1b

data (SITC 2018) in pancreatic cancer demonstrated safety of Cabiralizumab (CSF-1R inhibitor) with Nivolumab (PD-1 inhibitor) with a 6-month disease control rate of 13 percent and an ORR of 10 percent (33). Given this preclinical and early clinical data, our institution is currently investigating the toxicity of SBRT, PD-1 inhibition (Nivolumab) with a CSF-1R monoclonal antibody (Cabiralizumab (NCT03431948) in a phase 1 setting. Further trials examining this molecular target may identify subsets of patients that may benefit from combination of SBRT and immunotherapy.

Beyond modulating the immune microenvironment through 4-1BB agonism or CSF-1R inhibition, TGF-β in particular has shown to be a primary mechanism of tumor immune evasion by blocking the TH-1 effector phenotype, inhibit T cell division/function and natural killer (NK) cell function, and by promoting epithelial-mesenchymal transition (EMT) (34, 35). This microenvironment high in TGF-β signaling has further characterized a poor-prognostic phenotype in colorectal cancer, and preclinical models showed that inhibition of TGF-β stops disease progression in liver metastases from colon cancer (36). Moreover, a lack of response to PD-L1 monotherapy has been associated with increased TGF-β by creating an immune-excluded phenotype, and several preclinical studies examining the utility of TGF-β inhibition in promoting PD-L1 response (34, 37). In addition to these immune-exclusion aspects of TGF-β, increased TGF-β signaling has demonstrated radiation resistance (38), while inhibition of TGF-β cell lines promoted radiation sensitization (22). Thus, targeting these immune-excluding signaling molecules, may allow for improved response to PD-1/PD-L1 therapy and radiation therapy.

Another method of overcoming local PD-1/PD-L1 immune resistance is through the use of novel bispecific fusion protein technology. One such fusion protein, (M7824), combines an anti-PD-L1 monoclonal antibody with two TGF-β receptor 2 molecules to serve as a TGF-β "Trap." Urothelial cancer cell lines treated with this bispecific fusion protein demonstrated an increase in T-cell trafficking, TRAIL-mediated tumor lysis, and ADCC when compared to PD-L1 inhibition alone (39). In NSCLC, this bifunctional PD-L1 and TGF-β inhibitor prevented tumor endogenous mesenchalization compared with PD-L1 inhibition alone and enhance antibody-dependent cellular cytotoxicity (ADCC) in cervical, breast, and prostate cancer cell lines (40, 41). Also, when compared to PD-L1 monotherapy alone, this bifunctional inhibition demonstrated a decrease in TAMs and increases effector T cells, M1 cells, and improved the M1/M2 ratio (discussed above) (35). Combining this bispecific fusion protein with radiation therapy may promote an immune response while simultaneously decreasing immune exclusion. In pre-clinical models, this bifunctional inhibitor combined with radiation therapy promoted the inhibition of tumor growth, metastases and improved survival (42). Furthermore, murine models combining radiotherapy and a the bifunctional protein results in significantly greater irradiated tumor response as well as a secondary non-irradiated tumor response, suggesting secondary systemic beneficial effects of radiation on the immune response (35). With this new preclinical and early clinical data in mind, these novel bispecific monoclonal antibodies may prove beneficial in subsets of patients with oligometastatic disease and further testing is warranted.

As radiation therapy may promote pro-inflammatory effects in the tumor microenvironment, it may also promote immune-exclusion. For example, a preclinical study demonstrated that high doses of radiation has shown the ability to induce an immune-suppressive, M2-like phenotype, and that reversing this effect could improve local control of tumors and stimulate a more robust immune response (43). Thus, some patients receiving cytoreductive SBRT may gain a benefit from concomitant use of targetable signaling molecules (PD-1/PD-L1, 4-1BB, CSF-1R, and TGF- β) in order to limit the immune-exclusion and promote a more robust response to SBRT.

Beyond the initial concept of oligometastatic disease, the largest published benefit of immunotherapy to date comes from the PACIFIC Trial. Although these patients all had locally advanced non-small cell lung, presumably they may have had micrometastatic disease. In those treated with adjuvant Durvalumab, there was a tripling of median PFS and a 10% improvement in 2-year OS (44, 45). Thus, we hypothesize that patients with the lowest burden of metastatic disease, in this case possibly micrometastatic disease, may benefit the most from immunotherapy. Although a radiation-immunotherapy interaction may also be the rationale for this benefit, further surgical studies in locally advanced NSCLC combined with immunotherapy (i.e., ECOG-ACRIN E5142) may aid the argument of minimal micrometastatic disease benefitting the most from immunotherapy. On the opposite end of the disease spectrum, a recent prospective phase 1 trial from our group further supports the notion of possibly improving on the immune-exclusion microenvironment through cytoreduction of metastatic disease with high-dose SBRT and combined with pembrolizumab. The combination demonstrated a long median overall survival (9.6 months) with low rates of severe toxicity in a heavily pre-treated, non-oligometastatic patient cohort (46). Moreover, local control was no different between partial tumor radiation coverage (see **Figure 2**) for larger tumors and smaller ones suggesting a synergistic effect with the immunotherapy. In an exploratory analysis, the only predictor for overall survival was the local control of the irradiated tumor with high dose radiation (47). As oligometastatic states exist between "micrometastatic" and heavily pre-treated metastatic states, evidence from our group further confirms the necessity for local control of large metastatic lesions through cytoreductive SBRT to promote an inflammatory microenvironment and limit immune-exclusion.

SBRT alone to oligometastases is currently well-tolerated with around 30% grade 2+ toxicity, however given the grade 5 toxicities observed, there is continued concern that toxicity may increase with multi-site SBRT (3). These pro-immunologic benefits of SBRT, and especially with the combination with other pro-inflammatory molecular targets, may result in improved outcomes however there is concern over increased toxicity. Some strategies to limit toxicity are attempting to ameliorate this inflammatory response in the normal tissues (see **Figure 1**). For example, a recent study demonstrated that patients with non-small cell lung cancer showed an increased risk for radiation pneumonitis with increased TGF-β signaling (48), while a

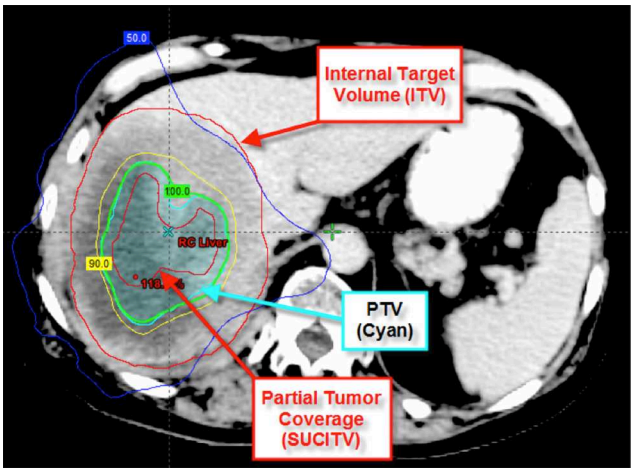

FIGURE 2 | Depicts partial tumor coverage of a large liver lesion. The 45 Gy in three fractions was prescribed to the central 65 cc of the tumor (SUCITV) with a 5 mm PTV expansion. ITV, internal target volume; SUCITV, seriously undercovered immuno-target volume; PTV, planning target volume.

preclinical study demonstrated a decrease risk for radiation pneumonitis in mice treated with TGF-β inhibition (49). Thus, inhibition of TGF-β, possibly in the bispecific antibody approach, may provide another means of limiting the toxicity from therapy. Another possible mechanism of limiting toxicity adopted by our group has been through decreasing dose to adjacent OARs. In patients receiving immunomodulatory agents, initial observation suggests that local control may be achieved despite significantly decreased doses to the tumor edge (see **Figure 2**) (46, 47). With this approach, we noticed that the majority of the center of the tumors received a high dose of radiation while the periphery of the tumor received a lower prescription dose. Interestingly, we were able to increase the dose to the center of the lesion without compromising control, while also limiting our dose to critical structures and subsequent toxicity. Another method of limiting toxicity, although logistically challenging, may be through adaptive radiation planning. This method of re-planning the SBRT treatment during the course of radiation may allow for the most accurate method of delivery as it accounts for tumor responses and relationship of adjacent OARs to target lesions. By using these various methods: TGF-β inhibition, limiting target coverage to spare adjacent OARs, and adaptive radiation planning, we may continue to treat more lesions with multi-site cytoreductive SBRT while also limiting toxicity and not compromising our primary objective of local control.

In conclusion, phase 3 trials of SBRT alone for oligometastasis are currently underway in various histologic disease sites. These studies are needed to demonstrate oligometastatic states while also being cognizant of emerging concepts regarding tumor biology and the microenvironment. As this data emerges, future trials examining cytoreductive SBRT combined with checkpoint inhibition and using novel agents against other molecular targets, such as TGF-β, CSF-1, and 4-1BB may demonstrate a logical progression of the current data. We believe there is promise in further translational and clinical studies identifying a synergistic mechanism to increase anti-tumor immunity through high-dose SBRT combined with systemic therapies. We believe the most promising to date revolve around cytoreduction of tumor burden combined with systemic treatments aimed at balancing toxicities (i.e., TGF-β), partial-tumor coverage of the prescription dose to avoid critical organs, and adaptive radiation planning.

AUTHOR CONTRIBUTIONS

BO conducted the literature search and wrote the majority of this manuscript. SC provided academic support and also contributed in writing this manuscript.

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Usefulness of Stereotactic Body Radiation Therapy for Treatment of Adrenal Gland Metastases

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Purpose: This study aimed to describe our institutional experience in the use of stereotactic body radiation therapy (SBRT) for the management of adrenal gland metastases from multiple primary cancers.

Materials and Methods: We retrospectively reviewed 31 patients who underwent SBRT as treatment for 33 adrenal gland lesions in the academic radiotherapy department of Oscar Lambret cancer center between May 2011 and September 2018. The primary study endpoints were 1- and 2-year local control rates, defined as the absence of progression at the treatment site based on the response evaluation criteria in solid tumors (RECIST). Toxicities were graded in accordance with the Common Terminology Criteria for Adverse Events version 4.03.

Results: The average tumor volume was 33.5 cm^3 (standard deviation: 51.7 cm^3), and the prescribed dose ranged from 30 to 55 Gy given in 3–9 fractions. The median biological effective dose was 112.5 Gy (range: 45–115.5 Gy), assuming $\alpha/\beta = 10$. Considering progression at distant sites or death as competing events, the 1- and 2-year actuarial local control rates were 96.5% (95% confidence interval: 84.9–99.7) and 92.6% (95% confidence interval: 79.2–98.7), respectively. According to RECIST, a complete response was achieved in 10 (32.3%) lesions, a partial response in 10 (32.3%) lesions, and stability in 8 (25.8%) lesions. Three patients presented with local relapse at 8.8, 14, and 49.4 months. After a median follow-up of 18 months (range: 4.4–66.4), the median overall survival was 33.5 months (95% confidence interval: 17–not reached), while the median progression-free survival was 7.4 months (95% confidence interval: 3.8–14.1). Treatment-related toxicity was grade 1 or 2 in 42.4% of patients, including nausea (27.3%), abdominal pain (18.2%), vomiting (15.2%), and asthenia (9.1%). None of the patients developed acute grade $\geq$3 or late toxicity.

Conclusion: SBRT seems to be a safe and effective treatment for adrenal gland metastases in patients whose primary tumor and metastatic spread are controlled by systemic treatment. With a 2-year local control rate of 92.6%, SBRT may be considered as one of the first-line treatments in oligometastatic patients with adrenal metastases.

Keywords: adrenal gland, metastases, stereotactic body radiation therapy, local control, oligometastatic

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INTRODUCTION

The adrenal glands are a preferential site for metastatic spread, especially from non-small-cell lung cancer, renal cell carcinoma, and melanoma (1).

Improvements in the management of metastatic disease and the widespread use of abdominal computed tomography (CT) and positron emission tomography during staging and follow-up increased the rate of detection of adrenal gland metastases (2, 3).

In this setting, the term "metastatic disease" covers several clinical presentations, ranging from a slowly progressive disease with a limited number of metastases to metastatic efflorescence. In 1995, Hellman and Weichselbaum described the "oligometastatic" concept as a limited metastatic spread in terms of number (maximum of five lesions) (4). In these cases, medical strategies recently evolved into potentially curative treatments, including the multimodal treatments of the primary and metastatic sites.

Adrenalectomy has been the definitive treatment for adrenal gland metastases since several surgical experiences have shown the possibility of long-term survival after resection of isolated adrenal metastasis, especially from non-small cell lung cancer (5–9).

Other local ablative treatments, such as radiofrequency ablation, cryoablation, and transarterial chemoembolization, have reported interesting results in terms of local control in small single institution studies (10, 11).

On the other side, radiation therapy has often been restricted in palliation goals, mostly in cases of abdominal pain (12).

The recent development of stereotactic body radiation therapy (SBRT), which delivers a highly focused ablative dose to the tumor and also spares the healthy surrounding tissues, could probably increase the local control of the oligometastatic disease. This allows the competitiveness of SBRT with other local ablative treatments.

However, only a few data have been published supporting the use of SBRT as treatment for patients with limited metastatic disease involving the adrenal glands. Most of the series concerned few patients, in which the biological effective dose was often $<$90 Gy ($\alpha/\beta = 10$), which is the dose necessary to sterilize most metastases of solid cancers, particularly non-small cell lung cancers (13–15).

Using a biological effective dose of more than 90 Gy, this study aimed to retrospectively describe our single institution experience in the treatment of adrenal gland metastases from various primary cancers in terms of response, local control, overall survival (OS), progression-free survival (PFS), and toxicity.

MATERIALS AND METHODS

Eligibility criteria were: patients aged $>$18 years, with histologically proven primary cancer disease, with metastatic spread evolution controlled by any systemic treatment administered before SBRT planification, with World Health Organization performance status of $\leq$2, who underwent SBRT delivered as an ablative therapy using a CyberKnife linear robotic accelerator between May 2011 and September 2018, and with no previous surgery or radiation therapy on the adrenal glands. In all patients included in this study, stability or partial response of primary and metastatic sites except the adrenal glands was completed by CT or positron emission tomography (PET) evaluation after previous systemic treatment given according to location and histology of the tumor. We identified the patients from the hospital patient files. All cases potentially eligible were reviewed to confirm the inclusion in the study. All consecutive cases matching with eligibility criteria were finally included in the study.

The study complies with the "reference methodology" adopted by the French Data Protection Authority (CNIL) and patients did not object to the use of their clinical data for the research purpose.

SBRT Treatment Planning

All treatments were delivered using a high precision CyberKnife linear accelerator, with 6-MV photons.

Treatment simulation was performed on a CT simulator that encompassed a free-breathing four-dimensional CT and a millimeter thickness abdominal CT.

Treatment planning was conducted in the following manner:

1) When possible, patients underwent transdermal implantation of a gold fiducial, which was placed in the center of the metastasis under CT scan control. In these cases, the clinical target volume (CTV) was the same as the gross tumor volume. The planning target volume (PTV) was generated by expanding the symmetric margin to 3–5 mm.

   In these patients, real-time tumor tracking was performed using Synchrony motion management, and respiratory motion of the lesions was compensated during treatment. A correlation model was built between orthogonal x-ray images acquired with regular intervals and the position of light emitting diodes located on the patient's chest obtained by infrared camera. This model was continuously updated and used to move the linear accelerator mounted on the robotic arm, anticipating target location with high accuracy.
2) In other patients, the CTV was expanded to the entire range of tumor motion across the respiratory cycle to create an internal target volume (ITV). This was delineated using a set of 5 CT scans acquired through the course of the respiratory cycle from maximum inhalation to maximum exhalation. The PTV was defined using a uniform 3–5 mm expansion. In those cases, real-time tumor tracking system was not used but respiratory motion management was performed.

The liver, kidneys, stomach, duodenum, spinal cord, and small bowels were contoured as organs at risk.

Follow-Up and Evaluation of Response to SBRT

Observation time started after the first fraction of SBRT.

The primary study endpoints were 1- and 2-year local control rates, defined as the absence of progression at the treatment site according to the Response Evaluation Criteria in Solid Tumors (RECIST).

The secondary study endpoints were best response to treatment according to RECIST, PFS, OS, and level of toxicity (acute and late) using Common Terminology Criteria for Adverse Events version 4.03.

Statistics

Descriptive statistics were summarized as average values, median, and range for continuous variables, and as frequencies and percentages for categorial variables.

One- and two-year local control rates were derived from the first day of SBRT with cumulative incidence of local relapse, according to the Kalbfleisch and Prentice method (16), considering death or progression at distant sites without local relapse as competing events.

PFS and OS were estimated using Kaplan-Meier method, from the first day of radiation therapy.

RESULTS

Patient Characteristics

Patients' characteristics are summarized in **Table 1**.

All patients matching with eligibility criteria were included in the study, leading to a total of 31 patients and 33 lesions. The median age was 63 years (range: 38–80 years). Two patients with bilateral adrenal metastases underwent SBRT; both lesions were treated at the same time for one patient and at 6-months interval for the second patient.

Sixteen right and 17 left-sided adrenal gland lesions were treated ($n = 33$).

Five adrenal metastases (15.2%) observed in 5 patients were diagnosed <6 months after their primary cancer diagnosis (synchronous metastases). Twenty-eight (84.8%) lesions observed in 26 patients developed after a minimal interval of 6 months (metachronous). In these patients, the median interval from the diagnosis of the primary cancer to the diagnosis of the adrenal metastasis was 16.35 months (range: 5–130.5 months).

Twenty five (75.8%) of 31 patients had metastatic sites other than the adrenal glands. Eighteen (58%) of 31 patients were strictly "oligometastatic" and had up to 5 lesions; about 13 (42%) of 31 patients had more than 5 metastatic sites.

All included patients had their metastatic spread controlled by systemic treatment except for adrenal gland metastasis. Stability or partial response of the primary and metastatic sites except the adrenal glands was confirmed by CT scan in 24 cases, PET in 3 cases, and both in 6 cases.

The average tumor volume was 33.5 cm^3 (standard deviation: 51.7 cm^3), and the largest diameter was 38.5 mm (standard deviation: 19.8 mm). The characteristics of cancer and metastatic tumors are summarized in **Table 2**.

None of the patients had a histologic confirmation of their adrenal gland metastasis before SBRT, which were diagnosed after repeated CT scans, which confirmed adrenal gland metastases enlargement according the larger diameter and volume measurements.

Treatment Planning

Among the 33 lesions, 28 (84.8%) were treated using a tracking system after CT-guided transdermal implantation of

TABLE 1 | Patients' characteristics.

Parameter ($n = 31$)	No.	%
Sex		
Male	20	64.5
Female	11	35.5
Age, median (range, yr) 63 (38–80)		
WHO* performance status		
0	16	51.6
1	14	45.2
2	1	3.2
Primary tumor site		
Lung	14	45.2
Melanoma	6	19.4
Kidney	3	9.7
Breast	3	9.7
Hepatocellular carcinoma	1	3.2
Stomach	1	3.2
Bladder	1	3.2
Esophagus	1	3.2
Merkel cell carcinoma	1	3.2
Total number of metastatic sites (including the adrenal gland)		
1	8	25.8
2	6	19.4
3	3	9.7
5	1	3.2
>5	13	41.9

WHO, World Health Organization.*

TABLE 2 | Cancer and metastases characteristics.

Parameter ($n = 31$)	No.	%
Laterality of adrenal gland metastasis		
Right	16	48.5
Left	17	51.5
Adrenal gland metastasis status		
Synchronous	5	15.2
Metachronous	28	84.8
Pain related before SBRT		
Yes	3	9.1
No	30	90.9
	Mean (SD)	**Median (range)**
Tumor volume (cm3)	33.5 (51.7)	13.1 (0.9–278.7)
Tumor largest diameter (mm)	38.5 (19.8)	33 (14–103)
Time from primary diagnosis to adrenal gland metastasis (months) (for metachronous metastases only)	34.5 (32)	16.35 (5–130.5)

SBRT, stereotactic body radiation therapy; SD, standard deviation.

gold fiducial. The side effects of fiducial implantation occurred in 3 (10.7%) patients: one had spontaneous hematoma resorption and two had pneumothorax, one of whom required a chest tube insertion.

Five (15.2%) lesions were treated with an ITV.

In 29 (87.9%) of 33 cases, CT planning and treatment were performed in the dorsal decubitus position. In patients treated according to an ITV, an abdominal compression using a belt was used to limit breathing movements.

Dosimetric Planning

All 31 patients underwent SBRT as ablative treatment, and the spread of all metastatic tumors was controlled by systemic treatment.

Of 33 lesions, 24 (72.7%) were irradiated using a dose of 45 Gy delivered in 3 fractions, on alternate days. In other cases, all SBRT treatment schedules and dosimetric characteristics are presented in **Table 3**.

The median biological effective dose (BED) was 112.5 Gy, assuming $\alpha/\beta = 10$, and ranged from 45 Gy for the 5 Gy $\times$ 6 fractions schedule to 115.5 Gy for the 11 Gy $\times$ 5 fractions schedule.

Among the 33 lesions, 27 (81.8%) were irradiated with BED >100 Gy.

The dose was prescribed to a median isodose of 83% (range: 62–90).

Clinical Outcome

Treatment outcomes are summarized in **Table 4**.

The median follow-up was 18 months (range: 1.4–89.5 months).

One- and two-year local control rates were 96.5% (95% confidence interval: 84.9–99.7) and 92.6% (95% confidence interval: 79.2–98.7), respectively (**Figure 1**). Competing events occurred in 22 patients. The first competing event was progression at distant site in 21 patients, and early death from a pulmonary embolism in one patient. No local relapse was observed after disease progression at distant sites.

The median overall survival was 33.5 months (**Figure 2**), with the lower bound of the confidence interval at 17 months. The upper bound was not defined by lack of events. The median PFS was 7.4 months (95% confidence interval: 3.8–14.1; **Figure 3**). Of 31 patients, 5 were free from any disease at the last follow-up.

Response to SBRT was evaluated in 31 (94%) of the 33 lesions; one patient died from a pulmonary embolism at day 44, and the other patient had a follow-up period of <3 months.

Abdominal CT was used to evaluate the clinical response of 24 patients (77.4%) and positron emission tomography in 7 patients (22.6%). A complete response was achieved in 10 (32.3%) lesions, a partial response in 10 (32.3%) lesions, and stability in 8 (25.8%) lesions.

At the date of analysis, a local relapse had been reported in three patients (at 8.8, 14, and 49.4 months). These patients were treated with a prescribed dose of 45 gray delivered in 3 fractions (BED = 112.5 Gy) using a real-time tracking system. Primary histologies of those three patients were non-small cell lung cancer in two of them, and hepatocellular carcinoma in the remaining. The median volume of the metastases were 22.3, 50.8, and 56.8 cm^3. The median volume of PTV receiving the prescribed dose was 87.5% (range: 71.3–98.2). The 3 local failures could be explained by the large volume of the lesions (>50 cm^3 in 2 cases), and the closeness of the organs at risk in all cases, which led to a degradation of PTV coverage.

In two cases, a partial response could be observed after a new SBRT treatment using the following schedules: 15 Gy $\times$ 3 fractions and 6 Gy $\times$ 6 fractions. In one case, the patient underwent an adrenalectomy.

TABLE 3 | Dosimetric characteristics.

Parameter	Mean	Median (range)
Total dose (Gy)	44.6	45 (30–55)
Fractions (n)	3.7	3 (3–9)
Dose per fraction (Gy)	13.2	15 (5-15)
BED* (Gy)	103.8	112.5 (45–115.5)
Isodose line (%)	82.4	83 (62–90)

BED, biological effective dose.*

TABLE 4 | Treatment outcomes and follow-up.

Parameter	No.	%
Clinical response (RECIST) on adrenal gland metastases ($n = 31$)		
Complete	10	32.3
Partial	10	32.3
Stable	8	25.8
Progression	3	9.6
Metastatic relapse ($n = 31$)		
Yes	23	74.2
No	8	25.8
Location of metastatic spread ($n = 23$)		
Nodal	9	39.1
Liver	7	30.4
Lung	6	26.1
Brain	5	21.7
Bone	5	21.7
Contralateral adrenal gland	4	17.4
Other	4	17.4
	Mean	**Median (range)**
Time from treatment to local relapse (months)	24.1	14 (8.8–49.4)
Time from treatment to metastatic relapse (months)	10.2	4.5 (0.6–86.2)

RECIST, Response Evaluation Criteria in Solid Tumors.

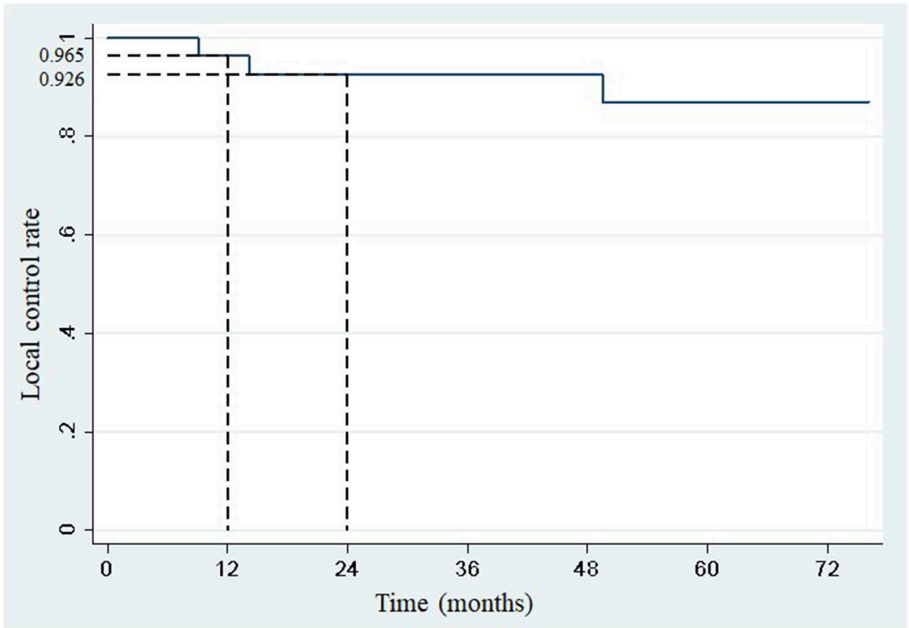

FIGURE 1 | One-year and 2-year local control rates after SBRT.

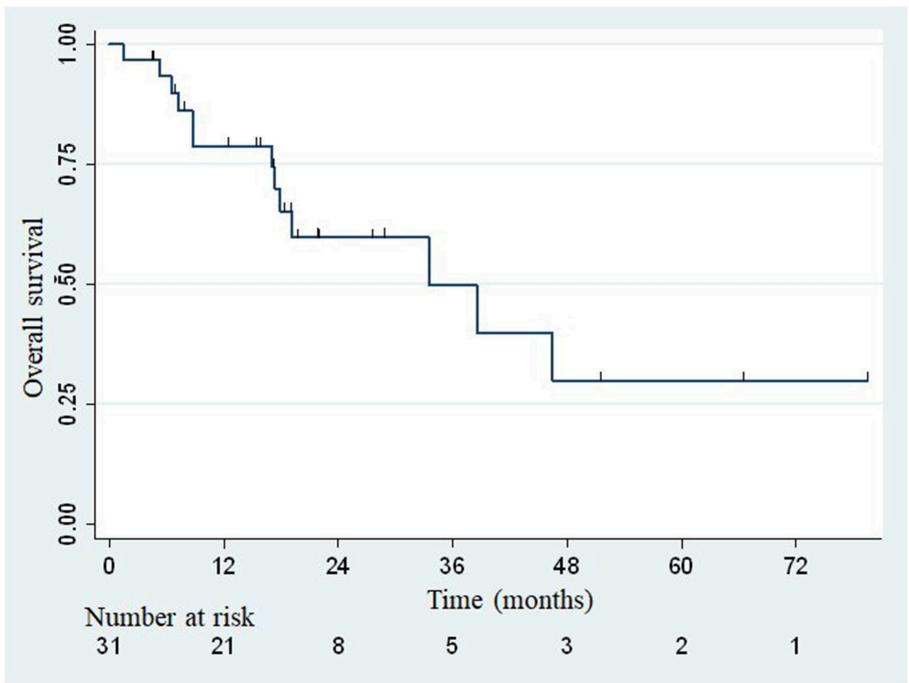

FIGURE 2 | Actuarial Kaplan-Meier overall survival for 31 patients treated with SBRT for adrenal metastases.

At the end of our study, 18 patients were still alive and 13 died of disease progression or intercurrent complication. No deaths related to treatment was reported. The 1- and 2-year OS rates were estimated at 78.8% (95% confidence interval: 58.6–89.9%) and 59.7% (95% confidence interval: 37.2–76.4%), respectively. A distant progression was described in 23 patients, after a median time of 4.5 months (range: 0.6–86.2). The sites of metastatic progression are shown in **Table 4**.

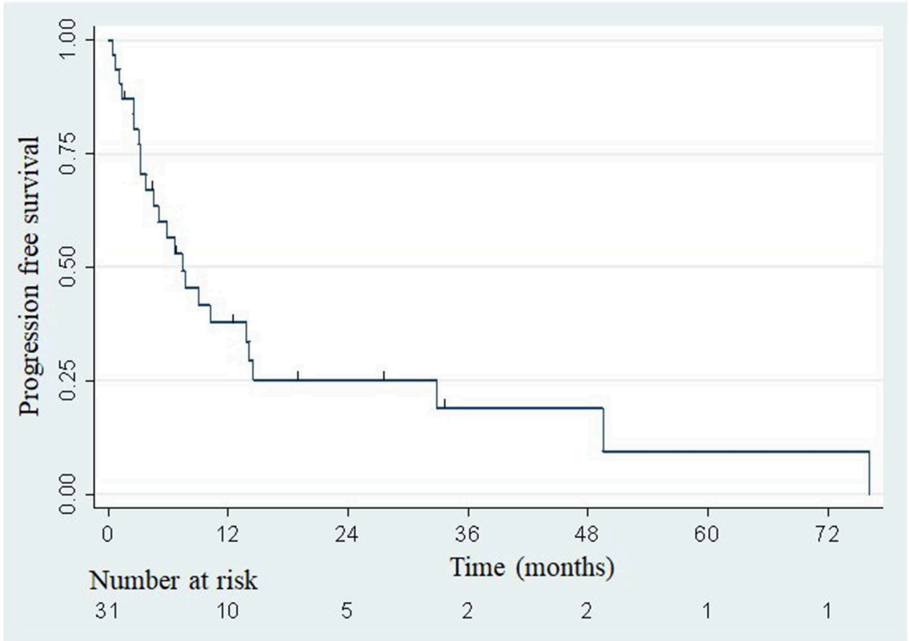

FIGURE 3 | Actuarial Kaplan-Meier progression-free survival for 31 patients treated with SBRT for adrenal metastases.

TABLE 5 | Treatment acute toxicity ($n = 33$).

	Grade 1 No. (%)	Grade 2 No. (%)	Total (%)
Toxicities related in 14 cases (42.4%)			
Asthenia	1 (3)	2 (6.1)	9.1
Abdominal pain	3 (9.1)	3 (9.1)	18.2
Nausea	5 (15.2)	4 (12.1)	27.3
Vomiting	3 (9.1)	2 (6.1)	15.2
Diarrhea	2 (6.1)	–	6.1

Toxicity

Adverse events associated with treatment are shown in **Table 5**.

Overall toxicity occurred in 14 (42.4%) of 33 patients. The most common acute side effects were grade 1/2 nausea ($n = 9$, 27.3%), abdominal pain ($n = 6$, 18.2%), vomiting ($n = 5$, 15.2%), and asthenia ($n = 3$, 9.1%). All of them occurred during the days following treatment and improved with symptomatic treatment.

None of the patients developed acute grade ≥3 or late toxicity.

DISCUSSION

In this study, we reported the outcome of a series of patients treated with SBRT for adrenal gland metastases. Despite a small number of patients and a wide variety of primary tumor histologies, local control could be achieved, with 1- and 2-year local control rates of 96.5 and 92.6%, respectively. No cases of grade 3 or greater toxicity was reported.

With the recent improvements in staging and treatment of most cancers, it is difficult to treat a patient based only on the histologic type or TNM classification. Consequently, the treatment decision relies on the multidisciplinary staff assigned to each patient and is based on the recent status of the primary lesion.

Regarding oligometastatic cancers, the first step to make an appropriate decision is to control the development of metastasis using the most adapted systemic treatment. Therefore, local treatment of the different metastases in various organs should be discussed. In this setting, Gomez et al. reported, in a multi-institutional phase II randomized study, that local consolidative therapy with radiotherapy or surgery improved outcome in 49 patients with oligometastatic non-small cell lung cancer that did not progress after front-line systemic therapy (17). With a median follow up of 38.8 months, the median PFS was 14.2 months in the patients who received local consolidative therapy on all metastatic sites and 4.4 months in the patients assigned to maintenance therapy or observation. A benefit on OS was also found in the local consolidative therapy group (41.2 vs. 17 months).

The results of the multicenter randomized phase II SABR-COMET trial also supported that SBRT delivered on oligometastatic sites from various primary histologies could improve survival (18). Indeed, patients who received SBRT on one to five metastatic sites could achieve a median OS of 41 months, compared to 26 months in patients who received standard of care treatment alone. Additionally, PFS was significantly higher for SBRT-treated patients (12 months) compared to the control group (6 months).

TABLE 6 | Comparative summary of the studies reporting on SBRT treatment of adrenal gland metastases.

Author	No. of patients	Median dose (range) (Gy)	No. of fractions	Median BED (range) $\alpha/\beta = 10$	Local control (%)	Overall survival (%)
Chawla et al. (19)	30	40 (16–50)	4 (4–10)	56 (22.4–75)	1 yr: 55% 2 yrs: 27%	1 yr: 44% 2 yrs: 25%
Holy et al. (20)	18	40 (20–40)	5 (3–12)	65.6 (22.5–72)	1 yr: 94.4% 2 yrs: 78.7%	Median: 21 mos
Torok et al. (21)	7	22 (10–36)	1 (1–3)	51.3	1 yr: 63%	Median: 8 mos
Oshiro et al. (22)	11	45 (30–60)	5 (1,–27)	85.5 (60–132)	6 mos: 94%	1 yr: 55.6% 2 yrs: 33.4%
Rudra et al. (23)	10	36 (24–50)	3 (3–10)	60 (43.2–79.2)	1 yr: 73% 2 yrs: 73%	1 yr: 90%
Casamassima et al. (24)	38	36 (21–54)	3	(60–137)	1 yr: 96% 2 Yrs: 90%	1 yr: 39.7% 2 yrs: 14.5 %
Guiou et al. (25)	9	25 (20–37.5)	5	47	1 yr: 44% 2 yrs: 44%	1 yr: 52% 2 yrs: 13%
Scorsetti et al. (26)	34	32 (20–45)	4 (4–18)	(30–56.3)	1 yr: 66% 2 yrs: 32%	2 yrs: 53%
Ahmed et al. (27)	9	(20–37.5)	5	(28–65.6)	1 yr: 44% 2 yrs: 44%	1 yr: 52% 2 yrs: 13%
Desai et al. (28)	14	54.5 (13–30)	3 (1–5)	42.5 (29–60)	1yr: 64%	1 yr: 87%
Franceze et al. (29)	46	40	4	80	1 yr: 65% 2 yrs: 40%	1 yr: 87%
Haidenberger et al. (30)	23	40.5 (20–45)	3 (1–3)	–	1 yr: 95% 2 yrs: 81%	1 yr: 77% 2 yrs: 72%
Present study (2019)	31	45 (30–55)	3 (3–9)	112.5 (45–115.5)	1 yr: 96.5% 2 yrs: 92.6%	1 yr: 78.8% 2 yrs: 59.7%

With regard to adrenal metastases, a multicenter French study revealed that the resection of a single adrenal metastasis from a treated lung cancer was associated with a 5-year overall survival of 59% among 46 patients (9).

Although SBRT is not only indicated in patients with a single adrenal metastasis like those reported in surgical case series, data on the results of SBRT are limited (**Table 6**).

Chawla et al. reported in 2008 a 1-year local control rate and OS rates of 55 and 44% in the first series of 30 patients (19). This low local control rate could be explained by the insufficient doses applied, since BED ($\alpha/\beta = 10$) ranged from 22.4 Gy (16 Gy in 4 fractions) to 75 Gy (50 Gy in 10 fractions).

In a retrospective study published in 2012, Casamassima et al. reported a series of 38 patients who underwent SBRT on 46 adrenal gland metastases from various origins. A higher BED was administered (range: 60–137 Gy) and was associated with a 1-year local control rate of 96%, weakened by a median follow-up of only 8.1 months and very heterogeneous schedules of SBRT (single-fraction and multi-fraction SBRT) (24).

More recently, Franzese et al. reported in 2016 the outcome of 46 patients, treated with a homogeneous schedule of 40 Gy delivered in 4 fractions (BED 10 = 80 Gy), with a median follow-up of 7.6 months (29). The 1- and 2-year local control rates were 65.5 and 40.7%, respectively. All of these studies confirmed the occurrence of mild toxicity after SBRT.

Considering these results, BED could influence the local control of adrenal gland metastases, regardless of the site of primary cancer.

To the best of our knowledge, this is the only study to use a consistent radiation dose and fractionation, since BED is >100 Gy in 81.8% of cases. This dose escalation is made possible with the use of a real-time tracking of the lesion realized after the implantation of fiducial markers, which minimized the irradiation of adjacent healthy tissues. Respiratory motion management should be recommended whenever possible.

With a median follow-up of 18 months, SBRT seems to be a safe and effective treatment for adrenal gland metastases in patients whose primary tumor and metastatic spread are controlled by systemic treatment.

With 1- and 2-year local control rates of 96.5 and 92.6%, respectively, SBRT may be considered as one of the first-line treatments in oligometastatic patients with adrenal metastases, but also as an alternative to surgery.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

This study complies with the reference methodology adopted by the French Data Protection Authority (CNIL) and patients

did not object to the use of their clinical data for the research purpose.

AUTHOR CONTRIBUTIONS

DP, FlT, EL, and XM designed the study and helped supervise the project. CS made substantial contribution to acquisition of data and wrote the paper. ER helped with the collection of dosimetric data. LL and JL performed the analysis and interpretation of the data. All authors discussed the results and commented on the final manuscript.

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REVIEW
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Frameless Image-Guided Radiosurgery for Multiple Brain Metastasis Using VMAT: A Review and an Institutional Experience

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We undertook a structured review of stereotactic radiosurgery (SRS) using linear particle accelerator (linac) equipment, focusing on volumetric modulated arc therapy (VMAT) technology, and frameless image-guided radiotherapy (IGRT), for the treatment of brain metastases. We analyzed the role of linac SRS and its clinical applications, exploring stereotactic localization. Historically, there was a shift from fixed frames to frameless approaches, moving toward less invasive treatments. Thus, we reviewed the concepts of VMAT for multiple-target applications, comparing its dosimetric and technical features to those of other available techniques. We evaluated relevant technical issues and discussed the planning parameters that have gained worldwide acceptance to date. Thus, we reviewed the current literature on the clinical aspects of SRS, especially its main indications and how the advantages of VMAT may achieve clinical benefits in such scenarios. Finally, we reported our institutional results on IGRT-VMAT for SRS treatments for patients with multiple brain metastases.

Keywords: radiosurgery, stereotactic, SRS, VMAT, brain metastases, linac, IGRT, frameless

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INTRODUCTION

Stereotactic radiosurgery (SRS) is a type of external conformal radiation therapy that uses special equipment to tridimensionally position the patient with higher precision than conventional methods, enabling the accurate delivery of single large doses of radiation to small tumors (1). This treatment uses a large number of coplanar or non-coplanar beams or multiple arcs that sequentially irradiate the target to produce a concentrated dose in the lesion while achieving steep dose gradients outside the treatment volume.

The mechanism of SRS differs from that of conventionally fractionated radiotherapy, since the high single doses promote ablation and necrosis of the irradiated target; thus, SRS requires small margins, special planning techniques, and equipment to achieve high conformity and avoid complications (1–3). It is used to treat brain tumors and other brain disorders that cannot be treated by regular surgery. Later, SRS was expanded to also include single-fraction treatments of spinal lesions and then to include fractionated high-dose treatments (4)—also referred to as stereotactic radiotherapy (SRT). SRS concepts and its technical refinements lead to the development of stereotactic body radiotherapy (SBRT), also referred to as stereotactic ablative radiotherapy (SABR), which is the delivery of such complex, accurate and high-dose treatments to extracranial targets (5).

Despite its broad and sometimes confusing definition (6), the term "SRS" is usually reserved for the treatment of intracranial lesions with a single fraction—as first described by the Swedish neurosurgeon Leksell (7) in 1951. In the current American College of Radiology—American Society for Radiation Oncology (ACR-ASTRO) Practice Parameter for the Performance of Stereotactic Radiosurgery, SRS is defined as follows: "For the purpose of this document, SRS is strictly defined as radiation therapy delivered via stereotactic guidance with ∼1 mm targeting accuracy to intracranial targets in 1–5 fractions" (4).

A more recent technology, called volumetric modulated arc therapy (VMAT) (8), has features of intensity-modulated radiotherapy (IMRT) as well as arc therapy and therefore produces dose distributions highly adapted to the target volume. This technology appears to be an option in the treatment of multiple brain lesions using a single isocenter (9, 10). The objective of this review is to discuss the specific scenario of treating multiple targets using SRS with VMAT.

LINAC-BASED SRS AND CLINICAL APPLICATION

Linear accelerator (linac)-based SRS may be delivered using either circular cones or micro-multileaf collimators (MLC) attached to the head of the linac to adjust the aperture through which the target volume is irradiated. The technique with circular cones is particularly useful for treating small and spherical lesions. This technique employs multiple non-coplanar arcs to form a spherical or ellipsoidal dose distribution. For large and irregular targets, it may be necessary to use multiple isocenters per lesion, increasing the dose inhomogeneity and treatment time.

Compared with cones, MLC-based SRS has been shown to produce better dose conformity and reduced treatment time when used to treat larger lesions (1). MLC consists of a computer-controlled array of leaves that can be moved individually to create an aperture, which is dynamically adapted to the target shape. In this modality, the treatment can be delivered as fixed beams or dynamic arcs, named three-dimensional conformal radiation therapy (3D-CRT) and dynamic conformal arc therapy (DCAT), respectively. The MLC also allows the use of intensity-modulated radiosurgery (IMRS), which is the delivery of radiosurgery dose to the patient through several static fields with non-uniform radiation fluency (11). This technique can produce complex dose distributions and is more advantageous for large and irregular tumors.

The major application of SRS is to treat brain metastases, whether in addition to whole-brain radiotherapy, in a post-operative scenario, or as the first treatment. SRS is already a well-established technique for patients with up to three lesions (12, 13), and are promising data for scenarios with more than three and up to ten lesions. The treatment of multiple brain metastases has been a challenging procedure because each one, traditionally, is treated individually. This means that each target needs to be planned to use one (or more) isocenter and several arcs with cones, conformal beams, or dynamic arcs with MLC or Gamma Knife™ (GK) (Elekta, Crawley, UK) shots—depending on the available technology (1, 14). Therefore, the time to accomplish such a procedure is dependent on the total number of targets. Considering that a reasonable time to treat one target is ∼20 min, the total time for multiple lesions can take hours to be done. Almost the same difficulties apply to the planning steps for this type of treatment, where each target's plan must be carefully built, calculated and tested. Nevertheless, there is an additional source of complexity: the planner must consider potential contributions of one lesion's plan to the others—and it becomes more difficult with the increase in the number of targets. **Figure 1** illustrates the complexity of an SRS plan treating 8 lesions with individual isocenters using static conformal beams compared to a single-isocenter VMAT plan. The resulting dose distributions for each plan are presented in **Figure 2**.

STEREOTACTIC LOCALIZATION—FROM FIXED FRAMES TO FRAMELESS APPROACHES

The core difference between SRS and conventional radiotherapy methods is the use of a stereotactic technique, in which the location of a target is related to a three-dimensional Cartesian coordinate system (7). Based on this concept, any intracranial location can be identified in relation to the frame, which was traditionally fixed to the patient's head using sharp pins against the skull. These minimally invasive frames play a role in

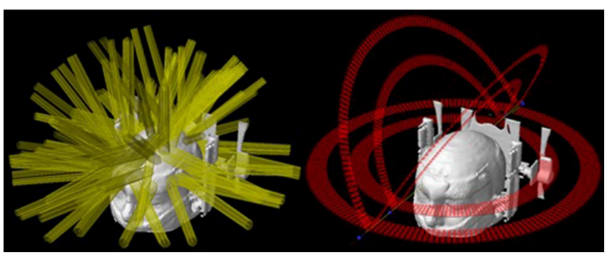

FIGURE 1 | Field arrangements for two treatment techniques. **(Left)** 3D-CRT with 8 isocenters and 62 beams. **(Right)** VMAT with 1 isocenter and 6 arcs.

Abbreviations: AAA, anisotropic analytical algorithm; AAPM, American Association of Physicists in Medicine; ACR-ASTRO, American College of Radiology, American Society for Radiation Oncology; CBCT, cone-beam computed tomography; CI, conformity index; DCAT, dynamic conformal arc therapy; DTF, distance to fall-off; EORTC, European Organization for Research and Treatment of Cancer; FSRT, fractionated stereotactic radiotherapy; GK, Gamma Knife; GS, grid size; GTV, gross tumor volume; Gy, Gray; HD-MLC, high-definition multileaf collimator; IGRT, image-guided radiation therapy; IMRS, intensity-modulated radiosurgery; IMRT, intensity-modulated radiotherapy; JROSG, Japanese Radiation Oncology Study Group; Linac, linear accelerator; Min, minute; MLC, multileaf collimators; MU, monitor unit; MV, megavoltage; OBI, on-board imager; PTV, planning target volume; RTOG, Radiation Oncology Group; SABR, stereotactic ablative body radiotherapy; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; VMAT, volumetric modulated arc therapy; VRS, volumetric radiosurgery; WBRT, whole-brain radiotherapy; 3D-CRT, three-dimensional conformal radiation therapy; 6-DOF, 6-degree of freedom.

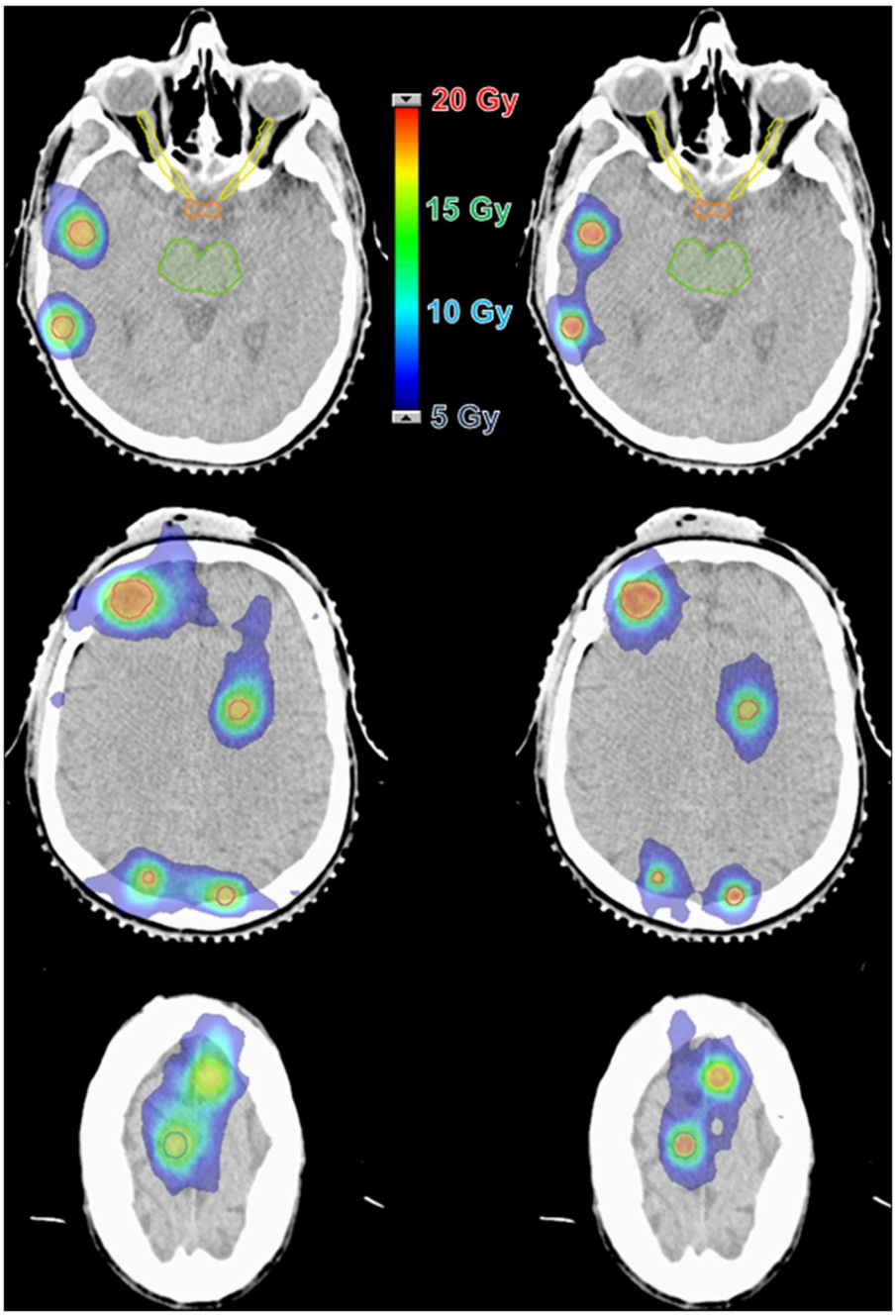

FIGURE 2 | Dose distribution comparison between two techniques for a case with 8 lesions and a prescription dose of 16 Gy. **(Left)** 3D-CRT with 8 isocenters and 62 beams. **(Right)** VMAT with 1 isocenter and 6 arcs.

both positioning and immobilizing patients and are considered effective, with reported accuracy better than 1 mm (2, 15, 16). However, such frames have many drawbacks, including patient anxiety, pain associated with frame fixation, and risk of bleeding and infection at the site of placement (17). If the frame is not properly placed, there is also a risk of movement or slippage (16). Finally, the entire process from simulation to treatment delivery needs to be concluded in a short time (∼8 h), since the patient must remain with the frame the entire time. This factor applies stress and pressure to the clinical team, who must complete the tasks as quickly as possible. Thus, depending on the number of lesions, the treatment may become unfeasible.

Advances in image-guided systems allow the development of frameless approaches (15, 16, 18, 19). These make use of non-invasive relocatable immobilizers (examples include precision thermoplastic masks, upper-jaw fixation molds, ear-canal-based

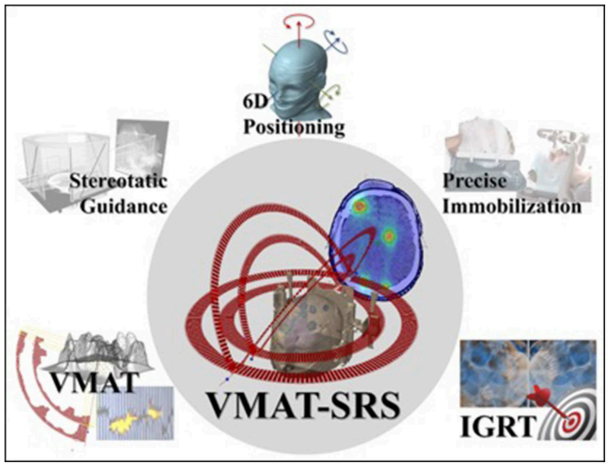

FIGURE 3 | VMAT for multiple-metastasis SRS and the technological tools for its successful clinical deployment.

positioners, and biteplates) combined with image-guided tumor localization techniques and intrafraction monitoring. The reported spatial accuracy (immobilization and positioning) for such methods are comparable to those achieved with traditional invasive alternatives (17, 20, 21). Although there is no randomized trial comparing those methods, the clinical outcomes are promising, showing an increased level of patient comfort (22–26). Logistically, the use of frameless approaches brings much more flexibility to the planning process, allowing more time to the whole team and even enabling the use of more complex delivery techniques such as VMAT (8).

VMAT FOR SRS OF MULTIPLE TARGETS

VMAT is a relatively new technique that allows the delivery of complex dose distributions to a volume in an efficient fashion in one or multiple modulated arcs. The RapidArc (Varian Medical Systems, Palo Alto, CA, USA) is an example of a commercial implementation of the VMAT, based on the work of Otto (8). The RapidArc technique produces highly conformal dose distributions by varying dynamically and simultaneously the dose rate, gantry rotation speed, MLC aperture shape during (up to) 360° arcs.

The feasibility of using VMAT as a delivery option for SRS on multiple metastases using a single isocenter has been demonstrated by Clark et al. (9). This means that the total treatment time becomes independent of the number of targets. The clinical application of this technique can drastically reduce the total treatment time, offering not only efficiency but also a major improvement in patient comfort. Nevertheless, the safe use of the VMAT technique for producing such complex volumetric dose distributions requires extensive dosimetric validation (27).

Additionally, targeting multiple lesions simultaneously has an increased risk of geometrical miss (28, 29). Patient localization errors usually involve both translational and rotational deviations. For single—and usually spherical—lesions placed at the isocenter, small rotational deviations do not play a significant role in treatment delivery accuracy. However, the farther a particular target is from the isocenter, the more displaced it will be from its planned position due to a given rotational deviation. In order to irradiate multiple targets correctly, it is highly desirable to account for both translational and rotational positioning errors. Thus, the successful use of VMAT for multiple brain metastases depends on combining different technologies (**Figure 3**).

Regarding the quality of the dose distribution in terms of conformity and healthy tissue sparing, although the non-coplanar planning shape is the most commonly used geometry, early comparisons between coplanar VMAT vs. GK for SRS on multiple metastases conducted by Ma et al. (30) found that the volumes of normal brain receiving 4 and 12 Gy were higher for the coplanar VMAT. However, it is clear that any coplanar beam geometry is much more limited than non-coplanar in terms of producing compact dose distributions, especially for lower doses due to the more limited number of beam paths. Later, Thomas et al. (10), using an arguably more refined non-coplanar VMAT planning technique, achieved equivalent dose distributions to those obtained by (GK). Thus, the differences do not seem to be clinically significant, and the dosimetric differences are still matter of debate (30–34).

DOSIMETRIC AND TECHNICAL CHARACTERISTICS

Is VMAT the Best Choice?

Stereotactic 3D-CRT, DCAT, IMRT, and GK techniques have been used in treating brain lesions for years. However, when treating multiple lesions, these techniques become too time consuming. Single-isocenter VMAT for multiple metastases seems to be equivalent to those techniques in plan quality while requiring less time.

Huang et al. (35) studied 17 patients with 2–5 brain lesions. For patients treated with DCAT/3D-CRT, VMAT plans were retrospectively created, and vice versa. The conformity index (CI) and coverage quality were superior or equivalent for VMAT plans. The mean number of monitor units (MU) decreased by 42%, and the treatment time was reduced by 49%. However, the volume receiving 5 Gy 46% was larger for VMAT. Considering the treatment time, target coverage quality and dose conformity, single-isocenter VMAT seems to be advantageous in multiple brain metastases.

Audet et al. (36) studied 12 patients with cranial tumors with planning target volumes (PTVs) ranging from 0.1 to 29 cm^3 and 2 multiple metastases. The plans were performed with RapidArc™ (1–6 non-coplanar arcs), DCAT (∼4 arcs), and IMRT (9 static fields). The mean CI for all plans was best for 4 non-coplanar arc VMAT (0.86). The volumes of healthy brain receiving at least 50% of dose prescription were the lowest for the same arc configuration of VMAT and for DCAT. The authors conclude that for lesions similar to those cited in this work and having a diameter larger than 7 mm, VMAT with multiple non-coplanar

arcs provides accurate and high-quality radiosurgery with low doses to healthy brain tissue and high dose conformity to the target, as well as the aforementioned time optimization.

Roa et al. (37) studied 16 patients treated with SRS or SBRT through IMRT and VMAT plans with 1 and 2 arcs. Dosimetric conformity, organs at risk (OAR) sparing and homogeneity were similar among the three techniques. The mean beam-on time was reduced by 73%, and MU was reduced by 43%. Since large treatment delivery time increases the probability of intrafractional errors, RapidArc™ seems to be useful in the delivery of SRS.

When comparing the plan quality of VMAT and GK plans, one can infer that both yield somewhat similar results. For example, Liu et al. (34) investigated 6 patients with 3 and 4 brain metastases (volume range 1.70–11.14 cm^3) based on plans with 4 to 6 non-coplanar partial arcs. For RapidArc™, the CI value was smaller than for GK (1.19 ± 0.14 vs. 1.50 ± 0.16, $p < 0.001$), and the gradient index (GI) was significantly higher (4.77 ± 1.38 vs. 3.65 ± 0.98, $p < 0.01$). The constraint V_{12Gy} for healthy brain was similar ($p = 0.58$), as were doses such as V_{6Gy}, $V_{4.5\,Gy,}$ and V_{3Gy}. GK had better results in doses <3 Gy (spread doses). In addition, GK treatment time is 3–5 times longer than VMAT. Furthermore, Thomas et al. (10) conducted 28 treatments of multiple metastases that received a prescription dose of 18 Gy. For the evaluation, 4 non-coplanar arcs was set as the optimal VMAT geometry. Thus, compared with GK, VMAT improved the median CI (1.14 vs. 1.65, $p < 0.01$), and no statistically significant difference was found in median dose fall-off ($p = 0.269$), V_{12Gy} ($p = 0.500$) and low isodose spill ($p = 0.490$).

Therefore, because of relatively low time requirements and similar dosimetric results to the aforementioned techniques, image-guided SRS-VMAT plans seem to be a powerful tool for treating multiple brain metastases with a single isocenter.

Coplanar vs. Non-coplanar

Once all these techniques were established to be accurate in delivering doses in SRS, linacs performing VMAT plans were revealed to be equivalent. Studies have been conducted to assess the benefits of using coplanar and non-coplanar arcs. Thomas et al. (10) started their article based on the assumption that single-isocenter SRS-VMAT plans are comparable to GK (multi-isocenter technique) considering only 4 non-coplanar arcs, which showed plan quality superior to 1 coplanar arc and 2-non-coplanar-arc plans. Moreover, Clark et al. (9) evaluated the feasibility of single-arc/single-isocenter, triple-arc (non-coplanar)/single-isocenter and triple-arc (coplanar)/triple-isocenter geometries for simulated patients with three near brain metastases. Multiple non-coplanar arcs presented slight improvements in dose conformation to the PTV compared with the other arc geometries.

Lau et al. (26) evaluated 15 patients undergoing SRS-VMAT for multiple targets using a single isocenter. A quantity of 1–4 arcs was used (coplanar except for 4 patients). The median total target volume was 8.3 cm^3 (range 1.9–93.7 cm^3), and the median number of tumors was 3 (range 2–13). As a result, the median Radiation Therapy Oncology Group conformity index (RTOG-CI) was 1.15 (range 0.29–2.04), and the median V_{12Gy} was 38 cm^3 (range 8–432 cm^3).

Our institution experience (38) is entirely based on multiple and non-coplanar arcs (plans are created at 3–4 couch angles of ∼0°, 60°, and 300°). One can see that the median degree of conformity is similar to those reported by the previously mentioned studies: 1.20 (range 0.69–3.14). However, the median V_{12Gy} is better (21.40 cm^3–ranging from 2.12 to 87.60 cm^3), considering that our sample also has a similar median total PTV volume (PTV volume summation per patient) of 12.06 cm^3 (range 0.89–65.05 cm^3) and that the median number of lesions is 3 (range 2–19).

The bottom line is that non-coplanar single-isocenter arc plans for the treatment of multiple brain lesions seem to be more advantageous (in terms of conformity and sparing of healthy brain tissue) than coplanar arcs.

Number of Arcs

The hypothesis of treating multiple lesions (single isocenter) with more than one arc may be rational. There is evidence that planning with triple-arc geometry shrinks the volume receiving 12 Gy in healthy brain compared with just one arc (9). Even with the dependence on total PTV volume and lesion number, this constraint ($V_{12Gy} < 10\ cm^3$) was not infringed, in majority, when compared to GK plans [$p = 0.51$; studies performed by Thomas et al. (10)]. Furthermore, a comparison between 2 coplanar arcs and 3 arcs (which the 3rd partial arc is located vertically) was performed by Wang et al. (39) and it was demonstrated that although the 3-arc plan showed better conformity, it resulted in slightly higher doses of healthy brain, brainstem and chiasm. Perhaps this degradation can be overcome by adding more arcs than just one-half arc, once it was already cited that good results were achieved by other authors. Yuan et al. (40) consider in their work that non-coplanar multiple-arc geometry is superior to coplanar. In this way, 2- and 4-arc geometries were compared, as shown in **Table 1**.

For doses up to 2.8 Gy, 4-arc geometry supports the assumption that more normal brain volume was irradiated with doses up to this level than 2 arcs. However, less healthy brain volume received more than 2.8 Gy with 4-arc than 2-arc geometry.

Audet et al. (36), on the study of non-coplanar arcs for cranial radiosurgery evaluated up to six non-coplanar arcs. The Paddick conformity index (Paddick-CI) (41) for 4 non-coplanar arcs (the best geometry) was 0.86. Also, the volume of healthy brain receiving 50% of the dose prescription was 1.9 times lower than using a single non-coplanar arc geometry. One can summarize that the mentioned arc geometry must be employed to obtain such high-quality SRS-VMAT plans for treating multiple lesions with one isocenter.

Based on our institutional experience (38), SRS-VMAT plans (single isocenter) for multiple targets are performed up to 6 arcs and from 3 to 4 couch angles: 1–2 full arcs at 0°, 4 partial arcs at couch angles around 60° and 300°. For dose prescriptions of 17, 18, and 20 Gy, our (RTOG-CI) and V_{12Gy}, as mentioned before, are comprised inside the interval of values reported by

TABLE 1 | Arc geometry set by Yuan et al. (40) for SRS-VMAT (single-isocenter) plans on treatment of multiple brain metastases.

Arc	Plan	Gantry start angle (°)	Gantry stop angle (°)	Gantry rotation direction	Table angle (°)
1	2-arc, 4-arc	181	179	Clockwise	0
2	2-arc, 4-arc	181	10	Clockwise	90
3	4-arc	10	181	Counterclockwise	45
4	4-arc	179	350	Counterclockwise	315

the literature, considering the number of tumors, and total target volume. In addition, the mean door-door treatment time was 42 min (ranging from 21 to 62 min), with no correlation with the number of tumors ($R^2 = 0.038$), but it seems to be correlated with the number of arcs ($R^2 = 0.959$). It is easy to infer that the more arcs in the plan, the more time is expended during treatment. However, although there is time dependence with the number of arcs, the time expended by SRS-VMAT plans is smaller than the other techniques aforementioned.

Single or Multiple Isocenters

VMAT planning of multiple targets with a single isocenter has been taking a relevant role in medical physics due its practicability and plan quality (9, 37, 39). One of the comparisons performed by Clark et al. (9) based upon triple arc (non-coplanar)/single isocenter and triple arc (coplanar)/triple isocenter. The V_{12Gy} remained the same for both, but for a single isocenter, small improvements in the CI were observed (this difference might be due to the non-coplanar or single-isocenter geometry as well). All in all, single-isocenter geometry was revealed to be only 50% as time consuming as multiple-isocenter geometry.

Clark et al. (42) studied the plan quality for 1 to 5 lesions based on a single-isocenter VMAT plan. For more than 1 lesion, they recommended 2–4 non-coplanar arcs. The RTOG-CI was (1.12 ± 0.13), and the GI was (3.34 ± 0.42). In addition, Huang et al. (35) enrolled 17 patients with 2–5 brain lesions to evaluate the benefits of this type of geometry for VMAT plans. Among the techniques that use more than one isocenter as DCAT and 3D-CRT, VMAT plans were equivalent to or better than the other two in CI—the authors mentioned that the quality of coverage by VMAT plans was superior and the total treatment time was reduced by 49%.

VMAT Treatment Planning

Clark et al. (9) used a multiple-arc geometry, limiting the sum of the arc spans up to 1,000°. The Varian High Definition 120 MLC (leaves of 2.5 mm in the centermost 8 cm and 5 mm in the periphery portion of the field) the 6-MV SRS photon beam and a maximum dose rate of 1,000 MU/min were used. The optimization objectives were set to obey the input of $D_{GTV}100 = 20$ Gy (PTV = GTV [gross tumor volume]) and $D_{Normal\ Brain}$ 1% = 10Gy (normal brain excludes the GTV). All in all, the isodose volume that accomplishes 100% of GTV was normalized to 100% dose. The triple arc rotations for single-isocenter geometry were set at couch angles of 0°, 30°, and 330° to produce non-coplanar arcs of (179°-181°), (179°-350°), and (181°-10°), respectively.

Clark et al. (42) published another paper related to SRS-VMAT frameless treatment performed by a 10 MV flattening filter-free (FFF) photon beam at a dose rate of 2,400 MU/min. The paper recommended summing all PTVs into one "PTV_total." In addition, rings must be created beyond the PTV with the following inner and outer surfaces: 1° ring, 0 mm to 5 mm; 2° ring, 5–10 mm; 3° ring, 10–30 mm. These regions receive 98, 50, and 40% of the prescribed intensity, respectively (each individual target was set to receive 102% of the prescribed intensity in 100% of each target volume). Yuan et al. (40) also conducted some studies based on these planning methodologies as well. However, it was not evident what grid size (GS) was set for the dose calculation.

Karen et al. (43) studied the effect of the GS to evaluate the accuracy of VMAT spine Stereotactic Body Radiation Therapy (SBRT). Although this study was performed over SBRT treatments, the outcomes related to dose-fall-off can be linked to SRS treatments, once both have the conjecture of producing a high dose gradient beyond the targets. GS of 1, 1.5, and 2.5 mm was investigated and evaluated based on distance to fall-off (DTF) between 90 and 50% isodose line, D10% and D0.03 cm^3 on spinal cord adjacent to target. Based on 1 mm GS, the DTF increased for 1.5 and 2.5 mm (e.g., 2.52 ± 0.54 mm; 2.83 ± 0.58 mm; 3.30 ± 0.64 mm, $p < 0.001$, respectively); The D10% and D0.03 cm^3: 6.24 and 7.81% (for 1.5 mm) and 9.80 and 13% (for 2.5 mm). Therefore, plans calculated with a GS of 1 mm have to be employed in situations where reaching a high dose gradient is aimed.

Based on the assumption of GS, one can discuss the study carried by Hossain et al. (44) who conducted a work with 1 patient possessing 12 lesions to compare the results between SRS-VMAT and GK plans. They concluded that for all VMAT results, the low isodose level volumes of 8- and 4-Gy were averaged (275 ± 132) % higher when compared to GK values. For 12-Gy and 16-Gy, the isodose volumes were approximately (179 ± 91) % and (129 ± 40) % higher than GK, respectively. Once the dose prescription for all targets was 20 Gy, 80, 60, 40, and 20% of the prescribed dose was evaluated. In that way, some uncertainties may add into this and the work conducted by Yuan et al. (40), once they used 2.5 mm of GS in the calculation process. However, Yuan et al. (40) did not compare VMAT with any other technique; only comparison among VMAT arc geometries was performed. Thus, the possible systematic errors associated with the calculus were present for all of them.

Our department's planning routine (38) consists, first of all, of creating a PTV margin of 2 mm from GTV to consider geometrical uncertainties due to the entire treatment process. A volume called "Healthy Brain" was created by subtracting GTV and, around each PTV, two spherical shells were created (the first starts at the PTV borders with 0.5 cm thickness and the second starts at 0.5 cm from PTV border with 2 cm thickness) to achieve steep dose fall-off at the vicinity of PTV. VMAT plans were created to run in a linear accelerator equipped with a high-definition MLC (HD-MLC) with 120 leaves—the innermost 8 cm with 2.5 mm width leaves and the other outermost leaves with 5 mm width, completing 22 cm longitudinal field size (Varian, Palo Alto, USA). The optimization was performed aiming at least 99% coverage of all PTVs with the prescribed dose. The maximum dose inside each PTV was controlled to remain encircled within the GTV. The final calculation was performed with Eclipse Anisotropic Analytical Algorithm (AAA) versions 10–15 with 1 mm of calculation GS.

Impact of Target Distance From the Isocenter

A common question might arise about how the target distance from the isocenter can negatively affect the plan quality. As mentioned by Clark et al. (42), when utilizing frameless SRS-VMAT plans with a single isocenter designed for the treatment of multiple metastases, care must be taken to guarantee accurate patient positioning. Small rotations can result in a major impact on dose coverage, especially for small lesions.

To address rotation errors impacts over dose delivery accuracy, a 6-degree of freedom (6-DOF) couch and image registration is recommended. Kim et al. (28) evaluated the positional variations of five off-axial metallic ball bearing markers for a single-isocenter SRS-DCAT (once, for this purpose, DCAT carries simple geometric interpretation and can generate the same geometric accuracy results as SRS-VMAT plans). The phantom was immobilized by a frameless thermoplastic mask, and an MLC margin of 3 mm was introduced outward PTV. The ExacTrack^{TM} 6D (BrainLab, Feldkirchen, Germany) patient positioning system was used, and a total positional error for the MLC aperture of 0.61 ± 0.2 mm was found along the rotational path of the arcs employed in this study. In addition, Adamson et al. (45) evaluated the challenges of implementing a single-isocenter SRS-VMAT plan for treating multifocal intracranial disease. They used a thermoplastic mask for immobilization and a VMAT technique with HD-MLC (2.5 mm with innermost leaves). Using 6-DOF positional correction, they concluded that a 1 mm margin was necessary to compensate for spatial uncertainty within the mask. In general, it is a good choice to perform frameless SRS-VMAT plans with 6-DOF couch corrections, considering the respective margins.

Tryggestad et al. (29) evaluated frameless positioning data of patients with brain tumors based on cone-beam computed tomography (CBCT) pre- and post-treatment scans. A set of four immobilization masks was studied to obtain the systematic inter- and intrafraction, as well as the random intrafraction for translation and rotation shifts. By focusing on setup and positioning rotational errors and the selection of a suitable mask, one can observe a systematic interfraction error with a mean (SD) of 0.00° (0.90°), −0.34° (0.80°), and 0.39° (0.90°), for medial-lateral (ML); cranial-caudal (CC); and anterior-posterior (AP) displacements, respectively. Random interfraction errors were 0.6, 0.8, and 0.7, respectively. The random intrafraction positioning error was approximately −0.06° (0.40°), −0.17° (0.5°), and −0.06° (0.60°), respectively. Therefore, once it was possible to handle systematic errors by the On-Board Imager (OBI) (Varian, Palo Alto, USA) such as CBCT or another equivalent, a PTV margin of 0.7 mm could be achieved based on the best thermoplastic mask they studied.

In this context, Clark et al. (46) conducted a work that evaluated the dosimetric effects when PTVs are shifted in 1°, 2°, and 3° each for roll, pitch and yaw, relative to isocenter and maintaining dose distribution constant. The targets had a mean volume of 2.1 cm^3 (range 0.1–18 cm^3) and a mean distance from the isocenter of 4.2 cm (range 1.0–7.1 cm). It was evident that rotations $\geq 2°$ reduced coverage below 95% of PTV volume receiving 95% of prescription. In conclusion, minimizing rotation error below 1° is vital for aimed coverage (especially for small lesions).

In addition, Roper et al. (47) determined the dosimetric effects of rotational errors on coverage as well. Considering ideal values of D95 $\geq$ 100% and V95 = 100%, they found that at 0.5° rotational error, D95 values and V95 coverage rates were larger than or equal to 95% in all 50 cases. For 1.0°, 7% of targets showed D95 and V95 below 95%. Finally, for 2° rotational error, 47% of the targets lied below 95% for D95 and V95 (consider the mean $\pm$ SD in PTV and distance from isocenter of 0.96 ± 1.25 cm^3 and 3.53 ± 1.61 cm).

Additionally, treating multiple lesions that are too far away (roughly > 10 cm apart) using a common isocenter brings other planning difficulties related to MLC mechanical limitations that need to be considered, such as MLC maximum field size, leaf span and, in the case of Varian Millennium HD-MLC, the use of outermost thicker 5 mm leaves. There are situations that may require planning maneuvers, such as increasing the number of arcs or even splitting the plan on more than one isocenter.

In summary, margins of PTV must be taken, and an appropriate image-guided radiotherapy (IGRT) program must be employed in all institutions that aim to treat multiple lesions distant from the isocenter in a single-isocenter VMAT technique.

CLINICAL ASPECTS

SRS Indication for Multiple Brain Metastases

Several Phase III studies (48–50) and meta-analyses support SRS and/or surgical resection as initial treatment for patients with few brain metastases compared to whole-brain radiotherapy (WBRT). The main benefits include non-inferiority in median survival, local control, and a decrease in the likelihood of having cognitive decline.

These findings can be exemplified by some trials, such as the individual patient data meta-analysis well-conducted by Sahgal

et al. (51), where they analyzed 3 pivotal Phase 3 trials [Aoyama [JROSG] (13), Kocher et al. (49) [EORTC 22952- 26001] and Chang et al. (52)], among others, involving patients with one to four brain metastases. They could correlate the age (50 years as cut-off) and the number of lesions (one as cut-off) as effect-modifiers for treatment. They also showed that the risk of mortality [HR: 0.72 (0.57–0.90)] and distant brain failure [HR: 0.63 (0.46–0.88)] were significantly higher in patients with 2 or more lesions. For patients ≤50 years and carrying one lesion, the overall survival was significantly better in the SRS group.

Notwithstanding, there are Phase III trials hypothesizing that SRS alone might be appropriate for patients with more than 4 lesions. In this context, upfront SRS or even SRS as salvage therapy after initial treatment (surgery or SRS) may be adequate for those patients (50, 53). The outcomes will be the maintenance of overall survival while avoiding the neurocognitive impairment caused by WBRT. Nonetheless, one may argue that WBRT also eradicates microscopic disease, which is not possible with SRS alone, and may be more cost effective than SRS (54)—the patients may not need further surgery or SRS, and they will not need to undergo control resonances quite as often. Furthermore, once multiple lesion treatment with SRS is performed, the difficulty of re-irradiating recurrent lesions increases because of the cumulative dose.

In a prospective observational non-inferiority trial conducted by Yamamoto et al. (55), Gamma Knife was applied to patients with up to ten brain tumors. They have observed that SRS with five to ten lesions compared with patients carrying one to four brain metastases were equivalent. The median overall survival were 10.8 months ($p = 0.78$; $p_{non-inferiority} < 0.0001$) and same percentage of treatment-related adverse event (9%, $p = 0.89$). Secondary outcomes like neurological death, local recurrence, repeat SRS for new tumors also maintained equivalent (56).

There might be some reasons for why patients with multiple tumors are unsuitable for SRS treatments beyond clinical features, such as neurocognitive decline. One of them is indeed the treatment time (10). Considering the time spent for each isocenter being 20–30 min, many patients are not supposed to be able to remain still for more than 30 min on the linac couch. Consequently, there must be necessary bringing the patient to radiotherapy facility more than one time to treat several isocenters. Thus, the possibility of treating more rapidly these patients might also improve the radiotherapy facility's workflow (57). The treatment time itself has never been studied as a surrogate for patient adherence, or treatment tolerance, even if in practical terms this situation is common.

There are some studies exploring the role of VMAT on the possibility of incorporating WBRT with protection of sensitive structures, such as hippocampi (58) and cochleae, and concomitantly treat grossly evident lesions with a SRS boost (59).

Since the development of VMAT technology, it has increasingly become one of treatments of choice in the event of brain metastasis, mainly due to its inherent advantages, such as the ability to treat multiple lesions concomitantly in a reduced timespan while maintaining the dosimetric characteristics of SRS. Today, it is possible to classify VRS (volumetric SRS) as such a treatment, according to the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. These groups defined SRS as "high-precision treatment sessions of 5 fractions" (60).

Clinical and Practical Results

Thus, far the majority of studies on VMAT have primarily discussed dosimetric issues. On the other hand, clinical trials involving the treatment of multiple metastases rarely mention the techniques that are used. Thus, it becomes worth reviewing the literature in hopes to connect these two sides.

The maximum number of metastases that can be treated with SRS is not well-established. Yamamoto et al. (53, 55) analyzed 80 patients with 10 or more metastases, totaling 1,710 lesions (median lesion number: 17 and median cumulative volume: 8.02 cm^3). Despite the use of single-fraction radiotherapy, the doses were ∼2.60–6.69 Gy in areas far from the targets, and only a small volume of normal brain tissue received high doses. In SRS for multiple lesions, the major drawback is based upon the increase in radiation doses to healthy brain because of the overlap in planning for each target. Therefore, in VMAT, it is possible to optimize all dose distributions in a single plan.

Using the rational benefit of WBRT plus SRS, Lee et al. (61) investigated the clinical application of VMAT for four or more brain metastases in association with WBRT, sequentially (15–30 Gy in 4–10 fractions) or simultaneously (48–50 Gy in 10–20 fractions). This retrospective study demonstrated 12-month overall survival of 41.7%, a median survival time of 9 months, and 12-month local progression-free survival of 62.5%. Although the analysis of late toxicity and marked worsening in cognition was not reported in detail by the authors, the fact that there was no serious neurocognitive deterioration makes it possible to infer that this treatment does not deliver severely damaging doses to healthy brain tissue.

In a similar Canadian study, Nichol et al. (62) analyzed 60 patients with one to ten brain metastases who underwent fractionated treatments (50 Gy in 5 fractions at 95% isodoses, delivered to gross lesions, concomitant to WBRT−20 Gy in 5 fractions). The investigators also used IGRT approaches. At a median follow-up time of 30.5 months, the median survival was 10.1 months, the rates of total and partial brain response were 56%, and the prevalence of local control was 88%. The rate of radionecrosis grades 3–5 was 25% for deeply located tumors and 1.9% for non-deep metastases.

From the point of view of clinical outcomes, there is no level I evidence supporting the use of SRS with VMAT compared to other techniques. The most robust related information is the multivariate analysis from the study of Andrews et al. (12), which compared clinical outcomes between Gamma Knife and linacs in the setting of SRS plus or minus WBRT for brain metastases, showing that there were no differences.

In a study by Lau et al. (26) at the University of San Diego, single-isocenter frameless VMAT was performed in 15 patients, with a median dose of 20 Gy in a median of 3 brain metastases. The median follow-up time was 7.1 months. At 1 year, local and regional control were achieved in 81.5 and 60% of cases, respectively, and the overall survival was 39%; there was no treatment-related toxicity of grade 3 of higher. The investigators

also reported a mean dose to normal brain of 4.2 Gy, median V_{12Gy} of 38.0 cm^3, and median $V_{4.5Gy}$ of normal brain of 350.5 cm^3. No discernible relationship between the dose to normal brain tissue and the degree of toxicity was observed.

Another study addressing the role of VMAT for multiple lesions was conducted by Fiorentino et al. (63), where they analyzed early clinical results in 45 patients treated with linac-based SRS/fractionated stereotactic radiotherapy (FSRT) FFF delivery using VMAT. The prescribed dose ranged from 15 Gy single-shot treatment to hypofractionated treatments (5 fractions). The authors included patients with up to 5 brain metastases and carrying good performance status. The mean "beam-on" time ranged from 90 to 290 s for each lesion. Their median follow-up was 12 months, where the local control achieved 93.2%, and the median overall survival reached 77%. In addition, they could not observe severe adverse events.

At our institution (64), we started using VMAT for multiple brain tumor treatments in 2012, after some specific training of our staff. Through this time, we evaluated 32 patients with a mean age of 61 years and 4 lesions per treatment (1–19), accounting for 141 lesions undergoing SRS with VMAT, of whom 28 lesions were treated with single-shot radiosurgery. We started expanding 2 mm the lesions toward PTV margins for any uncertainties, even though our quality controls would guarantee intrafraction errors of <1 mm. Only 5 cases presented with single lesions. The mean tumor volume per patient was 15.9 cm^3 (ranging from 0.89 to 74.70 cm^3). The medium follow-up time was 5.6 months. There were 12 brain recurrences (3 local and 9 diffuse). Five patients progressed with leptomeningeal disease, and 13 had distant disease progression. Regarding toxicity, 2 patients presented radionecrosis, and only 1 experienced neurocognitive decline. We can conclude by analyzing these findings that our results are compatible with the scarce literature.

CONCLUSIONS AND REMARKS

It is worth analyzing from the clinical point of view all the dosimetric advantages observed in all comparisons of VMAT with other cranial radiosurgery techniques, especially in the context of multiple lesions. As explained above, VMATs are similar to the "non-VMAT" approach in their conformality and heterogeneity; additionally, the possibility of concomitantly treating multiple lesions is attractive; and finally, the IGRT system allows frameless treatments.

Unfortunately, the medical literature is scant regarding clinical outcomes of VMAT use in the context of initial SRS treatments. The available references show few results, with few patients and only preliminary follow-up.

The state of this field can be discouraging, but we believe there are two important issues to be highlighted. First, perhaps the VMAT technique is now developed enough in terms of dosimetric safe which may render unnecessary any randomized studies that exclusively compare one technology against the other. The clinical advantages, such as the possibility of concomitant treatment of multiple lesions with safety and effectiveness, need not be directly tested. Second, the absence of robust clinical trials exclusively using VMAT as a therapeutic modality will continue to encourage scientists to seek the most useful evidence to support physicians.

Finally, given the existing dosimetric research on the safety and benefits of VMAT, there is an ample basis to indicate this technology as a therapeutic modality of SRS. Our institution has initiated this approach in patients with multiple metastases, and we are currently implementing this option without encountering any adverse events. Hastening treatment will undoubtedly impact patients' quality of life.

ETHICS STATEMENT

The retrospective dosimetric data collection of institutional plans was carried out with approval of Human Research Ethics Committee of the Sírio-Libanês Hospital (study 962). The study is also registered in the Brazilian Platform of Human Research (CAAE: 12157319.9.0000.5461).

AUTHOR CONTRIBUTIONS

All authors contributed equally to the design and revision of the article. AD, AM, and WN-J contributed to the physics parts, whereas RA and SH prioritized the clinical parts. SH conducted the final review.

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Stereotactic Body Radiation Therapy (SBRT) as Salvage Therapy for Oligorecurrent Pleural Mesothelioma After Multi-Modality Therapy

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Introduction: Therapy options for patients with oligoprogressive malignant pleural mesothelioma (MPM) are limited. Stereotactic Body Radiotherapy (SBRT) may be a promising therapeutic option, as it delivers a localized ablative dose of radiation and therefore balances efficacy and treatment related toxicities. The intent of this retrospective analysis was to evaluate the feasibility of SBRT for limited pleural recurrences.

Methods and Materials: This retrospective single-institution study is based on the 21 consecutive patients treated with hypofractionated radiotherapy for oligoprogressive MPM. Clinical and radiological data was collected at regular follow-up visits including toxicity, local control and survival.

Results: At primary diagnosis, 57% of the patients presented with stage III disease. Initial treatment of MPM consisted of induction chemotherapy ($n = 12$) prior to a macroscopic complete resection ($n = 18$). Three patients received additional intracavitary chemotherapy and another three patients were treated with chemotherapy alone without another treatment at the time of first diagnosis. A total of 50 lesions in recurrent MPM were treated with SBRT. The median number of radiotherapy fractions was 5 (range 3–20) with a median dose per fraction of 5 Gy (range 2.5–12.5 Gy). The median total treatment dose was 30 Gy (20–50 Gy) with a median prescription isodose line (IDL) of 65% (65–100%). Median follow-up of all patients from diagnosis was 28 months (range 7–152 months). Analyzing all lesions separately, the 12-months-local control from SBRT was 73.5%. The median progression free survival (PFS) after SBRT was 6 months (range 0–21 months) and the median OS from first first SBRT was 29 months (range 0–61 months). Only one patients experienced above Grade 3 toxicities.

Conclusion: This analysis demonstrates the feasibility of a SBRT approach for oligorecurrent MPM. SBRT was well-tolerated even after multiple repetitions and local control was high with a promising median OS.

Keywords: SBRT, malignant pleural mesothelioma, local recurrence, oligoprogression, retrospective analysis

INTRODUCTION

Malignant pleural mesothelioma (MPM) still has a devastating prognosis. Even after recent advances in therapy options within a multi-modality therapy setting combining chemo- and/or radiotherapy to mesothelioma resection, the median survival is up to 23 months (1–5).

The main limiting factor until today is a high local recurrence pattern for this disease. Due to anatomical restraints, microscopic tumor burden will be eventually left behind even after radical surgery. The role of adjuvant radiotherapy in this setting remains unclear. Although *in-vivo*, MPM cell lines shown a great variety of radiosensitivity, including highly radiosensitive lines, data regarding clinical outcome remains inconclusive (6–9).

In case of recurrent disease after initial multimodal treatment, standardized treatment recommendations for effective salvage strategies treatment are needed. According to ASCO guidelines, radiation therapy may be offered to patients with localized asymptomatic recurrence (moderate strength of recommendation). The dosage of fractionated radiotherapy depends on the site and extent of disease and should be discussed on an individual basis (10). Especially patients with very limited local pleural recurrences represent a challenge, as the optimal treatment strategy balancing toxicity and efficacy has not been defined yet (11). These patients may be candidates for a local ablative treatment and may benefit from an extended progression free survival (PFS) until systemic therapy is indicated. Stereotactic body radiotherapy (SBRT) might be a promising option for these patients since it delivers a local ablative biologic dose of radiation and was recently explored in the oligoprogressive setting of solid tumors with excellent local control rates, encouraging outcome, and low severe toxicity (12, 13). The benefit of locally ablative therapy could be shown for other tumor entities, e.g., by Gomez et al. in patients with stage IV non small cell lung cancer (NSCLC) with up to three metastases or Palma et al. in patients with up to five metastases of different primary tumors. Both could show a statistically significant improvement in overall survival by the use of SBRT, e.g., 41.2 months vs. 17 months for Gomez et al. (14, 15).

The intent of this retrospective analysis was to evaluate the feasibility of a novel strategy to integrate SBRT as first salvage therapy for limited pleural recurrences in pleural mesothelioma.

METHODS AND MATERIALS

Patient Characteristics

Our instituitonal database lists patients since 1999 and is simultaneously of prospective nature.

Between 2010 and 2018, 21 patients with the histo-pathological diagnosis of MPM were treated with hypofractionated radiotherapy for thoracic oligometastatic progression.

Most patients initially presented with IMIG stage III disease (57%). Only one patient had distant metastases upon first diagnosis. The median age at first diagnosis was 65 years with a range from 33 to 75 years.

TABLE 1 | Patient characteristics.

	n	%
Sex		
Male	17	81
Female	4	19
Histology		
Epithelioid	17	81
Sarcomatoid	2	9.5
Biphasic	2	9.5
Imig stage		
I	3	14.3
II	4	19
III	12	57.1
IV	2	9.5
Pre-SBRT therapy modalities		
Induction systemic therapy	12	67
Surgical resection	18	86
Intracavitary chemotherapy	3	25
Systemic therapy alone	3	14
Total	21	100

For initial treatment of MPM, 18 patients (ECOG 0-1) had received a macroscopic complete resection (MCR), of which 12 patients received systemic induction (platinum based) therapy prior to the surgical resection. Three patients were treated with chemotherapy alone without any other treatment. MCR consisted of (extrapleural) pleurectomy/decortication and one pleurectomy. In some cases additional intracavitary cisplatin/fibrin application was performed within our clinical phase I/II trial (Intracavitary Cisplatin-Fibrin Localized Chemotherapy after Pleurectomy/Decortication for the Treatment of Patients with Malignant Pleural Mesothelioma (INFLuenCe-Meso I/II). Further patient characteristics are shown in **Table 1**.

Radiation Treatment Planning and Delivery

Planning CT was acquired as 4D-CT with retrospective amplitude-based image sorting. In addition, a 3D-CT was performed in free breathing to allow for contrast i.v. injection.

Gross tumor volume (GTV) was contoured as the visible tumor in the planning CT supplemented by information from i.v. contrast 3D-CT or further imaging including FDG-PET or magnetic resonance imaging (MRI) if available. In FDG-PET CT scans, the FDG active lesions with an visible correlate in the i.v. CT scans were contoured. No additional clinical target volume (CTV) margin was added (i.e., GTV = CTV).

The internal target volume (ITV) was generated as a composite GTV from the different amplitude-based reconstructed CT scans complemented by a margin of 5 mm to derive the planning target volume (PTV). Treatment planning and delivery was done with either conformal or intensity-modulated (VMAT) techniques.

All plans were calculated by a radiation therapy technologist using common constraints for the organs at risk and target prescription standards and were multidisciplinary reviewed. For treatment planning, Eclipse software™ (Varian medical systems) was used. Patients were treated with either 6 or 18 MV. If necessary immobilization by individualized vacuum cast or abdominal compression was used.

Endpoints and Toxicity Definitions

During treatment, all patients were monitored daily for acute treatment related toxicity. Follow-up 6 weeks after completion of SBRT and every 3–4 months thereafter included physical examination and CT, PET-CT and/or MRI scans until tumor progression. Toxicity was scored according to the National Cancer Institute for Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria. Local failure of a metastatic lesion was defined as either reappearance after complete remission or re-growth after initial partial response on follow-up CT or MRI scans.

Statistical Analysis

Overall survival and PFS were calculated according to the Kaplan-Meier method. Overall survival (OS) was calculated from first diagnosis until death or last follow-up, PFS from SBRT until tumor relapse or last follow-up. Regarding radiation treatment parameters, descriptive statistics were calculated. Additionally, the biological effective dose (BED) as well as the 2-Gy equivalent dose (EQD2) were calculated according to the linear-quadratic (LQ) formalism using an alpha-beta for tumor tissue of 10 Gy. For statistical analysis, SPSS version 25 was used.

RESULTS

Radiation Therapy

A total of 21 patients received 1 course of radiation treatment, 10 of those received a second and 4 a third course of RT. A total of 50 lesions in recurrent MPM were treated with SBRT. The median number of PTVs treated during a course was 1 (range 1–3). 75 to 100% were treated with a locally ablative dose in an oligorecurrent setting at all courses, but up to 25% of patients were also treated with a palliative analgetic approach. Two patients received concurrent systemic therapy (Pembrolizumab). The median time between diagnosis of MPM and first radiation treatment was 15 months (range 5–90 months).

The median number of fractions at all courses was 5 (range 3–20) with a median prescription dose per fraction of 5 Gy (range 2.5–12.5 Gy). The median total prescription dose was 30 Gy (20–50 Gy) with a median prescription isodose line (IDL) of 65% (65–100%).

The median PTV volume of all lesions was 40.1 cc (range 3.3–774.3 cc). The median EQD2 (2-Gy-eqivalent dose) was 44.87 Gy (range 23.49–88.34 Gy). A detailed overview of the radiotherapy treatment parameters separately by RT courses are shown in **Table 2**. If there were multiple lesions treated at one timepoint the sum plan of all lesions was used if they were in relevant proximity.

Clinical Outcome

Median follow-up of all patients from diagnosis on was 28 months (range 7–152 months). At the time of analysis, 11 patients were still alive.

Local Control and Pattern of Progression

Intrathoracic out-of-field or in-field recurrence after SBRT was observed in up to 62% of patients. After the first course of SBRT, a total of 13/21 patients had a thoracic recurrence (11 out-of-field, 2 in-field). After the second and third course the number of patients with thoracic recurrence was 6/10 and 2/4, respectively (each with 50% in-field-recurrence).

When looking at all lesions separately the 12-months-local control of the irradiated lesions was 73.5%. **Figure 1** shows the local control after repeated courses of SBRT and **Figure 2** the patterns of failure.

Patients with a recurrence after the first SBRT received a variety of treatment modalities. Most patients received another SBRT (54%) and /or systemic therapy (38%). One patient received a pleurectomy/decortication. In case of another recurrence, most patients were treated with systemic therapy (86–100%).

PFS and OS

The median PFS after first SBRT was 6 months (range 0–21 months) and the median OS after first SBRT was 29 months (range 0–61 months). The OS at 3 years was 9.5%. **Figures 3**, **4** show the PFS and the OS from first SBRT.

Toxicity

Overall, the radiation treatment was very well-tolerated. Only 1 patient experienced $\geq$ Grade 3 toxicity. This patient whose MPM was infiltrating the esophagus and who received RT of the esophagus and mediastinal lesions was hospitalized during treatment due to upper gastrointestinal bleeding. The same patient died 3 months later due to massive esophageal bleeding and progressive disease.

DISCUSSION

In this retrospective single institution study, we analyzed the feasibility of SBRT as a salvage procedure in 21 patients with oligoprogressive MPM. Therapy options for patients with oligoprogressive malignant pleural mesothelioma (MPM) are limited. However, there is few data about SBRT as a salvage strategy for oligoprogressive MPM. Oligoprogression, wheter in MPM or otherwise, is not consistently defined throughout the literature. For our analysis, we specified it as a maximum of three lesions. SBRT is a promising treatment option in this setting as it delivers a local ablative radiation dose as recently explored in an oligometastatic setting of solid tumors with excellent local control rates, encouraging outcome, and low severe toxicity (14–18).

In our cohort, patients were treated with a median EQD2 of 44.87 Gy_{10}. Local control was very promising with a 12-months local control of the irradiated lesions of 73.5%. The applied radiation doses were not in the range of the ablative doses

TABLE 2 | Dosimetric parameters of RT courses.

RT course	1st		2nd		3rd	
PTV	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Volume (cc)	47.8	3.3–754.2	29.8	4.9–264.00	432.65	38.60–774.30
Dose/fraction mean (Gy)	6.6	2.5–14.45	6.3	2.55–13.87	3	2.61–9.14
Total dose mean (Gy)	38.22	20.11–50.00	32.32	30.00–57.50	33.69	30.00–45.70
BED mean (Gy)	56.82	28.19–106.00	51.35	38.45–99.37	43.19	39.00–87.48
EQD2 mean (Gy_{10})	47.35	23.49–88.34	42.79	32.04–82.81	35.99	32.5–72.90

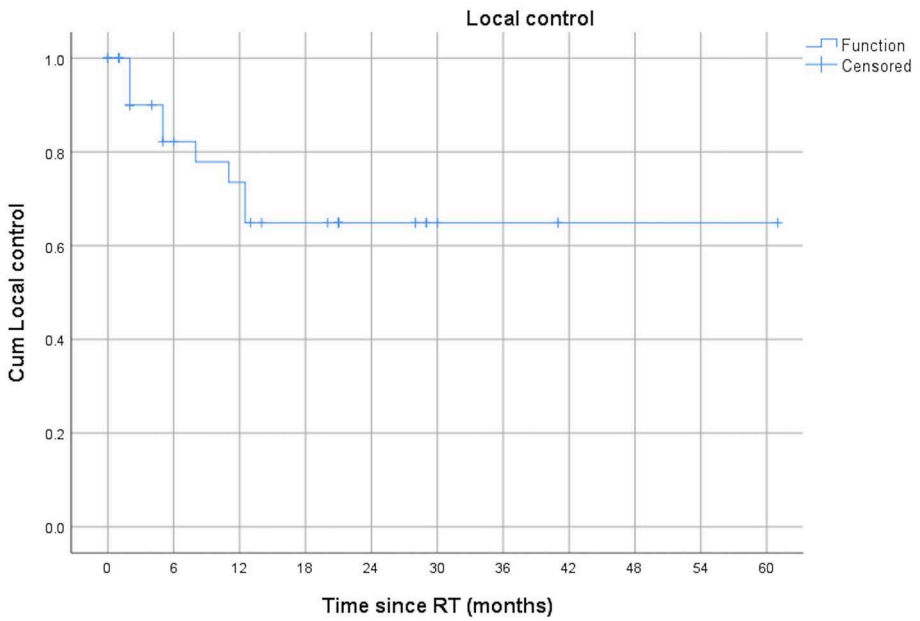

FIGURE 1 | Local control for all lesions after repeated courses of SBRT.

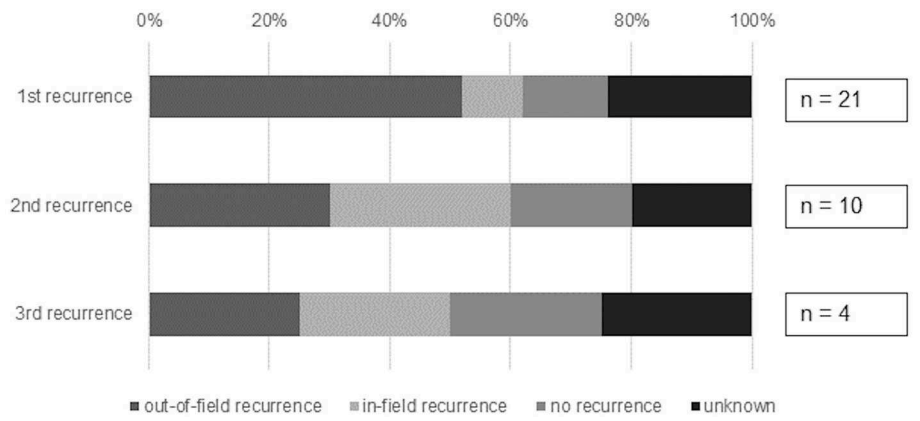

FIGURE 2 | Patterns of failure after repeated courses of SBRT for oligometastatic recurrence.

applied in phase I or II studies regarding oligometastatic lesions of other primary disease. In the NRG-BR001 and SABR-COMET trials, the treatment dose was 30–50 Gy in 3–5 fractions and 30–60 Gy in 3–8 fractions, respectively (15, 17). Nevertheless, the local control in our patient cohort appears to be very promising. Regarding SBRT in MPM patients there is only one case report

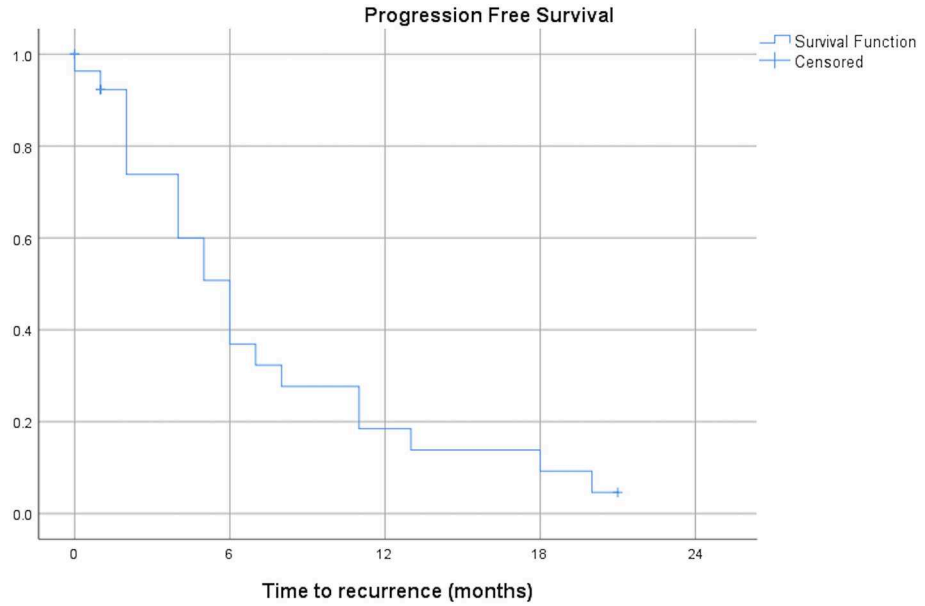

FIGURE 3 | Progression free survival after first SBRT (months, $n = 21$).

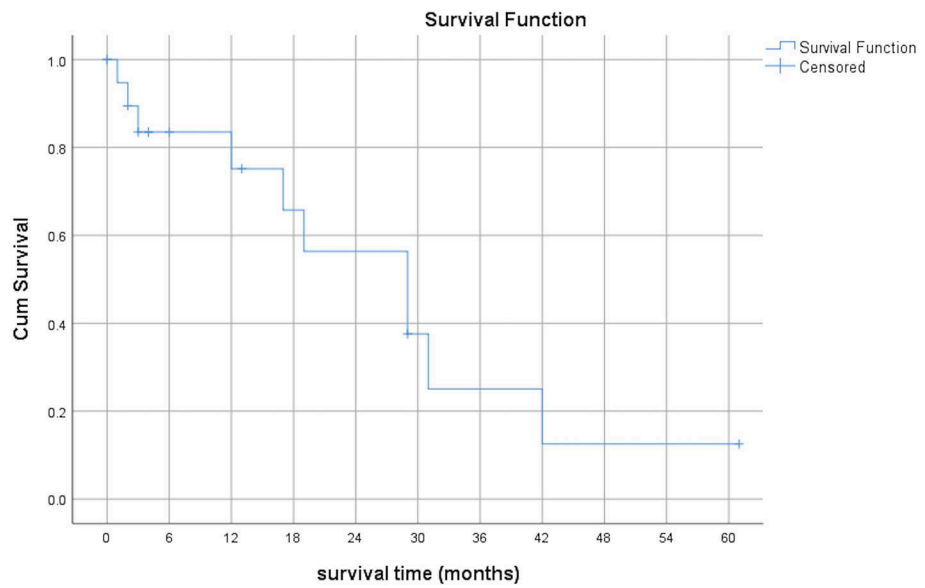

FIGURE 4 | Overall survival after first SBRT (months, $n = 21$).

about a patient receiving Cyberknife treatment (70 Gy/5 fx) for a focal paravertebral recurrence after MCR in MPM who remained disease-free at 40 months (19). Additionally, two case series exist about patients receiving palliative stereotactic IMRT by Munter et al., but not for an oligoprogressive setting as in our cohort (20, 21).

Looking at efficacy, although our results are promising, there are certainly challenges regarding the definition for an optimal target volume. Even with PET-CT based planning, lesions might be missed or underestimated due to the disease's nature, respectively its infiltrating pattern. Hence, not all of the lesions might be covered with a sufficient dose, resulting in recurrences. The close neighborhood to abdominal organs at risk (OARs), especially if targeting lesions close to the diaphragm, might also lead to dose compromises in the target volume necessary for sparing the OAR.

When looking at safety, our toxicity profile with only 1 patient experiencing $\geq$ grade 3 toxicity due to esophagus infiltration is promising. The patient was hospitalized during treatment due to resulting upper gastrointestinal hemorrhage and eventually

died of a massive bleeding later on. We interpreted this as a combination of the local radiation therapy in addition to the infiltrating and progressive disease. There were no signs of any severe pneumonitis in our cohort.

Due to the high local control, promising OS and low toxicity profile we propose that SBRT may be a promising approach to provide effective local control in a short overall treatment time to delay systemic therapy until further progression in selected patients.

We are aware of the limitation of this case series concerning the inhomogeneity of the patient cohort with their different therapies applied beforehand and divergent time points of radiotherapy. Nevertheless, oligoprogression is observed in MPM and SBRT appears to be feasible and safe, especially for patients with a reduced general condition after multiple previous therapies. Further studies are needed to determine the role of SBRT and should focus on optimizing fraction schemes as well as exploring the influence on the patient's quality of life.

DATA AVAILABILITY STATEMENT

The dataset for this manuscript are available upon request. Requests to access the datasets should be directed to the corresponding data.

ETHICS STATEMENT

The local ethics committee approved this retrospective analysis of the mesothelioma data base (StV 29-2009, EK-ZH 2012-0094).

AUTHOR CONTRIBUTIONS

CS and OL were responsible for conception and design, collection, and analysis of data as well as manuscript writing. NA was responsible for conception/design, collection and analysis of data, administrative support, and provision of patients. IO, MG, WW, RF, and RS provided administrative support and patients.

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MINI REVIEW
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Stereotactic Body Radiotherapy for Oligometastatic Disease in Non-small Cell Lung Cancer

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Metastatic non-small cell lung cancer (NSCLC) is associated with a limited survival when treated with palliative intent platinum-based chemotherapy alone. Recent advances in imaging and therapeutic strategy have identified a subset of patients with limited metastases who may benefit from early local ablative therapy with either surgery or radiotherapy, in addition to standard treatment. Stereotactic body radiotherapy (SBRT) is increasingly used in the treatment of extra-cranial oligometastatic NSCLC (OM-NSCLC) due its non-invasive conduct and ability to deliver high doses. Clinical evidence supporting the use of SBRT in OM-NSCLC is emerging and consistently demonstrates significant benefit in local control and progression-free survival. Here, we discuss the definition of oligometastases (OM), review current available data on SBRT treatment in extra-cranial OM-NSCLC including evidence for site-specific SBRT in lung, liver, and adrenal metastases.

Keywords: stereotactic body radiotherapy, non-small cell lung cancer, lung cancer, oligometastases, oligometastatic disease

INTRODUCTION

Lung cancer continues to be the leading cause of cancer death in many countries (1). Unfortunately, about two-thirds of non-small cell lung cancer (NSCLC) patients present with metastatic disease (Stage IV) at diagnosis and are considered incurable (2). For these patients, systemic therapy continues to be the mainstay of treatment. However, with conventional chemotherapy alone, the median survival hovers around 10 months, and long-term survival is unlikely (3). There can be considerable heterogeneity within stage IV classification, with a sub-group of stage IV patients (especially those with low-volume metastatic disease) having prolonged survival. This led to the 8th edition of American Joint Committee on Cancer (AJCC) to further categorize stage IV. In particular, patients with a single extra-thoracic metastasis was classified as M1b (Stage IVA), as opposed to patients with multiple lesions in one or multiple organs (M1c, Stage IVB) (4). Precisely

classifying these patients improves the prognostic value and in doing so, will help guide treatment; in particular, identifying patients with OM-NSCLC who may warrant aggressive management of the primary tumor, as well as the metastatic sites.

The term "oligometastatic" disease has been used commonly (and sometimes loosely) in the cancer literature ever since 1995. Hellman and Weichselbaum were the first to introduce this concept of OM disease, which represented an intermediate state in the spectrum between locally confined and widely metastatic cancer (5, 6). They proposed that the process of metastatic disease occurs in a step-wise manner, and patients with limited disease should be managed aggressively. In more recent years, advances in systemic/targeted therapy may render a greater proportion of patients with upfront widely metastatic disease to a state of limited volume metastatic disease. In these patients, aggressive management of drug-resistant clones may improve cancer outcomes.

Surgical metastasectomy was initially the only way to radically manage these patients (7). With the advent of intra-cranial stereotactic radiosurgery, high doses of ablative radiation delivered over a limited number of fractions were seen to be as effective as surgical resection (8, 9). Advances in imaging, treatment delivery and patient immobilization now allow us to perform ablative radiation to extra-cranial sites in the form of stereotactic body radiotherapy (SBRT) (10). SBRT has an advantage over surgical metastasectomy in that it is non-invasive, well-tolerated and has fewer interruptions to systemic therapy.

In this mini-review, we will discuss the definitions of OM disease (in the context of NSCLC), patient selection, prognostic factors as well as completed and ongoing trials to support the use of SBRT for OM-NSCLC.

INCIDENCE AND DEFINITION OF OLIGOMETASTATIC CANCER

To date, there is no universal definition of what constitutes OM with regards to the number of lesions or sites involved. The most accepted number of metastatic lesions is considered to be 5 or less (with up to 3 metastases in an organ) (11–14).

As definitions of OM vary from study to study, it is hard to estimate the exact incidence of OM in NSCLC at diagnosis. Moreover, the routine use of staging FDG/PET-CT scan and MRI brain imaging may increase the incidence of OM, due to increased sensitivity compared to older imaging modalities. The International Association for the Study of Lung Cancer (IASLC) Lung Cancer staging project found that 225 out of 1,025 (22%) patients had synchronous single metastatic lesion at diagnosis; this group of patients had a better prognosis compared to patients with metastases in multiple organs (15). In another study by Parikh et al., 26% of patients had 5 or fewer metastases at diagnosis, and half of these patients only had 1 metastases (16).

In terms of classifying oligometastatic cancer, there are three possible scenarios:

1) Synchronous oligometastatic disease: Patients who present with up to 5 metastatic lesions (in one or a few organs) at first or within 6 months of diagnosis. These typically occur in the brain, lung parenchyma, liver or bone (15).
2) Oligo-residual (or oligo-persistent) disease: Widely metastatic disease (>5) at diagnosis, which has responded well to systemic therapy (i.e., complete response), with the remaining lesions (up to 5) amenable to radical local therapy (e.g., surgery, SBRT, RFA) (17).
3) Metachronous (or oligo-recurrence): Patients who had been treated with curative intent, and then present with limited sites of metastatic disease (up to 5) after an interval of stable disease (18).

As oligoprogression is a biologically distinct entity whereby patients with upfront widespread metastases progress, in a limited number of sites, after initially achieving stable disease or partial response, we have not included it in this definition. It is possible that patients with oligoprogression have a worse prognosis compared to the above scenarios.

CHOICE OF LOCAL THERAPY: BETWEEN SURGERY, SBRT, AND RADIOFREQUENCY ABLATION

Selecting the most effective method for local treatment of oligometastases requires thoughtful considerations. Patient-related factors (e.g., age, performance status and organ function, patient preferences), tumor-related factors (e.g., location, size, proximity to vessels or nearby critical organs) and treatment-related factors (e.g., availability of expertise, cost, and waiting list) have to be taken into account.

In the latest National Comprehensive Cancer Network (NCCN) guideline for stage IVA NSCLC, definitive RT to OM, with particular mention of SBRT, is recommended as an appropriate option in suitable patients with good performance status provided it can be delivered safely (19). This reflects a growing trend and clinical evidence supporting the use of SBRT for OM. A survey of 1,007 radiation oncologists from 43 countries published by Lewis et al. in 2017 reported that 83% have been using SBRT for extracranial OM since 2005 (with over 30% since 2010) with treatment response and durability as the main reason for choosing SBRT (20). The survey reported the most common treated organs were lung, liver, and spine (90, 75, and 70%, respectively).

There are no head-to-head studies comparing surgery, SBRT, and RFA. In liver metastases, SBRT is superior to RFA in treating larger lesions >3 cm, or for lesions near blood vessels where there can be a heat-sink effect with RFA (21, 22). Widder et al. retrospectively analyzed 110 patients with pulmonary OM who were offered surgery as first line treatment for OM and SBRT if they were unsuitable for surgery (23). Although SBRT was offered as an alternative option, OS and local control rates were comparable between the two groups. As such, due to its non-invasive conduct and ability to deliver highly conformal high dose radiotherapy, SBRT has been increasingly used to target OM lesions especially for patients with technically unresectable lesions or those who are unfit for surgery.

PROGNOSTIC FACTORS AND PATIENT SELECTION

Patient selection is not only important to ensure the safe delivery of SBRT but also has prognostic significance (24). Several previous studies have attempted to streamline patient selection through identifying prognostic factors.

In a retrospective cohort study involving 186 patients, ECOG performance status >2, higher nodal-status (N2-3), squamous histology and metastases to multiple organs were associated with a worse prognosis (16). Ashworth and colleagues performed an individual patient meta-analysis using data from 757 patients treated curatively at the primary site, and with up to 5 metastatic lesions, treated radically with local therapies such as surgical resection, SBRT, high-dose radical RT (25). Surgery was the most commonly used treatment for the primary site (83.9%) and the metastatic sites (62.3%). The median survival of these patients was 26 months, and approximately a third survived 5 years. Key findings from this study are that patients with metachronous metastases, lower N status and adenocarcinoma histology were predicted to have longer OS. The authors proposed stratifying patients into three risk groups: low-risk (metachronous metastases, 5-year OS 47.8%), intermediate-risk (synchronous metastases with N0 disease, 5-year OS 36.2%), and high-risk (synchronous metastases with N1/N2 disease, 5-year OS 13.8%) (25), however this classification scheme is yet to be formally validated in clinical trials.

The number (and possibly volume) of metastatic sites has also been shown to be a potential prognostic factor. In a SWOG study by Albain et al., involving 2,531 patients with advanced NSCLC, median survival was highest in patients with a single lesion (8.7 months), compared to patients with multiple lesions in one organ (6.2 months) and multiple lesions in multiple organs (5.1 months) (26). Similarly in the subgroup analysis of RTOG 9508 trial, which allowed up to 3 brain metastases, survival improvement (with the addition of stereotactic radiosurgery) was only found in patients with a single lesion compared to 2–3 lesions (27). Looking at the use of SBRT in particular, patients with up to 3 lesions had a better OS compared to patients with 4–5 lesions (2-year OS 60.3 vs. 21.9%). However, it must be noted that only 11 of 61 patients had NSCLC (28).

SBRT TO EXTRA-CRANIAL SITES COMMONLY SEEN WITH OLIGOMETASTATIC NSCLC (LUNG, LIVER, ADRENAL)

A) Lung: Prior studies on SBRT in primary NSCLC have reported local control rate comparable to surgery when the biologically effective dose (BED) of SBRT was at least 100 Gy (29–32). De Rose et al. reviewed 60 patients treated with SBRT for lung metastases in NSCLC with 60 Gy in 3 fractions to peripheral lesions <2 cm, 48 Gy in 4 fractions to peripheral lesions between 2 and 5 cm, and 60 Gy in 8 fractions to central lesions (30). All patients received a BED > 100 Gy resulting in a 2-year local control rate of 88.9% and 1- and 2-year OS of 94.5 and 74.6%, respectively. Laterality of metastatic disease does not seem to influence survival outcomes. For example, the survival was not significantly different between ipsilateral (T4, M0) vs. contralateral (M1a) surgical metastasectomy in 43 patients with NSCLC (27 vs. 43%) (33). Notably, none of the patients with mediastinal node involvement achieved long-term survival. More accurate staging with FDG-PET scan prior to SBRT significantly improved 1- and 2-year OS (82.7 vs. 72.8% and 64.8 vs. 52.6%, respectively, $P = 0.012$) (34). Pre-treatment performance status, maximum metastasis diameter, primary tumor histology, number of metastases, and time interval between primary tumor diagnosis and SBRT treatment significantly influenced OS (35). SBRT to the lung is generally well-tolerated with most patients experiencing grade 1–2 late pulmonary toxicity and grade 3 pulmonary toxicity in the minority (30, 31) and the BED at the planning target volume (PTV) isocenter was the only factor reported to influence toxicity in a database analysis of 700 patients treated with SBRT for oligometastatic lung disease (35).

B) Liver: Ahmed et al. evaluated the radiosensitivity of liver metastases from different primary histology using a multigene expression index for tumor radiosensitivity (RSI) (36). They suggested that NSCLC has an intermediate radiosensitivity (median RSI 0.31). Majority of the series reporting outcome of SBRT to liver metastases involve colorectal primaries. In the context of NSCLC, the presence of liver metastases has been associated with a worse prognosis compared to metastases to other sites in NSCLC (37, 38). Milano et al. evaluated the use of 50 Gy in 5 fractions for SBRT to treat hepatic metastases (∼20% lung primary) and reported a 2-year local control rate of 67% (39). Rusthoven et al. (also ∼20% lung primary) reported a higher 2-year local control rate of 92% with SBRT regimen of 30–60 Gy in 3 fractions (40). In a pooled analysis involving 474 patients with 623 liver metastases (with mainly colorectal and breast primary), increasing the maximum isocenter BED to >150 Gy EQD2Gy, increased 1- and 2-year control rate of treated lesions from 77–83% and 64–70%, respectively (41).

C) Adrenal: SBRT to adrenal metastases in OM-NSCLC was specifically evaluated in a study by Celik et al. whereby 15 patients received 42 Gy in 6 fractions of CyberKnife® SBRT (42). One and two-year local control rates were 60 and 46.6%, respectively. Patient with metachronous metastases had a more favorable 2-year overall survival of 91.2% compared to 42.8% in patients with synchronous adrenal metastases. Holy et al. reported an overall median PFS of 4.2 months in their group of 18 patients with adrenal metastases from NSCLC treated with SBRT (range 20–40 Gy in 5 fractions) (43). Of these, 13 patients with isolated adrenal metastasis had longer median PFS of 12 months, local control rate of 77% (median follow-up: 21 months), and median OS of 23 months. SBRT for adrenal metastases is reasonably tolerated with previous studies reporting grade 1–2 toxicities including gastrointestinal toxicity, fatigue, rarely duodenal ulcers, and possibly late adrenal insufficiency (42, 44, 45).

TABLE 1 | Selected studies of SBRT treatment in oligometastatic NSCLC.

References	Year	Patients (*n*)	Site of oligo-met	*N*	Dose (Gy/fraction)	Systemic therapy	Median follow-up (months)	Median PFS (months)	Median OS (months)
RETROSPECTIVE STUDIES									
Inoue et al. (47)	2010	41*	Brain, lung, adrenal	<5	48/8 (adrenal) 35–60/4–8 (lung)	NA	20	3-year PFS 20%	24
Holy et al. (43)	2011	18	Adrenal	NA	20–40/5	Various	21	4.2 (all) 12 (1 met)	23 (1 met)
Hasselle et al. (48)	2012	25	Multiple	<5	24–70/3–20	Chemo or targeted therapy	14	7.6	22.7
De Rose et al. (30)	2016	60	Lung	<5	48–60/3–8	Chemo	28	32.2 (actuarial)	32.1 (actuarial)
Celik et al. (42)	2017	15	Adrenal	<5	42/6	Chemo	24	10.5	2-year OS 46.6%
SINGLE ARM PROSPECTIVE TRIALS									
Salama et al. (28)	2012	61*	Multiple	<5	24–48/3	Chemo	20.9	2-year PFS 22%	2-year OS 56.7%
De Ruysscher et al. (49)	2012	40	Multiple	<5	54/3**	Chemo	27.7	12.1	13.5
Collen et al. (50)	2014	26	Multiple	<5	50/10	Chemo	16.4	11.2	23
RANDOMIZED PHASE II TRIALS									
Gomez et al. (12)	2016	49	Multiple	<3	NR	Chemo	12.4	14.2 vs. 4.4	41.2 vs. 17
Iyengar et al. (11)	2018	29	Multiple	<5	21–37.5/1–5	Chemo	9.6	9.7 vs. 3.5	Not reached vs. 17
Palma et al. (13)	2019	99	Multiple	<5	35–60/3–8	Chemo	25	12 vs. 6	41 vs. 28

N, number of oligometastatic lesions per patient; OS, overall survival; NR, data not reported; PFS, progression free survival.
**Various primary histology including NSCLC. **Only one patient received SBRT.*

SUMMARY OF EVIDENCE SUPPORTING SBRT IN OM-NSCLC

A retrospective analysis of patterns-of failure after first-line systemic therapy in 387 patients with NSCLC reported local progression as the predominant pattern-of failure and suggested that local consolidative therapy with SBRT to known sites of disease following systemic therapy to prolong the time to first progression (46). Since then, trials of patients with limited metastatic NSCLC treated with SBRT have demonstrated significant survival benefit in both first and second line settings (**Table 1**).

Single Arm Prospective Trials

1) Collen et al. reported on 26 patients with synchronous OM-NSCLC patients with up to 5 metastases treated with SBRT (50 Gy in 10 fractions) (50). Notably, patients with uncontrolled primary tumors were eligible. The primary endpoint was complete metabolic response (CMR) on PET (3 months post-SBRT). Seventeen patients underwent SBRT after upfront chemotherapy, and the remaining underwent SBRT (to all sites) as primary treatment. Sixty percent of patients achieved metabolic response, with half of reaching CMR. The median PFS was 11.2 months, and median OS 23 months.
2) De Ruysscher et al. included 40 patients with synchronous OM-NSCLC ($\leq$5 lesions) who were amenable for radical therapy to all tumor sites including the primary (surgery, stereotactic radiosurgery, fractionated RT to a dose of 60 Gy, and one patient received treatment with 54 Gy in 3 fractions of SBRT) (49). The vast majority had a single metastatic focus, and were treated with upfront chemotherapy, and approximately half had brain metastases. They report a median PFS of 12.1 months, and OS of 13.5 months. The inferior results compared to the Collen study may be related the larger proportion of patients with brain metastases in this cohort, or the use of conventionally fractionated RT.
3) Bauml et al. recently published their single-arm Phase II trial comprising of 51 patients with $\leq$4 lesions who completed locally ablative therapy to all sites, following which they were given pembrolizumab. They reported a median PFS of 19.1 months and 1-year OS of 90.9%. This is notably much improved compared to historical controls (51).

Randomized Phase II Trials

1) Iyengar et al. then conducted a randomized phase II trial for 29 patients with NSCLC and up to 5 OM lesions. NSCLC who had achieved partial response or stable disease to first-line chemotherapy (11). EGFR/ALK positive patients were excluded. They were randomized to SBRT + maintenance chemotherapy vs. maintenance chemotherapy alone. The trial was stopped early due to significant improvements with the addition of SBRT (PFS 9.7 vs. 3.5 months, $P = 0.01$). Toxicities were similar in both arms.

2) Gomez et al. conducted a multi-center Phase II randomized study in 49 patients with up to 3 OM NSCLC with no progression for at least 3 months post 1st line chemotherapy (12, 52). Eighty-four percent were EGFR/ALK negative. Patients were assigned to local therapy (surgery or radical RT) vs. maintenance chemotherapy or observation. Like the previous trial, this study was stopped early due to significant improvements in PFS in the local therapy arm (PFS 14.2 vs. 4.4 months, $P = 0.022$). OS was also significantly improved (OS 41.2 vs. 17 months, $P = 0.017$). There are two observations from this study. Firstly, the OS benefit was seen despite patients crossing-over from maintenance/observation to local therapy, suggesting earlier local therapy to be superior to local therapy on progression. Secondly, none of the patients suffered from Grade 3 toxicity.
3) Palma et al. conducted the international SABR-COMET Phase II trial including 99 patients with up to 5 OM lesions from a variety of primary histological types (20% lung primary) (13). Patients were randomized to SBRT to all sites vs. palliative standard of care alone. The primary endpoint, which was OS,

TABLE 2 | Selected ongoing trials of SBRT treatment in oligometastatic NSCLC.

Title	Patients	Study design	Estimated completion
Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON). A Randomized Phase III Trial. (53) Institution: University College London ClinicalTrials.gov identifier: NCT02417662	340	Phase 3 multi-center: chemotherapy alone (standard platinum based doublet chemotherapy or chemotherapy + radical radiotherapy (conventional RT and SABR) Primary histology: all NSCLC *1–3 oligometastatic lesions* Primary outcome measure: OS	August 2022
Maintenance Systemic Therapy vs. Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial (NRG LU-002) Institution: NRG Oncology ClinicalTrials.gov identifier: NCT03137771	300	Phase 2/3 multi-center: maintenance chemotherapy or SBRT + maintenance chemotherapy Primary histology: all NSCLC *1–3 oligometastatic lesions* Primary outcome measure: PFS	April 2022
Randomized Phase III Trial of Local Consolidation Therapy (LCT) After Nivolumab and Ipilimumab for Immunotherapy-Naive Patients With Metastatic Non-small Cell Lung Cancer (LONESTAR) -Strategic Alliance: BMS Institution: M.D. Anderson Cancer Center ClinicalTrials.gov identifier: NCT03391869	270	Phase 3 multi-center: systemic treatment only with nivolumab and ipilimumab or induction nivolumab and ipilimumab followed by local consolidative therapy with surgery and/or radiotherapy Primary histology: all NSCLC *>1 oligometastatic lesions* Primary outcome: OS	December 2022
A Randomized Trial of Conventional Care vs. Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases (CORE) Institution: Royal Marsden NHS Foundation Trust ClinicalTrials.gov identifier: NCT02759783	245	Phase 2/3 multi-center: standard of care or standard of care + SBRT Primary histology: breast, prostate, or NSCLC *1–3 oligometastatic lesions* Primary outcome measure: PFS	October 2024
A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4–10 Oligometastatic Tumors (SABR-COMET 10) Institution: Lawson Health Research Institute ClinicalTrials.gov identifier: NCT03721341	159	Phase 3 multi-center: stereotactic ablative radiotherapy, plus standard of care treatment: chemotherapy, immunotherapy, hormones, or observation given at the discretion of the treating oncologist Various histology including NSCLC *4 to 10 oligometastatic lesions* Primary outcome: OS	January 2029
Randomized Phase II Trial of Local Consolidation Therapy (LCT) After Osimertinib for Patients With EGFR Mutant Metastatic Non-small Cell Lung Cancer (NSCLC) (NORTHSTAR) Institution: M.D. Anderson Cancer Center ClinicalTrials.gov identifier: NCT03410043	143	Phase 2 multi-center: osimertinib followed by local consolidative therapy with surgery and/or radiotherapy or maintenance osimertinib alone Primary histology: NSCLC *>1 oligometastatic lesion* Primary outcome: PFS	January 2023
A Multicentre Single Arm Phase II Trial Assessing the Efficacy of Immunotherapy, Chemotherapy and Stereotactic Radiotherapy to Metastases Followed by Definitive Surgery or Radiotherapy to the Primary Tumor, in Patients With Synchronous Oligo-metastatic NSCLC Institution: European Thoracic Oncology Platform ClinicalTrials.gov identifier: NCT03965468	47	Phase 2 multi-center: durvalumab, carboplatin/paclitaxel chemotherapy, followed by SBRT to all oligometastases. Restaging at 3 months Definitive local treatment with surgical resection of primary tumor or RT 60–66 Gy to the primary tumor if no disease progression. *1–3 oligometastatic lesions* Primary outcome: PFS	December 2021

RT, radiotherapy; SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy; OS, overall survival; PFS, progression free survival.

was prolonged with addition of SBRT (41 vs. 28 months, $P = 0.09$). Unfortunately, there were significantly more toxicity in the SBRT arm (29 vs. 9%) with treatment-related death (Grade 5) being experienced by three patients (4.5%).

Phase III Trials

No Phase III trial has reported the benefit of SBRT in OM-NSCLC. In view of the convincing Phase II data, there are multiple ongoing Phase III trials which are eagerly awaited. These trials are summarized in **Table 2**.

FUTURE DIRECTION AND UNANSWERED QUESTIONS

Considerable progress has been made in the realm of OM-NSCLC. Improvements in survival stem partly from more effective systemic therapy, but also aggressive consolidation therapies (surgery, radiation) in patients with a favorable disease biology. Although the results from randomized Phase II data are exciting, adequately powered Phase III trials with clear inclusion/exclusion criteria (e.g., synchronous, metachronous, oligorecurrence) and appropriate primary endpoints are much awaited to change practice. The upper limit of the number of acceptable OM lesions were set rather arbitrarily. It remains unclear if we should limit this to 3, 5 or 10 (54). As such, two randomized Phase III trials are being planned. SABR-COMET 3 (NCT03862911) for 1–3 lesions, and SABR-COMET 10 (NCT03721341), for 4–10 lesions. Moreover, most of the prospective OM-NSCLC trials have been performed in the Caucasian population where EGFR/ALK driver mutations are known to be much lower than in Asian countries. There remain many unanswered questions about how best to manage these patients including clinical uncertainty if these principles can be extrapolated to populations with higher prevalence of driver mutations. Lastly, most of the studies were conducted prior to the use of immunotherapy. Therefore, the role of SBRT in the context of immunotherapy is uncertain.

CONCLUSION

Stage IV NSCLC represents a heterogenous group of patients with an overall poor outcome. However, a sub-group of patients with limited metastatic disease may achieve long-term survival with effective systemic therapy and aggressive local therapy. SBRT is a good option to obtain durable local control, and possibly prolong survival for these patients. At the same time, SBRT can be a double-edged sword, with toxicities in a minority of patients. As always, appropriate patient selection remains paramount, and ongoing Phase III trials will provide clarity.

AUTHOR CONTRIBUTIONS

CW, BV, and SL contributed conception and design of the study. CW and BV organized the database and wrote the first draft of the manuscript. All authors wrote sections of the manuscript, contributed to manuscript revision, read, and approved the submitted version.

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Stereotactic Radiation Therapy (SRT) for Brain Metastases of Multiple Primary Tumors: A Single Institution Retrospective Analysis

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Purpose: To evaluate the efficiency and side effects of stereotactic radiation therapy (SRT) with or without other treatments for brain metastases (BM) from various primary tumors.

Methods: This was a retrospective analysis of 161 patients with brain metastases treated with SRT. Clinical data, EGFR mutation status and survival data were collected. Follow-up data was analyzed until December 2018. Kaplan-Meier and Cox proportional hazards regression analyses were used for the survival analysis.

Results: The median overall survival (OS) was 19 months. No difference was observed in OS between SRT group and SRT + whole brain radiation therapy (WBRT) groups ($p = 0.717$). Statistically significant factors of better OS after univariable analysis were no extracranial metastases ($p = 0.016$), BED_{10}-SRT≥50Gy ($p = 0.049$), oligometastases (1–3 brain metastases) ($p < 0.001$), GPA score≥2.5 ($p = 0.003$), RPA class I ($p = 0.026$), NSCLC tumor type ($p = 0.006$), targeted therapy ($p < 0.001$) and controlled extracranial disease ($p = 0.011$). Multivariate analysis indicated that higher BED_{10}-SRT (≥50Gy, HR = 0.504, $p = 0.027$), controlled extracranial disease (HR = 0.658, $p = 0.039$) and targeted therapy (HR = 0.157, <0.001) were independent favorable predictors for OS. Besides that, we also find that the median overall survival (OS) was 22 months in NSCLC patients and controlled extracranial disease (HR = 0.512, $p = 0.012$) and targeted therapy (HR = 0.168, < 0.001) were independent favorable predictors for OS.

Conclusion: For patients with brain metastases, stable extracranial disease, higher BED_{10}-SRT (≥50Gy) and targeted therapy may predict a favorable prognosis.

Keywords: stereotactic radiation therapy, brain metastasis, overall survival, prognostic factors, non–small-cell lung cancer

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INTRODUCTION

Brain metastases are the most common intracranial malignancies, about 10–30% cancer patients develop brain metastases during the course of their diseases (1, 2) and 20 to 30% of patients with BM die as a result of poor local control (3). BM is one of the main causes seriously reduces the patients' life quality (4). Almost 40% patients will develop brain metastases during

the course of their disease in non–small-cell lung cancer (NSCLC), and it may be even higher in those patients with epidermal growth factor receptor (EGFR) mutation (4, 5). Patients with EGFR-mutation may have a greater proportion of being diagnosed with brain metastases because of longer survival owing to targeted therapy and Central Nervous System (CNS) imaging technique improvement (6, 7).

There are various approaches for the treatments of brain metastases including surgical resection, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), systemic steroids and other combinations. Mintz et al. (8) demonstrated that surgery followed by WBRT obtained longer overall survival and better response to treatment compared to WBRT alone; but no differences were found in recurrence rate in metastasis site. Similar results were also published by Mintz et al. (8) Patchell et al. (9), and Vecht et al. (10).

In the RTOG 9508 trial (11), 333 patients with 1–3 brain metastases were randomly assigned to either WBRT or SRT-WBRT. WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable metastasis. In the secondary analysis performed after 10 years (12), 252 patients have been rearranged according to the GPA score. Survival advantage was found only in patients with higher GPA score (3.5–4) no matter the numbers of brain metastases.

METHODS AND MATERIALS

Patient Selection

From February 2012 to June 2017, 161 patients with single or multiple (up to 7) brain metastases with good performance status and synchronous/metachronous primary tumor were treated at the Radiation Therapy Department, Changhai Hospital, Naval Medical University. Follow-up data was analyzed until December 2018. The study was approved by the independent Ethics Committee of our hospital and all patients signed informed consents. Data necessary for analysis were extracted, compiled, and verified against patients' archived medical records. Data analyzed included primary cancer, karnofsky performance score (KPS), Graded Prognostic Assessment (GPA) score, recursive partitioning analysis (RPA) classification at the time of SRT, site of intracranial metastases, number of lesions treated, present of extracranial metastases, and date of death or last follow-up, SRT treatment records, WBRT treatment records, and status of primary disease and systemic disease at SRT.

Abbreviations: SRT, Stereotactic Radiation Therapy; BM, brain metastases; WBRT, whole brain radiation therapy; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; CNS, Central Nervous System; SRS, stereotactic radiosurgery; OS, overall survival; GPA, Graded Prognostic Assessment; RPA, recursive partitioning analysis; BED_{10}-SRT, biological effective dose of SRT; KPS, karnofsky performance score; TKI, Tyrosine Kinase Inhibitor; QOL, quality of life.

TABLE 1 | Patients characteristics.

Characteristics	No./median (range)	Proportion (%)
Sex		
Male	103	64
Female	58	36
Age (y)	61 (33–87)	
KPS		
≤70	90	55.9
>70	71	44.1
Histology		
NSCLC	105	65.2
SCLC	11	6.8
Breast	7	4.3
Renal	3	1.9
Gastrointestinal	19	11.8
Others	16	10.0
Primary tumor		
NSCLC	105	65.2
None NSCLC	56	34.8
Synchronous BM		
YES	53	32.9
NO	108	67.1
Extracranial metastases		
YES	91	56.5
NO	70	43.5
Number of treated lesions		
1	99	61.5
2	31	19.3
3	11	6.8
4	8	5.0
5	2	1.2
>5	10	6.2
Time from diagnosis to brain metastasis (M)	10 (0–300)	
System therapy cancer*	93	57.8
Total BM volume		
Per patient (cc)	8.79 (0.113–179.31)	
Prescription dose	27 (20–40)	
Fraction	5 (3–6)	
BED_{10}	38.016 (16.6–84.375)	
Fraction	5 (3–10)	
SRT alone	99	61.5
SRT+WBRT	62	38.5
Controlled of primary tumor		
Controlled	92	57.1
Uncontrolled	69	42.9
GPA score		
0.5	9	5.6
1.0	22	13.7
1.5	40	24.9
2.0	30	18.6
2.5	30	18.6
3.0	20	12.4

(Continued)

TABLE 1 | Continued

Characteristics	No./median (range)	Proportion (%)
3.5	9	5.6
4.0	1	0.6
RPA classification		
I	50	31.1
II	92	57.1
III	19	11.8

**System therapy cancer: together with chemotherapy or targeted therapy.*
KPS, Karnofsky performance status; BM, brain metastases; GPA, graded prognostic assessment; RPA, recursive partitioning analysis; SRT, stereotactic radiation therapy; WBRT, whole-brain radiotherapy.

TABLE 2 | Pre-SRT clinical symptoms and Post-SRT functional outcomes.

Pre-SRT symptoms	*n*	Post- SRT	*n*
Headache	40	Improved	33
Dizziness	32	Improved	26
Weakness	2	Improved	2
Dysarthria	11	Improved	6
Vomitting	18	Improved	18
Visual dysfunction	11	Improved	10
Epilepsy	3	Improved	1
Central ataxia	14	Improved	12
Cognitive dysfunction	4	Improved	2
Motor weakness	38	Improved	35
Hemiplegia	10	Improved	8
Hyperspasmia	7	Improved	5
Asymptomatic	63	New developed	15

SRT, stereotactic radiation therapy.

RADIATION TREATMENT TECHNIQUE

WBRT treatments were administered with 21EX Linear Accelerator (Varian Medical Systems, Palo Alto, CA) using 3D-CRT. SRT were delivered with CyberKnife robotic radiosurgery system (Accuray, Sunnyvale, USA) Metastases were diagnosed based on contrast enhancement MRI imaging. The contours were delineated and reviewed by attending radiation oncologists. Gross tumor volume (GTV) was defined as the area of contrast enhancement on T1-weighted MRI images. The dose was prescribed to a 75% (at least) isodose. The precise prescription varied with tumor volume, site, and neurologic symptoms.

PATIENTS' FOLLOW UP

Patients were followed up at regular intervals (every 3 month within 1 year, every 6 month 1 year later) to determine tumor status and the presence of symptoms. All data (clinical, radiological, therapeutic options and response to treatment) were collected by two physicians and the accuracy of the data were confirmed by two administrators. Toxicities were scored according to the Common Toxicity Criteria Adverse Events version 4 (CTCAE v.4). Acute toxicity was defined within 3 months following treatment. Toxicities were graded per RTOG acute central nervous system (CNS) morbidity scoring criteria. Acute toxicity outcomes included patient reported fatigue, headache, nausea/vomiting, dizziness/imbalance, motor neuropathy, sensory neuropathy, edema, neurocognitive dysfunction, and seizures.

TABLE 3 | Numbers of patients with 1–5 toxicities.

Grade	Symptom	*n*
1	Headache	15
	Dizziness	9
	Weakness	4
	Seizure	2
2	Edema	15
	Hemorrhage	2
	Seizure	2
3	Edema	9
	Hemorrhage	2
4	Edema	3
	Hemorrhage	1
	Cerebral necrosis	2
5	Hemorrhage	1
	Cerebral necrosis	2
Total		69

FORMULAS AND STATISTICS

The biological effective dose (BED) was calculated for every metastasis treated according to the following formula, where n is the number of fractions and d is the dose per fraction. Following the Linear quadratic model, a value of 10 was used for the α/β-ratio. BED = nd*[1+d/(α/β)]. OS started with the first day of irradiation and was estimated using Kaplan–Meier analysis. Subgroups were compared using the log-rank test for univariate analysis and the Cox proportional hazard model for multivariable analysis. A $p < 0.05$ was considered statistically significant. A $p < 0.1$ was considered a trend and was the criterion for inclusion in multivariable analysis. All statistical analyses were performed using IBM SPSS Statistics 19 (New York, USA).

Patient characteristics were presented with descriptive statistics. Overall survival (OS) curves were calculated by the Kaplan–Meier method. Median OS and 95% confidence intervals (CIs) were reported. To identify potential predictive factors of OS, a univariate analysis was done with Cox proportional hazards regression within the training cohort. Factors with a $p < 0.05$ in the univariate analysis were entered as candidate variables into a multivariate stepwise Cox regression model (conditional backward selection).

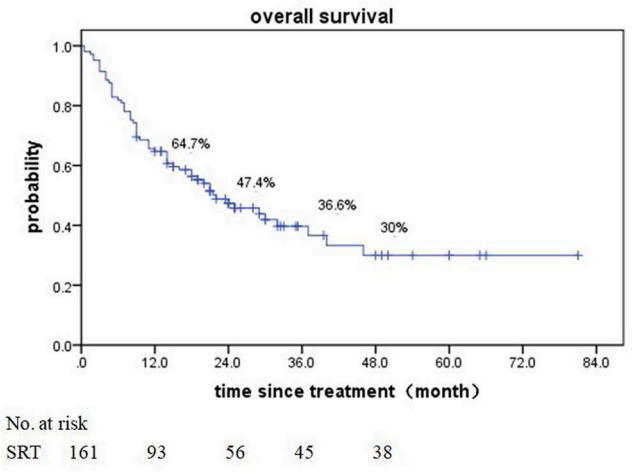

FIGURE 1 | Overall survival of all 161 patients after SRT.

RESULTS

Patient Clinical and Treatment Characteristics (Table 1)

One Hundred and sixty-one patients with 305 brain metastases treated with SRT between February 2012 and June 2017 were enrolled in the study. The number of lesions ranged from 1 to 7 (median number of metastases was one). Most Patients (88.2%) had the KPS of 70 or higher. The majority of the patients were male (64%) and the median age was 61 years (range, 33–87). 32.9% patients showed synchronous brain metastases. 56.5% patients showed extracranial metastases. Ninety-three patients (57.8%) had systemic therapies including chemotherapy or targeted therapy. The patients demonstrated a range of primary malignancies, including non-small-cell lung cancer (NSCLC) (65.2%), gastrointestinal cancer (11.8%), small-cell lung cancer (SCLC) (6.8%), breast cancer (4.3%), renal cell carcinoma (1.9%), and others (10 %). Most patients had oligometastases (87.6%) (13). 61.5% metastases were treated with SRT and 38.5% were treated with SRT + WBRT. The concurrent WBRT was defined according to Hunter et al. (14) as WBRT was completed within 1 month before or after SRT. In our study, 90% patients received concurrent WBRT and 10% patients received WBRT pre or post SRT.

Patients treated with a median dose of 27Gy (20–40 Gy) were with 5–6 fractions. Ninety-one of ninety-nine patients who had neurological symptoms showed remission after SRT. Forty-nine (30%) patients suffered grade 1–2 toxicities with headache, dizziness, weakness, seizure, or edema. Four (2.5%) patients had serious cerebral necrosis and needed long-time treatment of bevacizumab (**Tables 2**, **3**).

Overall Survival

Of patients alive at last follow-up, the median follow-up was 48.5 months. The median overall survival (OS) after SRT was 19 months (range, 0.5–81 month) (**Figure 1**). The median BED was 39.15Gy (range, 16.8–84.375Gy). The median time from diagnosis to brain metastasis was 10M (range, 0–300 month). The median total lesion volume was 8.79 cc (range, 0.113–179.31cc).

TABLE 4 | Univariate analysis of predictors associated with OS.

Variable	HR	95%CI	*p*-value*
Age (≤61 vs. >61)	1.173	0.794–1.733	0.424
Gender (Male vs. Female)	1.481	0.977–2.246	0.064
Tumor volume (>8.79 cc vs. ≤8.79 cc)	1.332	0.855–2.074	0.296
KPS score (>70 vs. ≤70)	0.678	0.454–1.011	0.057
Synchronous BM (No vs. Yes)	0.811	0.538–1.224	0.319
Extracranial metastases (Yes vs. No)	1.640	1.096–2.453	**0.016**
BED_{10} (≥50 vs. <50)	0.547	0.299–0.999	**0.049**
Number of metastases			
Single vs. multiple	0.569	0.384–0.841	**0.005**
1–3 vs. >3	0.351	0.208–0.592	**<0.001**
GPA score (≥2.5vs. ≤2)	0.522	0.340–0.801	**0.003**
RPA classification			
Class I vs. II	0.592	0.373–0.940	**0.026**
Class I vs. III	0.729	0.367–1.450	0.368
Class II vs. III	1.208	0.650–2.245	0.549
Extracranial disease (Uncontrolled vs. Controlled)	1.672	1.127–2.481	**0.011**
Symptoms (YES vs. NO)	1.168	0.780–1.750	0.451
Treatment (SRT vs. SRT+WBRT)	0.930	0.627–1.380	0.717
Targeted therapy (YES vs. NO)	0.162	0.102–0.257	**<0.001**
Chemotherapy (YES vs. NO)	0.587	0.333–1.034	0.065
Tumor type (NSCLC vs. none NSCLC)	0.576	0.388–0.854	**0.006**

**Univariable analysis with Cox proportional hazards regression; CI, confidence interval; Bold values indicate p < 0.05.*

The univariable analyses with Cox proportional hazards regression are shown in **Table 4**. The BED_{10}-SRT (≥50 vs. <50, $p = 0.05$), a GPA of 2.5 significantly influenced OS ($P = 0.003$), the number of lesions treated (single lesion vs. multiple lesions, $p = 0.005$ and 1–3 lesions vs. more than 3 lesions, $p < 0.001$) significantly influenced OS. Targeted therapy also significantly influenced OS (24 months for targeted therapy vs. 13 months for no targeted therapy, $p < 0.001$). Combined with extracranial metastasis significantly influenced OS (13 months for with extracranial metastasis vs. 24 months for without, $p < 0.016$). Furthermore, controlled of extracranial disease also achieved significance (13.5 months for uncontrolled vs. 24 months for controlled, $p = 0.011$). RPA class I achieved a median OS of 31.5 months and class II achieved a median OS of 14 months ($p = 0.026$). Primary tumor type significantly also influenced OS (NSCLC achieved a median OS of 22 months and non-NSCLC achieved a median OS of 11 months, $P = 0.005$).

SRT only, compared with concurrent WBRT, had no statistical significance ($p = 0.717$). There is no statistical significance for the time from diagnosis to brain metastasis ($p = 0.319$). Neurological symptoms before treatment had no significant influence ($p = 0.451$). There was a trend toward better survival rates for together with chemotherapy and higher KPS.

Of all 161 patients, multivariable analyses were shown in **Table 5**. BED_{10}-SRT≥50Gy ($p = 0.027$), targeted therapy

TABLE 5 | Multivariate analysis of predictors associated with OS.

Variable	HR (95%CI)	*P*-value*
Extracranial metastases		
YES	NA	0.509
NO	NA	
BED_{10}		
≥50Gy	0.504 (0.275–0.924)	**0.027**
<50Gy	1 (ref)	
Number of metastases (1–3 vs. >3)		
Single	NA	0.279
Multiple	NA	
1–3	NA	0.529
>3	NA	
GPA score		
≥2.5	NA	0.883
≤2	NA	
Extracrinal disease		
Uncontrolled	1 (ref)	**0.039**
Controlled	0.658 (0.442–0.978)	
Targeted therapy		
YES	0.157 (0.098–0.250)	**<0.001**
NO	1 (ref)	
RPA classification		
Class I	NA	0.628
Class II	NA	
Tumor type		
NSCLC	NA	0.182
None NSCLC	NA	

**Multivariate analysis using the Cox proportional hazards model; NA, Not Available; CI, confidence interval; Bold values indicate p < 0.05.*

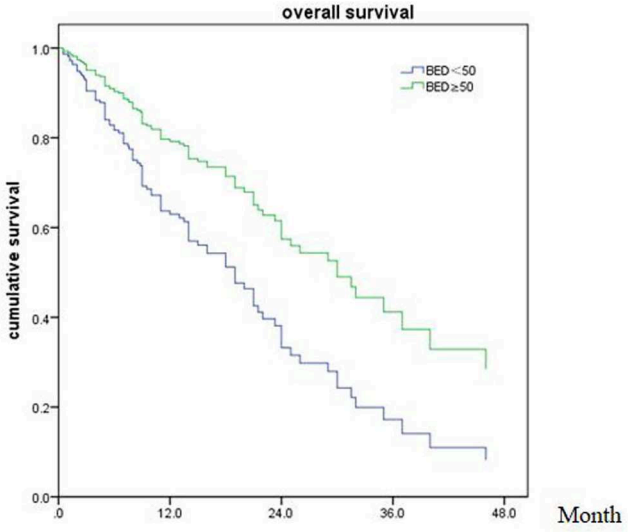

FIGURE 2 | Overall survival of patients with BED ≥ 50 Gy and BED < 50 Gy ($p = 0.027$).

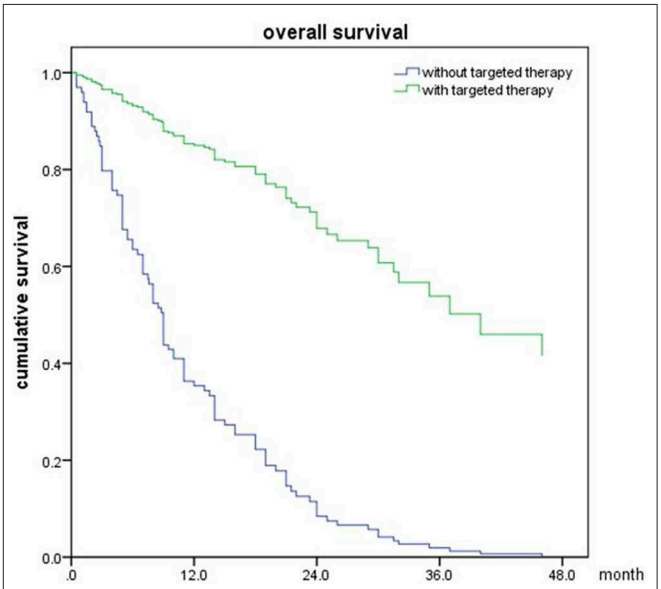

FIGURE 3 | Overall survival of patients with targeted therapy and no targeted therapy ($p < 0.001$).

($p < 0.001$) and controlled of extracranial disease ($p = 0.039$) were significant predictive factors (**Figures 2**–**4**).

In the meantime, the median OS after SRT was 22 months (range, 0.5–81 month) in NSCLC (**Figure 5**). The univariable analyses are shown in **Table 6**. In multivariable analysis, controlled of extracranial disease ($p = 0.012$) and targeted therapy (EGFR-TKI) ($p < 0.001$) were associated with improved OS (**Table 7**; **Figures 6**, **7**).

DISCUSSION

In our study, we collected data of 161 eligible patients with BM in this study. The results showed that higher BED_{10}-SRT, controlled of extracranial disease and targeted therapy were significant predictive factors.

WBRT is the common approach to the treatment for the patients with BM historically. Compared with WBRT, SRT alone or in combination with other modalities is generally used as the standard option for patients with BM especially oligometastasis, which leads to more clinical benefit and less toxicity.

For multiple brain metastases, WBRT was a standard choice for most cases over a long period of time. But the neurocognitive dysfunction cannot be ignored in longtime survival patients. Therefore, SRT has been more and more commonly used recently. Recent studies have shown that local treatments may minimize long-term neurocognitive dysfunction and improve quality of life (QOL) without compromising OS (15). Contrarily, Brown et al. (16) demonstrates that SRT alone may be associated with improved neurocognitive effects and quality of life despite the increased intracranial relapse rate. However, there have been no definitive conclusions whether treatment with SRT is as

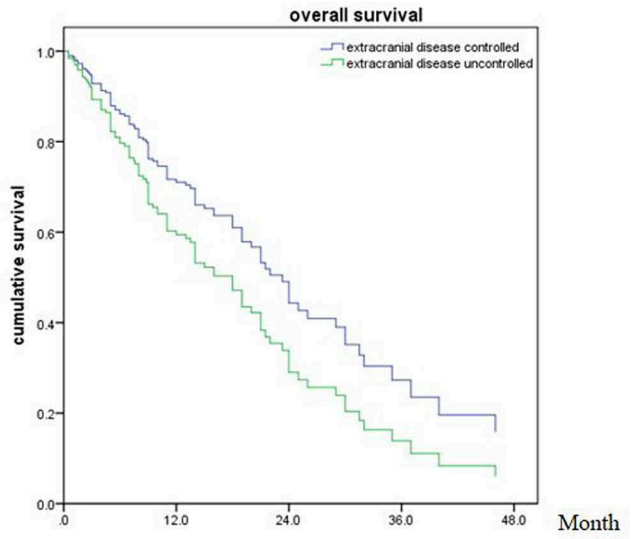

FIGURE 4 | Overall survival of patients with extracranial disease controlled and uncontrolled ($p = 0.039$).

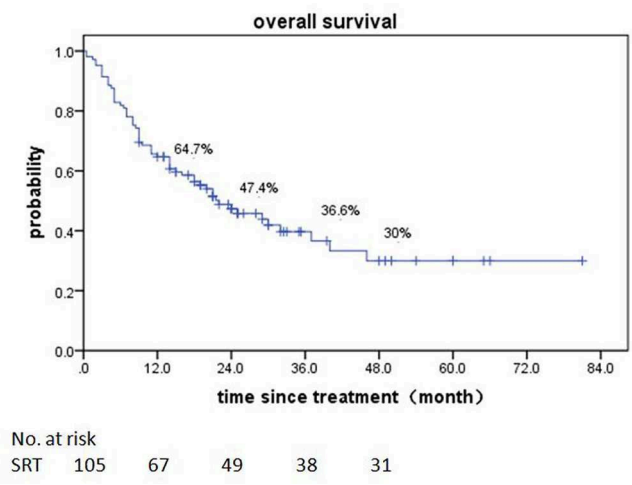

FIGURE 5 | Overall survival of NSCLC patients after SRT.

TABLE 6 | Univariate analysis of predictors associated with OS in NSCLC.

Variable	HR	95%CI	*p*-value*
Age (≤61 vs. >61)	1.193	0.794–1.733	0.502
Gender (Male vs. Female)	2.275	0.977–2.246	**0.009**
Tumor volume (≤8.79 cc vs. >8.79 cc)	1.332	0.855–2.074	0.296
KPS score (>70 vs.≤70)	0.674	0.401–1.135	0.138
Synchronous BM (No vs. Yes)	0.729	0.435–1.222	0.231
Extracranial metastases (Yes vs. No)	1.603	0.956–2.689	0.074
BED_{10} (≥50 vs. <50)	0.547	0.299–0.999	0.090
Number of metastases (1–3 vs. >3)			
Single vs. multiple	0.665	0.397–1.113	0.121
1–3 vs. >3	0.386	0.165–0.908	**0.029**
GPA score (≥2.5 vs. ≤2)	0.628	0.370–1.067	0.085
RPA classification			
Class I vs. II	0.543	0.289–1.020	0.057
Class I vs. III	0.729	0.367–1.450	0.368
Class II vs. III	1.208	0.650–2.245	0.549
Extracranial disease (Uncontrolled vs. Controlled)	2.096	1.244–3.532	**0.005**
Symptoms (Yes vs. No)	1.214	0.723–2.039	0.463
Treatment (SRT vs. SRT+WBRT)	1.204	0.721–2.009	0.473
Targeted therapy (YES vs. NO)	0.161	0.088–0.294	**<0.001**
Chemotherapy (YES vs. NO)	0.587	0.333–1.034	0.083

**Univariable analysis with Cox proportional hazards regression; CI, confidence interval; Bold values indicate p < 0.05.*

TABLE 7 | Multivariate analysis of predictors associated with OS in NSCLC.

Variable	HR (95%CI)	*P*-value*
Number of metastases (1–3 vs. >3)		
1–3	NA	0.513
>3	NA	
Gender		
Male	NA	0.378
Female	NA	
Extracranial disease		
Uncontrolled	1 (ref)	**0.012**
Controlled	0.512 (0.303–0.865)	
Targeted therapy		
YES	0.168 (0.092–0.307)	**<0.001**
NO	1 (ref)	

**Multivariate analysis using the Cox proportional hazards model; NA, Not Available; CI, confidence interval. Bold values indicate p < 0.05.*

effective as that with WBRT or WBRT plus SRT in some specific number of brain metastases.

The prognostic factors related to better OS for patients with brain metastases have been studied in a large amount of clinical trials. Many prognostic scoring systems (17) have been proposed in the last 30 years to define the prognosis and better therapeutic option.

Study series showed that the factors of RPA class, GPA score, KPS, primary tumor category, extracranial diseases status, and number of brain lesions were variables associated with overall survival post-SRT (18, 19). A smaller trial (20) showed that combined WBRT and radiosurgery for patients with two to four brain metastases significantly improves local control of brain disease, but no improvement of survival.

Besides intracranial tumor burden, other clinical factors play an important role in treatment decisions. Performance status, age, extracranial metastases, and primary tumor control are all present in the GPA classification (21). As small samples and the paucity of data for SRT treating brain metastases, we analyzed the outcomes of patients with brain metastases treated with SRT with or without other treatments in different primary cancers.

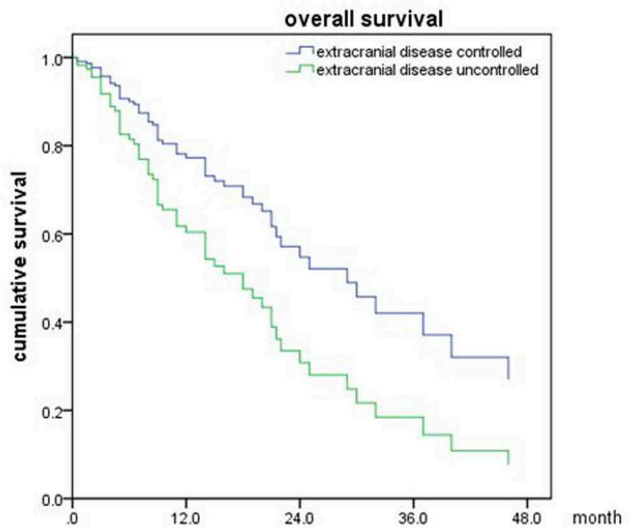

FIGURE 6 | Overall survival of NSCLC patients with extracranial disease controlled and uncontrolled ($p = 0.012$).

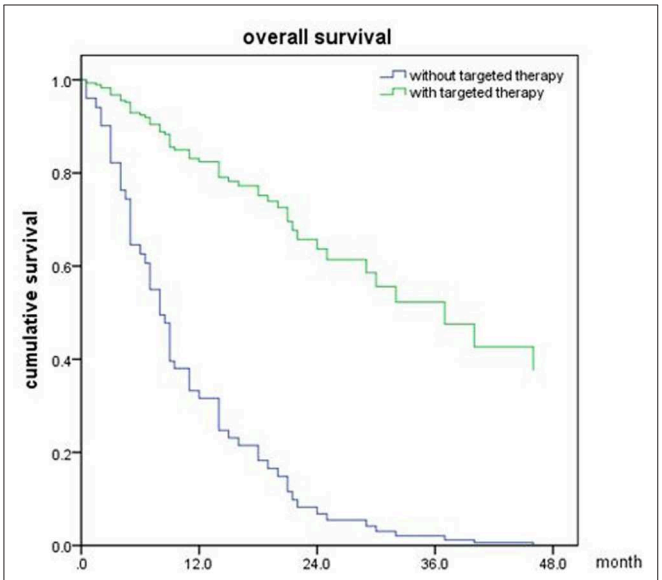

FIGURE 7 | Overall survival of NSCLC patients with targeted therapy and no targeted therapy ($p < 0.001$).

Similarly, our study also explored extracranial diseases status (controlled vs. not controlled) were variables predicting OS. But we didn't find the relationship between OS and RPA, GPA, KPS score as well as the number of brain lesions. Possibly because patients who received SRT had better KPS and less neurological symptoms before treatment.

The most common primary cancers that metastasize to the brain are lung cancer, renal cancer, melanoma, colorectal cancer, and breast cancer. About 6% of those patients, brain metastases occur within 1 year of the diagnosis of the primary cancer (22). The failure of medical therapies in BM was well-known due to the lack of blood brain barrier (BBB) penetration. Fortunately the molecular targeted therapies have shown efficacy in the management of BM patients with activating mutations. Moreover, the target therapy was observed as a prognostic factor in BM patients, which can be effective for both intracranial as well as extracranial disease post-SRT.SRT alone had been widely accepted for treatment of oligo-brain metastases (1–4 brain metastases) In previous studies, the role of radiosurgery alone for patients with multiple brain metastases is still controversial. WBRT has classically been the standard treatment, while radiosurgery is commonly considered as a salvage therapy (23, 24).

Although the addition of WBRT improves intracranial control, it induces an increased risk of cognitive impairment without benefit in OS in the population of patients with brain metastasis, including patients with NSCLC (25–27).

A multi-institutional prospective observational study enrolled 1,194 patients with 1–10 brain metastases with an accumulated volume of all metastases <15 ml, treated with radiosurgery, showed that overall survival and toxicity did not differ between those with the 2–4 and 5–10 metastases groups ($p = 0.78$ median overall survival, 10.8 vs. 10.8 months, respectively) (28), which suggests that SRT-alone may be a reasonable treatment for patients with multiple brain metastases. The same result was also obtained in our study, WBRT was not independently associated with improved OS, no matter the primary tumor category or the number of brain lesions. However, the prospective randomized clinical trials are needed to evaluate the role of radiosurgery alone with omission of upfront WBRT in patients with multiple BM.

In the meanwhile, BED_{10} as an independent prognostic factor with OS was rarely reported before. In our study, an average prescription dose of 27Gy (20–40Gy) in 5–6 fractions was schemed, which was believed to be safe and effective dose for BM (29). Kumar et al. (30) reported that a higher total BED_{10} was statistically significant for improved local control ($p = 0.04$) with a threshold $BED_{10} \geq 48$Gy associated with better local control for BM patients after surgical resection. We observed that $BED_{10} \geq 50$Gy was associated with overall survival in the whole population of patients with BM, but not in BM from NSCLC. Previously the medical treatment was limited in BM patient because of blood-brain barrier. In the last decade, the targeted therapies of TKI had contributed to local control with concurrent radiotherapy for most NSCLC with activating mutations. Based on our data, we would recommend a higher BED_{10} for the patients lack of effective target drug or with relative radiation resistance primary tumor.

Some studies have reported nearly 10% of new NSCLC patients have brain metastases at diagnosis (31) and a further 25–40% patients will develop brain metastases during the course of disease (32). The NSCLC patients with EGFR mutation have a higher diagnosis rate of BM. The median OS is ∼3–6 months or even less for patients without treatment (5, 33). A retrospective study showed SRT achieved better OS than WBRT or EGFR TKI alone (46 vs. 30 vs. 25 m respectively) in NSCLC patients with EGFR mutated (34).So cranial radiotherapy plays a critical role in

patients with BM in NSCLC. In our research, we also find that EGFR-TKI ($p < 0.001$) and controlled of extracranial diseases ($p = 0.012$) were associated with improved OS in NSCLC patients.

Numerous studies have demonstrated that radiotherapy plus EGFR-TKIs led to more promising results than EGFR-TKIs or radiotherapy alone (35). SRT might be an optimal treatment for patients with EGFR mutations rather than WBRT. Thus, extracranial disease control is of the highly relevant with the OS of BM patients.

There are also some limitations in this study. Firstly, this is a retrospective study in a single institution, which included unrecognized biases and confounding factors. Secondly we could not collect much more details about the progression of the BM lesions during the long interval time of the follow-up, which caused the unmeasured intracranial PFS.

CONCLUSION

As the development of radiotherapy, SRT adoption has dramatically improved the treatment outcomes compared with conventional fractionated radiotherapy for the BM patients. There was no difference in overall survival that has been observed between SRT alone compared to SRT plus WBRT in limited number of BM patients. The concurrent WBRT with SRT should be a cautious choice for selected patients. Our study confirmed that excellent extracranial disease controlled and BED_{10}-SRT≥50Gy may predict a favorable prognosis in BM patients treated with SRT.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

LG and SQ have made equal contribution to the study and provided the largest writing contribution of the manuscript. HZ was the main principal of this study. XZ, XJ, YC, ZJ, YS, FC, and FF have performed collection and organization of data. All authors approved it for publication.

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