

Critical Review

Single-Fraction Stereotactic Body Radiation Therapy: A Paradigm During the Coronavirus Disease 2019 (COVID-19) Pandemic and Beyond?



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Abstract

Purpose: Owing to the coronavirus disease 2019 (COVID-19) pandemic, radiation oncology departments have adopted various strategies to deliver radiation therapy safely and efficiently while minimizing the risk of severe acute respiratory syndrome coronavirus-2 transmission among patients and health care providers. One practical strategy is to deliver stereotactic body radiation therapy (SBRT) in a single fraction, which has been well established for treating bone metastases, although it has been infrequently used for other extracranial sites.

Methods and Materials: A PubMed search of published articles in English related to single-fraction SBRT was performed. A critical review was performed of the articles that described clinical outcomes of single-fraction SBRT for treatment of primary extracranial cancers and oligometastatic extracranial disease.

Results: Single-fraction SBRT for peripheral early-stage non-small cell lung cancer is supported by randomized data and is strongly endorsed during the COVID-19 pandemic by the European Society for Radiotherapy and Oncology-American Society for Radiation Oncology practice guidelines. Prospective and retrospective studies supporting a single-fraction regimen are limited, although outcomes are promising for renal cell carcinoma, liver metastases, and adrenal metastases. Data are immature for primary prostate cancer and demonstrate excess late toxicity in primary pancreatic cancer.

Conclusions: Single-fraction SBRT should be strongly considered for peripheral early-stage non-small cell lung cancer during the COVID-19 pandemic to mitigate the potentially severe consequences of severe acute respiratory syndrome coronavirus-2 transmission. Although single-fraction SBRT is promising for the definitive treatment of other primary or oligometastatic cancers, multi-fraction SBRT should be the preferred regimen owing to the need for additional prospective evaluation to determine long-term efficacy and safety.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has compelled the oncology community to rethink cancer treatment delivery to maintain high-quality and effective cancer care while minimizing the risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission among medically vulnerable patients and health care providers.¹ Patients with cancer in particular have a higher risk of morbidity and mortality from COVID-19.²⁻⁵

For radiation oncology, one practical strategy to mitigate the risk of contracting SARS-CoV-2 is to shorten radiation therapy regimens.⁶ As such, stereotactic body radiation therapy (SBRT) delivered in up to 5 fractions should be preferred over conventionally fractionated regimens when medically appropriate.⁷⁻⁹ Abbreviating SBRT regimens whenever possible should also be considered; delivery of a single fraction not only offers the most convenient option for patients with cancer but also represents a means to reduce the risk of SARS-CoV-2 transmission compared with multi-fraction regimens.

Ablative single-fraction radiation therapy dates back to the 1950s, when Dr Lars Leksell developed the gamma knife for stereotactic radiosurgery to treat intracranial lesions.¹⁰ In the 1990s, investigators at the Karolinska Institute pioneered the use of single-fraction SBRT in extracranial malignancies.¹¹ Since that time, advances in image guidance, motion management, and treatment planning have further expanded the ability to deliver high-quality SBRT for extracranial targets, especially for spinal metastases, for which the single- and multi-fraction SBRT literature is extensive.¹² In contrast, the published literature on single-fraction SBRT to definitively treat visceral anatomic targets and extraspinal bone metastases is limited although expanding.

The objectives of this critical review are to appraise the currently available data on the efficacy and toxicity of single-fraction SBRT and discuss the potential of expanding indications in the definitive treatment of primary extracranial malignancies in addition to oligometastatic extraspinal disease. The published prospective studies involving the use of single-fraction SBRT in the definitive and oligometastatic settings are summarized in [Tables 1](#) and [2](#), respectively.

Methods and Materials

A PubMed search of published articles in English related to single-fraction SBRT was performed using the keywords “single fraction/dose stereotactic body radiotherapy or radiation therapy,” “cancer,” “metastasis,” and “oligometastatic.” Studies that reported on the use of single-fraction SBRT in the definitive treatment of

primary extracranial cancers and oligometastatic extraspinal disease were included in this critical review.

Thoracic

Some of the initial advances in extracranial SBRT were pioneered for the treatment of thoracic malignancies. Several landmark studies assessed the feasibility and safety of single-fraction SBRT for lung tumors.^{13,14} Decades of increasingly widespread use have led to a range of acceptable prescriptions being used with excellent local control (LC) as long as the biologically effective dose (BED) is significantly high.¹⁵ Although a 2013 survey found only 1% of surveyed United States practitioners treated early-stage peripheral T1N0 non-small cell lung cancer (NSCLC) to 25 to 34 Gy \times 1 fraction,¹⁶ single-fraction treatments remain strongly justifiable by extant phase II and retrospective data.¹⁷

Peripheral early-stage NSCLC

Radiation Therapy Oncology Group 0915 was a phase II multi-center trial that randomized patients with T1-T2 peripheral NSCLC to 34 Gy \times 1 (BED₁₀ 149 Gy) versus 48 Gy in 4 fractions (BED₁₀ 106 Gy); planning was done with heterogeneity corrections. At a median follow-up of 30.2 months, comparable tumor control rates and toxicities were demonstrated, with 1-year LC of 97%¹⁸ for 34 Gy \times 1, thus demonstrating the efficacy and safety of single-fraction SBRT. These excellent outcomes persisted on long-term follow-up with 5-year LC of 89.4% and grade \geq 3 adverse events reported in <5% for the 34 Gy cohort.¹⁹ These findings were corroborated by another phase II clinical trial that randomized 98 patients with early-stage peripheral NSCLC to 30 Gy \times 1 fraction or 20 Gy \times 3 fractions (not using heterogeneity corrections), showing equivalent LC at median follow-up of 4.5 years.²⁰ The grade \geq 3 adverse event rate was 16% in the 30 Gy arm, and improved quality-of-life was noted with single-fraction treatment.²⁰ A retrospective analysis showed similar outcomes using prescription doses of either 30 or 34 Gy.²¹ Taken together, 30 to 34 Gy \times 1 fraction is safe and effective for peripheral tumors. Single-fraction SBRT should be strongly considered for peripheral early-stage NSCLC, especially during the ongoing COVID-19 pandemic according to a recently published European Society for Radiotherapy and Oncology–American Society for Radiation Oncology (ESTRO-ASTRO) consensus statement.²²

Central tumors

The 2 completed randomized single versus multi-fraction trials were limited to patients with “peripheral” tumors, characterized as >2 cm from the proximal bronchial tree as defined in Radiation Therapy Oncology Group 0236.²³ Central tumors are associated with higher

Table 1 Prospective studies involving the use of single-fraction SBRT in the definitive treatment of extracranial malignancies

Authors (year)	Study type	Primary diagnosis	N ^o patients	Dose (Gy)	Median follow-up (months)	Local control	Acute/late grade ≥ 3 toxicity
Videtic et al (2015, 2019) ^{18,19}	Phase II	NSCLC	94	34	30.2	1 y 97% 5 y 89.4%	2.6%
Singh et al (2019) ²⁰	Phase II	NSCLC	98	30	53.8	2 y 94.9%	16%
Koong et al (2004) ³⁵	Phase I	Pancreas	15	15-25	NR	1 y 100%	0% acute
Schellenberg et al (2008) ³⁶	Phase I/II	Pancreas	16	25	9.1	1 y 100%	6% acute 13% late
Schellenberg et al (2011) ³⁸	Phase I/II	Pancreas	20	25	11.8	1 y 94%	0% acute 5% late
Stahler et al (2015) ⁵⁰	Phase I/II	RCC	30	25	28.1	9 mo 98%	0% acute 0% late
Siva et al (2017) ⁵²	Phase I/II	RCC	17	26	24	2 y 100%	0% acute 3% late
Greco et al (2018) ^{60,*}	Phase II	Prostate	15	24	NR	NR	0% acute

Abbreviations: NR = not reported; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.

* Abstract only.

risk of grade 3 to 5 toxicities, and single-fraction SBRT should be approached cautiously. An early phase I dose-escalation trial of single-fraction SBRT from Stanford noted pulmonary toxicities occurred at doses of at least 25 Gy, including 3 posttreatment deaths.¹⁴ Toxicities were noted 5 to 6 months after single-fraction SBRT, with the majority occurring in patients treated for central tumors. Similarly, the Roswell Park Cancer Institute evaluated outcomes of 42 patients who underwent SBRT for centrally located lung tumors; 1-year LC was 100% among the 11 patients treated with 26 to 30 Gy \times 1, although 5

patients experienced grade 3 to 4 toxicities at a median of 14.6 months posttreatment.²⁴ This included a bronchopulmonary hemorrhage after treatment to 26 Gy, necessitating pneumonectomy and ultimately leading to death.²⁵ In comparison, the same group published outcomes of single-fraction SBRT to 30 Gy in peripheral early-stage NSCLC, with a complete absence of grade ≥ 3 toxicities at a median follow-up of 22 months.²⁶

Single-fraction SBRT may be feasible for central lung tumors at lower doses. Although standard SBRT protocols prescribe a uniform dose regimen for lung tumors

Table 2 Prospective studies involving the use of single-fraction SBRT in the treatment of extracranial/extraspinal oligometastatic disease

Authors (year)	Study type	Primary diagnosis	No. patients	No. metastases	Treated site(s)	Dose (Gy)	Median follow-up (months)	Local control	Acute/late grade ≥ 3 toxicity
Siva et al (2018) ⁷²	Phase I/II	Prostate	33	50	Bone, lymph node, or both	20	NR	1 y 97% 2 y 93%	3%
David et al (2020) ⁷¹	Phase I/II	Breast	15	19	Bone	20	24	2 y 100%	0% acute
Nuytens et al (2015) ⁷⁷	Phase II	Multiple	30	57	Lung	30	36	2 y 74%	17% acute 10% late
Goodman et al (2010) ⁸⁵	Phase I	Multiple	26	40	Liver	18-30	17.3	1 y 77%	0%
Meyer et al (2016) ⁸⁶	Phase I	Multiple	14	17	Liver	35-40	30	2 y 100%	0%

Abbreviations: NR = not reported; SBRT = stereotactic body radiation therapy.

irrespective of tumor size, prior studies suggest that smaller tumors may be controlled with lower doses than larger tumors. Stanford treated 83 patients with 97 tumors using a volume-adapted dose strategy, prescribing 18 to 25 Gy \times 1 fraction (BED < 100 Gy) for small tumors with gross volume <12 cm³.²⁷ LC in this cohort was >90% at 12 months, and no grade \geq 3 toxicities were noted at a median follow-up of 13.5 months. A retrospective study from Rome demonstrated 1-year LC of 89% and minimal grade 3 toxicities after 23 Gy \times 1 fraction in 49 central tumors at a median follow-up of 15 months.²⁸ Additionally, the Peter MacCallum Cancer Center showed acceptable LC with 18 Gy \times 1 fraction to central targets; with median follow-up of 2.1 years, no grade \geq 3 toxicities were reported.²⁹

Single-fraction SBRT has not been established as an appropriate alternative to multi-fraction SBRT for central lung cancers. Future studies should evaluate whether such an approach is feasible for central lesions using novel image guidance modalities such as magnetic resonance imaging (MRI), which provides superior soft tissue visualization compared with computed tomography, continuous intrafraction visualization, and daily online adaptive replanning to achieve optimal target and normal organ doses.^{30,31}

Unique clinical scenarios: Synchronous tumors and recurrent disease in the lung

Expanding beyond definitive treatment for standard early-stage disease, SBRT may be used for the definitive management of both synchronous (\geq 2) lung tumors and locally recurrent disease. The early Stanford study of tumor volume-adapted SBRT dosing included 20 patients with multiple (2-4) tumors treated during the same treatment course, with no grade \geq 4 toxicities.²⁷ More recently, a single-institution series compared outcomes of 26 synchronous primary patients versus those with nonsynchronous disease, including some utilization of single-fraction SBRT in both groups. At a median follow-up of roughly 1 year, no significant differences were noted with respect to survival or progression patterns between the groups.³² An international collaboration between Canada and the Netherlands treated a small minority (4%) of the total 84 patients with synchronous lung tumors to 34 Gy \times 1 fraction. SBRT was delivered using multi-isocenter volumetric-modulated arc therapy technique, as synchronous lesions were at a substantial distance from one another (half of the patients had bilateral disease). Many patients underwent simultaneous treatment to all lesions during a single session and severe toxicity was uncommon, with grade \geq 3 events observed in only 2% of patients.³³

Another increasingly common scenario is the patient with recurrent or persistent lung cancer despite prior definitive treatment. In the absence of alternative

interventions, SBRT represents a potential treatment option for these patients. A retrospective series evaluated outcomes of 100 patients who were treated with SBRT for recurrent lung cancer, 31% of whom received 20 Gy \times 1 fraction, with the remainder being treated to 45 to 60 Gy in 3 to 5 fractions.³⁴ At a median follow-up of 51 months, there was no reported severe toxicity. Single-fraction SBRT was associated with inferior overall survival on univariate analysis; this finding was subject to multiple confounders and accordingly lost significance on multivariable regression. However, general prudence suggests that single-fraction SBRT is most appropriate for radiation-naïve patients with peripherally located tumors in whom single-fraction dose escalation to \geq 30 Gy is feasible.

Abdomen/pelvis

Pancreatic cancer

The feasibility and toxicity of using single-fraction SBRT in the treatment of locally advanced pancreatic cancer was first reported in a phase I study from Stanford.³⁵ A total dose of 25 Gy \times 1 fraction achieved 100% LC without causing significant acute gastrointestinal (GI) toxicities.³⁵ In subsequent studies by the same group, this single-fraction SBRT regimen continued to demonstrate 1-year LC of >90% for locally advanced pancreatic cancer, but was associated with significant risk of late GI toxicities when gemcitabine was used before and after SBRT.³⁶⁻³⁹ A single-fraction SBRT study using CyberKnife reported 19% and 6% acute grade \geq 2 and grade \geq 3 GI toxicity rates, respectively, as well as 47% and 13% late grade \geq 2 and grade \geq 3 GI toxicity rates, respectively.³⁶ When linear accelerator (LINAC)-based SBRT was used to deliver the same single-fraction dose, acute grade \geq 2 and grade \geq 3 GI toxicity rates were 15% and 0%, respectively; late grade \geq 2 and grade \geq 3 GI toxicities were 15% and 5%, respectively.³⁸

Given the significant risk of late GI toxicities associated with single-fraction SBRT, various multi-fraction regimens (ie, 33 Gy in 5 fractions, 24-36 Gy in 3 fractions, or 25-50 Gy in 5 fractions) were evaluated and shown to confer good LC with less severe GI toxicity.³⁹⁻⁴⁶ Of note, 33 Gy in 5 fractions was estimated to be equivalent to 25 Gy \times 1 fraction in terms of BED using the universal survival curve.⁴⁷ At present, multi-fraction SBRT is conditionally recommended by ASTRO in the 2019 clinical practice guidelines for the management of locally advanced and borderline resectable pancreatic cancer.⁸

Renal cell carcinoma

First-line therapy for renal cell carcinoma (RCC) is surgical resection. For patients with significant medical comorbidities or unresectable disease, SBRT is an

emerging treatment option.⁴⁸ Several retrospective studies have reported outcomes of single-fraction SBRT to the kidney. Hanzly et al⁴⁹ retrospectively evaluated 4 patients who were prescribed 15 Gy \times 1 fraction for rapidly growing renal masses without histologic confirmation. Three of the 4 patients had tumor size reduction (average 0.85 cm) at 13.8 months follow-up. No toxicities or significant decline in renal function from baseline were observed. From a prospective institutional database that included 45 renal tumors (15 transitional cell carcinoma and 30 RCC) in 40 patients treated with CyberKnife to 25 Gy \times 1 fraction, 98% LC rate was reported at 9 months posttreatment.⁵⁰ Renal function remained stable from baseline to follow-up and there was no grade 3 toxicity. A pooled analysis from the International Radiosurgery Oncology Consortium of Kidney assessed the role of SBRT in the management of RCC.⁴⁸ Of the 233 patients with RCC from 9 institutions analyzed, 118 underwent SBRT in a single fraction ranging from 14 to 26 Gy with a median follow-up of 2.6 years. The single-fraction SBRT cohort was younger and had smaller tumors, with mean diameter of 37.1 mm. Single-fraction treatment caused a higher rate of nausea (17.0% vs 6.8%; $P = .005$), although otherwise there was no difference in toxicity. There was no observed difference in reduction of mean renal function (-6.1 mL/min vs -4.9 mL/min; $P = .660$). Multivariable analysis demonstrated poorer progression-free survival (PFS) (hazard ratio, 1.13; $P = .02$) and cancer-specific survival (hazard ratio, 1.33; $P = .01$) among patients who received multi-fraction SBRT. LC at 4 years was excellent (97.8%); 1 local failure occurred in the single-fraction cohort and 2 local failures in the multi-fraction cohort ($P = .60$).

In a pilot trial investigating the immunologic effect of high dose radiation therapy on RCC cell lines and the safety of SBRT followed by nephrectomy, 16 patients with metastatic RCC were enrolled.⁵¹ Each patient received 15 Gy \times 1 and then 14 proceeded to nephrectomy 4 weeks after treatment. Only 1 patient experienced grade 3 toxicity (anemia), whereas acute grade 2 toxicities were experienced by 4 patients in total. Qualitative reports from surgeons noted that surgery was not significantly more difficult, and no postsurgical complications were reported. Furthermore, a prospective interventional trial was conducted to assess the feasibility and safety of SBRT for RCC.⁵² Thirty-seven patients were enrolled and stratified according to RCC size. Seventeen patients with RCCs < 5 cm in diameter received 26 Gy in a single fraction and were followed for a minimum 12 months. Overall survival rates at 1 and 2 years were 100% and 92%, respectively. After SBRT, tumor size reduced in 61% of RCCs. No acute grade 3 toxicities were observed and only 1 grade 3 late toxicity was seen (fatigue). Mean baseline glomerular filtration rate was 55 mL/min, which decreased by 11 mL/min from baseline at 1- ($P < .001$) and 2-year follow-up. No subgroup analysis of the

single-fraction cohort was available. This treatment regimen is presently being investigated in a multi-center phase II clinical trial (NCT02613819).⁵³

Single-fraction SBRT for primary RCC appears to be a viable treatment option in unresectable or comorbid patients, although additional prospective evaluation is warranted.

Prostate cancer

Definitive treatment options for localized prostate cancer include surgical resection, external beam radiation therapy, brachytherapy or active surveillance. Broadly, the evolution of fractionated radiation therapy has sought to take advantage of tumors having a higher α/β ratio than late-responding surrounding normal tissues. Prostate cancer, however, has a low α/β ratio, with estimates of 1.85 Gy.⁵⁴ As such, the rationale for SBRT in prostate cancer is to harness the cancer's sensitivity to high dose per fraction treatment. Current dose-fractionation schedules run upwards of 7 weeks with daily bowel/bladder preparation, which can be burdensome for patients. Evidence for moderately⁵⁵⁻⁵⁷ and extremely hypofractionated^{58,59} radiation therapy is becoming increasingly used. Despite this, the current literature reporting the safety and efficacy of single-fraction SBRT in prostate cancer is scarce.

In a phase II randomized trial investigating SBRT for intermediate risk prostate cancer, presented in abstract form only,⁶⁰ 30 hormone-naïve patients were randomized to receive 45 Gy in 5 fractions or 24 Gy \times 1. At 16 months median follow-up, there were no grade ≥ 2 toxicities in either group and no significant difference in mean Expanded Prostate Cancer Index Composite (EPIC) scores for all domains. Prostate-specific antigen at 18-month follow-up demonstrated similar responses between the 2 groups (< 1 ng/mL). There was no detectable disease on MRI in any case at 6 months. A multi-center phase I/II study assessing the toxicity and efficacy of single-fraction SBRT of 19 Gy in patients with low- to intermediate-risk prostate cancer is currently underway.⁶¹

Given the paucity of data for single-fraction SBRT in prostate cancer, some lessons may be extrapolated from brachytherapy experience to provide a strong rationale to further evaluate a single-fraction approach. A phase II study comparing single- and multi-fraction high dose rate (HDR) brachytherapy for intermediate- and high-risk localized prostate cancer included 293 patients, 49 of whom received 19 or 20 Gy \times 1 fraction.⁶² At 4-year follow-up, biochemical recurrence free survival was 94% for the single fraction arm (no difference in 2- and 3-fraction arms; $P = .54$). Grade 3 urinary toxicity was worse in the 3-fraction arm ($P = .01$). Contrastingly, Morton et al⁶³ showed inferior outcomes with single-fraction brachytherapy. In 170 patients with either low or intermediate prostate cancer randomized to receive

HDR using 19 Gy \times 1 fraction ($n = 87$) versus 13.5 Gy \times 2 fraction ($n = 83$), there was a significant difference in 5-year biochemical disease free survival (73.5% vs 94.9%; $P = .001$). The cumulative incidence of biopsy proven local failure at 5 years for the single-fraction arm was 29.4%. There was no difference in late toxicity between the 2 arms.

The evidence supporting single-fraction SBRT for prostate cancer is in its infancy. The potential for SBRT to harness prostate cancer's favorable radiobiological characteristics makes this an enticing area for further investigation. Results from single-fraction HDR brachytherapy, especially poorer 5-year biochemical disease free survival in 1 randomized study, urges caution in rapid adoption of this approach. With global practices heading toward truncation of radiation therapy courses to moderate and extreme hypofractionation for prostate radiation therapy, consideration should be given to await more robust data to emerge in the single-fraction setting before recommending this approach.

Oligometastatic disease

Multiple randomized phase II trials have demonstrated that the use of multi-fraction SBRT in addition to chemotherapy can achieve significantly prolonged PFS and also potentially overall survival compared with chemotherapy alone in patients with 1 to 5 metastatic lesions.⁶⁴⁻⁶⁶ Although most patients who received SBRT in these trials had 3 or fewer lesions, the potential indication of SBRT for 4 or more lesions is being evaluated (NCT03721341). It is in this context of delivering SBRT to multiple lesions that single-fraction SBRT is particularly attractive, which not only enhances patient convenience, but also optimizes resource utilization. There are promising data demonstrating the efficacy and safety of single-fraction SBRT to treat oligometastases, although these findings are limited to single-institution retrospective reviews and small prospective trials.⁶⁷⁻⁷³

An earlier retrospective analysis included 20 patients with recurrent and metastatic abdominopelvic cancers, 87% of whom were treated with SBRT to a total median dose of 18 Gy (range, 10-25 Gy) in 1 fraction and the remaining in 2 or 3 fractions.⁶⁷ At the median follow-up of 6.3 months, the authors reported 48% overall response rate (sum of complete and partial responses); 74% LC rate (sum of response rate and stable disease); 85% metabolic response rate (sum of complete and partial responses based on standardized uptake value_{max} assessment of fluorodeoxyglucose-positron emission tomography scans); 55% and 6% grade 1/2 acute upper and lower GI toxicities, respectively; and 0% grade ≥ 3 toxicity at 1 month post-SBRT. In a more recent retrospective review of 132 patients mostly with genitourinary, GI, and lung primaries and 186 sites of metastatic disease

(predominantly lung and bone metastases) treated with single-fraction SBRT, the 1- and 2-year freedom from widespread disease were 75% and 52%, respectively, whereas 1- and 2-year freedom from local progression were 90% and 84%, respectively.⁶⁹ The only grade ≥ 3 treatment-related toxicity was a lumbar vertebral compression fracture. The prescription dose for single-fraction SBRT in this study varied depending on the anatomic site of metastatic disease; for instance, 20 Gy was used for spine, 18 Gy for centrally located lung tumors, 20 Gy for bone (from breast and prostate cancer), and 24 Gy for nonvertebral bone and soft tissues.⁶⁹ This study highlighted that single-fraction SBRT may be comparable to multi-fraction SBRT in achieving high rates of LC and freedom from widespread disease with minimal toxicity in the oligometastatic setting. In another single-institution retrospective review of patients with oligometastatic prostate cancer who developed 1 to 3 abdominopelvic lymph node metastases after radical treatment to the primary (radical prostatectomy or definitive radiation therapy), single-fraction SBRT of 24 Gy resulted in 1- and 2-year biochemical progression-free survival of 40% and 26%, respectively, and no grade ≥ 1 treatment-related toxicity.⁷⁰

Furthermore, in the single-institution prospective POPSTAR trial from the Peter MacCallum Cancer Center that included 33 patients with oligometastatic prostate cancer with 1 to 3 metastases involving bone, lymph node, or both, single-fraction SBRT of 20 Gy resulted in a 1- and 2-year local PFS of 97% and 93%, and a 1- and 2-year distant PFS of 58% and 39%, respectively.⁷² Two grade 2 and 1 grade 3 fractures were observed.⁷² The 2-year freedom from androgen deprivation therapy was 48% in those patients who were not on it before SBRT.⁷²

Some of the aforementioned studies were all-inclusive with respect to the anatomic metastatic targets being treated and the primary oncologic diagnoses,^{67,69} whereas others involved patients with oligometastatic disease from only 1 primary cancer (prostate or breast) and bone being the predominant anatomic target of single-fraction SBRT.⁷⁰⁻⁷² The published evidence on the use of single-fraction SBRT in targeting other specific anatomic sites of oligometastatic disease is reviewed in separate sections.

Lung metastasis

Because several early studies of single-fraction SBRT for lung tumors included patients with pulmonary metastases, single-fraction SBRT has been solidified as an effective, feasible, and safe treatment modality for local consolidation of oligometastatic sites.⁷⁴ Randomized controlled trials of local consolidative therapy have only entailed multi-fraction prescriptions to date^{65,66,75}; however, a fair amount of data support the utility of single-fraction SBRT in the oligometastatic setting. For

example, an early retrospective study evaluated outcomes after single-fraction SBRT to 103 pulmonary metastases in 66 patients with a median follow-up of 15 months. Prescription doses were 23 and 30 Gy for 49 central tumors and 54 peripheral tumors, respectively. One- and 2-year LC rates were 89% and 82%, respectively, with favorable toxicity profiles including just 2 cases of grade 3 pneumonitis.²⁸ The University of Torino also reported clinical outcomes for 67 patients treated with single-fraction SBRT of 26 Gy to 90 lesions with a longer median follow-up of 24 months.⁷⁶ Actuarial 1- and 2-year LC rates were 93% and 88%, respectively, with minimal acute toxicity and limited grade 2 to 3 late toxicity (<15%). After these reports, a retrospective comparison of single- versus multi-fraction SBRT among 65 patients treated for 85 pulmonary metastases was published.²⁹ Single-fraction SBRT was prescribed to 26 Gy for peripheral targets and 18 Gy for central targets, with 41 of 65 patients receiving single-fraction treatment. At a median follow-up of 2.1 years, there were no significant differences in survival, time to progression, or toxicity rates between the single- and multi-fraction cohorts. The 2-year freedom from local progression was 93%, with LC comparable between the groups. No grade ≥ 3 toxicities were reported.

Contrary to these studies, a phase II trial from the Netherlands demonstrated lower efficacy with single-fraction SBRT of 30 Gy for 23 oligometastatic lung tumors,⁷⁷ with an actuarial 1-year LC rate of 74%. In a larger retrospective study from the same institution, the investigators once again reported single-fraction SBRT of 30 Gy to be associated with inferior LC compared with multi-fraction prescriptions up to 60 Gy.⁷⁸ Perhaps the ongoing TROG 13.01/ALTG 13.001 SAFRON II study will serve as a definitive comparison of single- versus multi-fraction SBRT for pulmonary metastases.⁷⁹ This multi-center phase II trial randomizes patients with up to 3 peripheral lung metastases to either 28 Gy in a single fraction or 48 Gy in 4 fractions. While we eagerly await these data, single-fraction SBRT remains a reasonable option in the consolidative setting. It should be noted that some histologies have been demonstrated to be radio-resistant (eg, colorectal metastases) and may still benefit from higher BED₁₀ prescriptions (eg, 54-60 Gy in 3 fractions).

Liver metastasis

Although surgery is the gold standard for management of liver metastases, most patients are not appropriate surgical candidates because of extensive intrahepatic disease or suboptimal baseline liver function.⁸⁰ Radiation therapy for liver cancer was first reported in the 1950s as a noninvasive means to provide effective palliation for liver metastases.⁸¹ Since then, technological advances have allowed for highly conformal delivery of ablative doses that demonstrated safe and durable LC in several

prospective trials for appropriately selected patients.⁸² Although published liver SBRT data mostly include outcomes from 3- to 5-fraction regimens, mounting evidence suggests the feasibility of delivering ablative doses in a single fraction.^{11,83-86}

The first reports of single-fraction liver SBRT were published by investigators from the Karolinska Institute, inspired by their successful intracranial radiosurgery experience.^{11,83,87} In 1998, Blomgren et al⁸³ reported their initial SBRT outcomes for 50 patients with 75 thoracic and abdominal tumors treated using a novel stereotactic body frame with abdominal compression. The first 5 patients who received a single fraction were excluded from the formal analysis because of unfavorable outcomes, including fatal radiation-induced liver disease in a patient with hepatocellular carcinoma with a 229 cm³ lesion that was prescribed 30 Gy; 4 other patients had local tumor progression, likely due to the use of exceptionally tight margins.

Recognizing the lessons learned from the Karolinska experience, other investigators subsequently limited patient selection for single-fraction treatment to those with smaller tumors and used more generous margins while continuing to ensure rigid patient immobilization and employ motion mitigation techniques. Three phase I single-fraction trials evaluating a range of doses from 14 to 40 Gy (BED₁₀, 33.6-200 Gy) have been completed, predominantly including patients with colorectal cancer, with inclusion criteria of ≤ 3 -5 liver metastases measuring ≤ 5 -6 cm.^{82,84-86} The first 2 trials successfully achieved dose escalation to 26 Gy⁸⁴ and 30 Gy,^{84,85} respectively, without dose-limiting toxicity, and LC at 12 to 18 months was ~70% to 80%. Of note, in the second trial,^{84,85} there were grade 2 duodenal ulcers in 3 patients who had treated lesions in the porta hepatis region; they concluded that multi-fraction SBRT is preferred for such lesions instead of single-fraction. A more recent phase I/II trial included 14 patients with the aim to further improve LC by escalating dose from 35 Gy (BED₁₀, 157.5 Gy) to 40 Gy (BED₁₀, 200 Gy) in a single fraction. Patients were only eligible for enrollment if they had peripheral lesions, defined as outside a 2-cm expansion from the portal vein to its bifurcation. With a median follow-up of 30 months, 2-year LC was 100%, and 69% tumors had a complete radiographic response. No grade ≥ 3 toxicity was reported. These prospective trials collectively demonstrated that ablative doses delivered in a single fraction are safe and can potentially achieve excellent long-term tumor control. The largest series of single-fraction SBRT for liver metastases was reported in a retrospective analysis that included 138 liver lesions in 90 patients, most with either primary colorectal (51%) or breast (20%) cancer.⁸⁸ The median prescription dose was 24 Gy (range, 14-30 Gy), typically prescribed to the 80% isodose line. At the median follow-up of 21.7 months, the LC (69.9% at 12 months) and adverse event profile (no severe toxicity)

were similar to what has been reported in prospective studies.

Single-fraction SBRT is promising for treating peripheral liver metastases, although the published data are limited. Randomized evaluation of single- versus multi-fraction SBRT is warranted based on the existing phase I/II evidence. It is expected that ablative doses can be safely delivered to limited volumes of the liver regardless of the fractionation schedule, provided that baseline liver function is adequate.⁸⁹ Long-term tumor control was excellent in the trial by Meyer and colleagues,^{82,84-86} which prescribed the highest dose (35-40 Gy) of the completed single-fraction trials; dose escalation for liver metastases has been recommended by many published studies,⁹⁰⁻⁹² especially for patients with more inherently radio-resistant tumors.⁹³ Future studies should explore the use of MRI guidance for treatment of liver metastases, especially for central lesions where smaller margins and online adaptive replanning may facilitate the safe application of a single-fraction regimen.^{93,94}

Adrenal metastasis

The adrenal gland is a common site of metastasis, especially from lung cancer, GI cancers, and melanoma.⁹⁵ Adrenalectomy is an effective means to achieve long-term survival for select patients with oligometastatic adrenal metastasis.⁹⁶ For patients who are not surgical candidates, SBRT may be a reasonable alternative based on the published literature demonstrating excellent LC and minimal severe toxicity.⁹⁷⁻⁹⁹ However, the supporting evidence is limited to several small retrospective studies. In an effort to collectively evaluate these data, a recently published meta-analysis/systematic review was conducted of 39 retrospective studies that included 1006 patients with adrenal metastases who were prescribed a median dose of 38 Gy in a median of 5 fractions.¹⁰⁰ Outcomes were favorable, with 2-year LC of 82% and only 1.8% grade 3 or higher toxicity. The majority was treated with multiple fractions, although a single fraction was used with prescription doses ranging from 13 to 30 Gy.¹⁰¹⁻¹⁰⁵

The feasibility of single-fraction SBRT is unclear given its limited utilization and because there is no publication dedicated only to single-fraction outcomes; 2 studies have attempted to compare these different fractionation schedules. Investigators from the University of Florence included 48 patients treated with SBRT for adrenal metastasis; 8 received a single fraction (mean, 23.5 Gy; range, 21.7-27.0 Gy), whereas the remainder received multiple fractions (mean, 34.9 Gy; range, 30.2-54.1 Gy).¹⁰² The overall 2-year LC was 90% and no patient experienced grade ≥ 3 toxicity. There was no significant difference in outcomes on univariate and multivariate analyses based on the number of fractions. More recently, Shah et al¹⁰⁴ reported excellent LC and no severe toxicity among patients who received a single fraction (16 lesions;

median, 18 Gy; range, 14-18 Gy) or multiple fractions (38 lesions; median, 30 Gy; range, 16-40 Gy), although the follow-up was limited to only several months. Although a single-fraction strategy seems promising, additional evaluation is clearly needed to better understand its appropriateness compared with multiple fractions for patients with adrenal metastases. Particular attention should be focused on determining the safety of delivering a single fraction with respect to the proximity of luminal GI structures, especially for left-sided lesions that may abut both the stomach and small bowel.

Discussion

Many radiation oncologists have been hesitant to use single-fraction SBRT for the management of extracranial/extraspinal cancers because of the established safety and efficacy of multi-fraction regimens, concern about potential suboptimal tumor control and/or increased toxicity, and lack of prospective data. The ongoing COVID-19 pandemic has increased awareness of the existing single-fraction SBRT literature that includes not only retrospective but also multiple prospective (including some randomized) studies. There has been increasing enthusiasm for using single-fraction SBRT in select patients, with the strongest indication existing for peripheral early-stage NSCLC based on the European Society for Radiotherapy and Oncology–American Society for Radiation Oncology guidelines.²² As we eventually transition out of the current pandemic and the impetus wanes to minimize patient footfall in the hospital to reduce SARS-CoV-2 transmission, there are potential advantages, such as patient convenience, to consider for implementation and further investigation of single-fraction SBRT.

A biological advantage of SBRT is immunomodulation, and emerging data indicate that factors including radiation therapy delivery technique and fractionation strongly influence the ability of SBRT to achieve clinically meaningful tumor-specific immune responses.¹⁰⁶ Preclinical data have demonstrated that massive tumor cell death after high dose per fraction leads to the release of tumor antigens and inflammatory cytokines, thereby stimulating an antitumor immune response.^{107,108} SBRT also increases tumor vascular permeability, leading to increased extravasation of antigen-presenting cells and effector T cells.¹⁰⁸ These immune-related effects of SBRT have sparked interest in combining SBRT with immunotherapy to treat various malignancies.¹⁰⁹⁻¹¹¹ Although the optimal SBRT dose fractionation schedule for this combinatorial strategy is unknown and may differ according to tumor type, the applicability of 1 or few fractions has been demonstrated in preclinical and clinical studies.^{51,112} Furthermore, multi-fraction SBRT has been shown to spare circulating lymphocytes due to smaller irradiated tissue volume and blood volume compared with

conventional fractionation.¹¹³⁻¹¹⁵ Single-fraction SBRT is likely to be more lymphocyte sparing than multi-fraction SBRT because of a lower integral dose delivered to the blood pool, rendering it an appealing regimen to be evaluated in combination with immunotherapy. In fact, delivery of fewer SBRT fractions has been correlated with less severe lymphopenia.¹¹⁶ The safety of combining single-fraction SBRT and immunotherapy is not well-established, although emerging data suggest that it is well-tolerated.¹¹⁷ These data support future clinical trials to better understand the clinical scenarios in which single-versus multi-fraction SBRT may be best suited for use with novel systemic agents such as immunotherapy.

Single-fraction SBRT is advantageous from a cost perspective. As health care expenditures rise, the selection of efficient and cost-effective radiation therapy options should be prioritized. This is especially pertinent in the United States, where the Centers for Medicare and Medicaid Services is developing an alternative payment model to transition from a traditional fee-for-service to an episode-based payment, with the goal being to provide less costly care.¹¹⁸ In this context, SBRT delivered in the shortest possible course (1 fraction) would be preferable, provided that clinical outcomes are at least not inferior to established multi-fraction regimens. The cost savings of a single fraction can be substantial; for instance, SBRT for NSCLC delivered in 1 fraction would cost 40% less compared with 3 fractions using 2009 Medicare rates.¹¹⁹ With regard to the current COVID-19 pandemic, a single-fraction solution would also indirectly provide savings by reducing staffing requirements and personal protective equipment needs, especially as a lengthy recovery is expected.

It cannot be understated that appropriate expertise and technical capability must be incorporated in the planning and delivery of high-quality SBRT, regardless of the fractionation schedule, especially considering that extracranial targets are routinely subject to inter- and intra-fraction positional changes.¹²⁰ Rigid immobilization and image guidance are critical; this is especially relevant for single-fraction SBRT because the mitigation of random setup error effects achieved by delivering multiple fractions is not applicable. In addition, early adopters of single-fraction SBRT have recognized that accounting for and minimizing motion are crucial, and therefore they routinely use techniques including an internal target volume with abdominal compression for LINAC-based treatment^{19,20,86} or with tumor tracking on CyberKnife.^{70,85} Interestingly, there is a paucity of single-fraction SBRT outcomes reported with patients treated in breath hold, which is 1 of the most effective means to reduce the volume of normal tissue receiving at least the prescription dose and therefore the risk of potentially severe toxicity.¹²¹

One of the barriers to broader adoption of single-fraction SBRT may be the concern of a potential

geographic miss. Much of the concern about a geographic miss originates from the inability to visually ensure that appropriate target localization is maintained throughout treatment once pretreatment images have been approved. Using MRI-guided radiation therapy can alleviate this concern by providing continuous real-time visualization of the target and surrounding organs at risk with no need for implanted fiducial markers and with no added radiation dose to the patient.^{122,123} Smaller margins and superior soft tissue visualization compared with computed tomography may improve clinical outcomes. Furthermore, the ability of an MR-LINAC to perform daily on-line adaptive replanning within minutes to account for the current day's tumor and normal organ anatomy may facilitate safe dose escalation for high-risk targets such as pancreatic¹²⁴ and central/ultracentral lung¹²⁵ tumors; whether this is feasible in a single fraction remains unclear.

Conclusions

Reducing the number of radiation therapy fractions whenever possible should be prioritized during the ongoing pandemic to mitigate the risk of significant morbidity and mortality from COVID-19 in the cancer patient population. Although consensus guidelines strongly recommend single-fraction SBRT for peripheral early-stage NSCLC, single-fraction SBRT has not been clearly proven as a reasonable alternative to multi-fraction SBRT for other primary or oligometastatic targets. However, promising early outcomes suggest that the role of single-fraction SBRT may expand beyond the pandemic when the advantages of reduced cost, potential immune-related effects, and enhanced convenience especially for treating multiple metastatic lesions are considered. Future clinical trials should aim to incorporate a tumor volume-adapted approach for defining the optimal prescription dose range in a single fraction that balances tumor control and surrounding normal tissue toxicity for each primary cancer histology. With these innovations, we may ultimately show that sometimes less accomplishes more.

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