Review Article

Is single fraction the future of stereotactic body radiation therapy (SBRT)? A critical appraisal of the current literature

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ABSTRACT

Stereotactic Body Radiation Therapy (SBRT) is a standard of care for many localizations but the question of the optimal fractionation remains a matter of concern. If single fraction sessions are routinely used for intracranial targets, their utilization for mobile extracranial lesions is a source of debate and apprehension. Single session treatments improve patient comfort, provide a medico-economic benefit, and have proven useful in the context of the SARS-CoV 2 pandemic. However, both technical and radiobiological uncertainties remain. Experience from intracranial radiosurgery has shown that the size of the target, its proximity to organs at risk, tumor histology, and the volume of normal tissue irradiated are all determining factors in the choice of fractionation. The literature on the use of single fraction for extracranial sites is still scarce. Only primary and secondary pulmonary tumors have been evaluated in prospective randomized trials, allowing the integration of these fractionation schemes in daily practice, for highly selected cases and in trained teams. The level of evidence for the other organs is mainly based on dose escalation or retrospective trials and calls for caution, with further studies being needed before routine use in clinical practice.

Introduction

For several years, radiotherapy (RT) has increasingly evolved towards hypofractionation, on the basis of both radiobiological rationale and the technical possibility of safely delivering higher doses per fraction. Hypofractionation has added advantages in terms of patient convenience and faster patient turnover in RT departments. Moderate or severe hypofractionation, including stereotactic body radiation therapy (SBRT), is a current standard of care for many intra- and extracranial localizations. Several fractionation regimens exist, from single-fractionation (SF-SBRT) to multi-fractionation (MF-SBRT).

The period of the SARS-CoV 2 pandemic was a major practice-changing trigger for radiation oncologists, who aimed to minimize the risk of infection without jeopardizing the quality of care. The question of extreme hypofractionation, with the end of the spectrum being single fraction RT, remains a matter of debate. Its generalization may be hindered by technical apprehensions and the lack of robust data regarding its effectiveness and safety. A previous review of the literature discussed the available evidence supporting the use of SF-SBRT for extracranial localizations [1]. The aim of this article is to analyze the criteria for choosing the best SBRT fractionation scheme and to discuss the conditions necessary for the applicability of single fraction in selected clinical scenarios.

A brief history of fractionation in RT

Radiotherapy fractionation has historically been the only way to deliver high tumoricidal doses while sparing organs at risk (OAR), exploiting the difference in radiosensitivity between healthy tissues and the tumor (differential effect). Conventional fractionation allowed time for the healthy cells to repair DNA damage between fractions. Radiobiological concepts had also described that increasing the dose per fraction induced similar mortality rates between healthy tissues and the tumor, and thus a loss of the differential effect. It was not until the 1950′s – thanks to pioneers such as Lars Leksell who enabled the development of radiosurgery (SRS) – that it became possible to safely deliver high doses per fraction to small volumes. This method was initially dedicated to the treatment of benign and malignant brain lesions, before technical improvements in the 1990 s made it possible to consider moving targets and to finally extend the indications to extracranial lesions (SBRT).
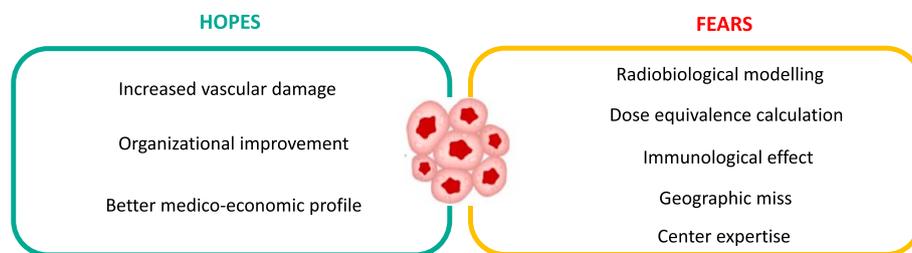
Fig. 1. Hopes and fears of single-fraction SBRT.

SRS and SBRT: definitions and concept

The therapeutic index in RT is based on the delicate balance between the probability of controlling the tumor (Tumor Control Probability, TCP) and the probability of inducing toxicities to OARs (Normal Tissue Complication Probability, NTCP). While healthy tissues are particularly sensitive to high doses per fraction based on a classically low α/β ratio, the therapeutic index shrinks with increasing dose per fraction. Therefore, maintaining a favorable therapeutic ratio requires a reduction in the volume of healthy tissue receiving high doses (i.e. the PTV/GTV ratio) [2]. This ability to deliver a high dose in a volume with reduced margins is the basis of SRS/SBRT. The word "stereotactic" is a general term referring to both SRS, a term historically devoted to highly precise treatments of brain lesions in a single high dose session, and SBRT, a term adapted to the treatment of intra- or extracranial lesions, generally in one to five fractions.

Several parameters can characterize stereotactic irradiation. Physical criteria include a precise delineation of the target (usually necessitating multimodality imaging), millimetric GTV to PTV margins, a very steep dose gradient outside the treated volume, and image guidance to improve patient setup and/or tumor tracking during treatment. Furthermore, stereotactic RT has a different radiobiological basis compared to conventional fractionation. Notably, the "5 Rs" of radiobiology (reoxygenation, DNA repair, radiosensitivity, redistribution in the cell cycle and repopulation) are no longer applicable to high doses per fraction. In addition to direct cell injury due to DNA damage, high doses per fraction induce endothelial cell apoptosis via the ceramide pathways [3]. Thus, while phenomena of vascular normalization are described for conventional doses (1.8–2 Gy/fraction), high doses per fraction (>8–10 Gy) lead to indirect tumor cell death due to tumor ischemia. Moreover, it has been shown that several fractionation schemes induce different immunological effects. When the dose per fraction increases, a dose-dependent production of tumor antigens and damage-associated molecular patterns occur [4], which can promote lymphocyte priming. This explains the current trend of combining SBRT with immunotherapy agents.

Pros and cons of SF-SBRT (Fig. 1)

A single fraction could offer several advantages:

- Several pre-clinical models have reported an increase in endothelial cell apoptosis with increasing dose, even for a very high range of doses [5]. A single high dose treatment could therefore be theoretically more toxic for the vascularization of the tumor and its microenvironment.
- For the patient, a single session decreases travel time and hospital stay, and limits possible interruptions of systemic therapies.
- Hypofractionation (moderate or extreme) offers an organizational advantage at a departmental level by reducing the occupancy of machines; particularly useful with the continuously increasing number of patients treated with RT. This could also be translated into a benefit from a medico-economic perspective, in case of per session reimbursement.

Conversely, a single fraction treatment raises several questions:

- Radiobiological questions:
- Uncertainty exists in the modelling and calculation of equivalent dose. Several studies have questioned the relevance of the linear quadratic model for high doses per fraction, some having indicated an overestimation of cell survival observed *in vitro*, others an underestimation of the effect observed in clinical practice. Some models have been created to try to approach the observed cell survival at high doses as precisely as possible, such as the universal survival curve model, which combines both the linear quadratic and the multitarget model. This in particular allows calculating equivalences between single and multi-fraction schemes; however, there is no consensus and the debate continues [6].
- Another concern with single fraction is a likely reduction in immunogenicity at very high doses, Vanpouille-Box et al. showed that doses above 12 Gy stimulated the *Trex1* exonuclease, leading to the degradation of cytosolic DNA and therefore to the inhibition of the *cGAS/STING* pathway, which is essential for promoting radiation-induced immunological response [7]. This phenomenon explains why hypofractionated regimens (3 × 8 Gy) could be preferred over single fractions when combined with immunotherapy.
- Finally, some have reported that hypoxia may persist as a limiting factor despite the use of very high doses per fraction. Secondary brain and lung lesions have been shown to exhibit a better TCP with multi *versus* single fractionation, suggesting that it may be preferable to fractionate the treatment for hypoxic tumors to allow for reoxygenation [8].
- Technical questions:
- One of the concerns about SF is geographic miss, as a one-shot treatment implies a unique chance to deliver the planned dose in the correct volume. Due to the inherent physical characteristics of SBRT, even minimal shifts can have deleterious consequences (underdosing the GTV or overdosing the OAR). SF-SBRT necessitates the highest accuracy in treatment delivery, which is challenging especially for mobile extra-cranial lesions. Specific techniques (gating, deep inspiration breath hold, tracking, 4D planning) are mandatory to treat these lesions.
- Another matter of debate is the ideal margins to apply. Fractionation allows mitigation of potential random errors through the repetition of sessions. By definition, a single session has no random error but can be subject to systematic errors (sub-optimal fusion between the dosimetric CT and the MRI for brain lesions for instance), with potentially deleterious effects.

How to choose between SF- or MF-SBRT?

Several criteria should be considered in the choice of SBRT fractionation. They can be derived from the experience in intracranial lesions for which single session treatments were first developed, facilitated by the immobility of the targets in a rigid anatomy.

- *The target volume*: the RTOG 9005 dose-escalation trial aimed to determine the maximal tolerated dose in one fraction for previously

irradiated primary or secondary lesions, with stratification by tumor size. This trial concluded that the maximum tolerated dose decreased with increasing lesion diameter, in relation to the dose delivered to the healthy brain: 24 Gy, 18 Gy, and 15 Gy for tumors ≤20 mm, 21–30 mm, and 31–40 mm in maximum diameter respectively [9]. Considering the risk of reducing local control (LC) in larger tumors by decreasing the dose, hypofractionation is an alternative solution to allow the delivery of tumoricidal doses (high α/β ratio) while limiting the biologically equivalent doses on surrounding tissue (low α/β ratio) [10].

- *The proximity of dose-limiting structures:* the closer the lesion is to tissues with low α/β ratios, the greater the risk of toxicity with high doses per fraction. A large retrospective study of 260 patients with brain tumors compared single (median dose 20 Gy) with multi-fraction schemas (35 Gy/7 and 40 Gy/10). LC and survival rates were comparable between arms. Although patients receiving fractionated SBRT had larger lesions and/or were nearer critical structures, grade 1–3 toxicity rate was lower [11].

- *The volume of irradiated normal tissue:* for intracranial RT, it has been demonstrated that both V10 and V12 Gy were significantly correlated with the risk of brain radionecrosis. Milano et al. modeled this risk as a function of dose and treated volume, and reported that fractionated irradiation decreased the risk of radionecrosis for larger treatment volumes *versus* single fraction [12].

- *The tumor histology*: the more radio-resistant the tumor, the higher the dose per fraction required to increase LC. This was described by Zelefsky et al. in a cohort of extracranial metastases from renal cell carcinoma. The 3-year local PFS was 88 %, 21 %, and 17 % for lesions having received a high single-dose (24 Gy; n = 45), a low single-dose (<24 Gy; n = 14), or hypofractionated regimens (n = 46) respectively. In multivariate analysis, receiving a single dose *versus* hypofractionation was a significant predictor of improved local PFS (p =.008) [13].

SF- *versus* MF-SBRT: practical application through selected localizations

Primary tumors

● Lung tumors

SBRT is now a well-established option for peripheral (according to RTOG 0236 [14]) early stage (T1-2N0 M0) non-small cell lung cancer (NSCLC) in inoperable patients. Two prospective randomized phase II trials have reported the efficacy and safety of a single fraction in this setting. The RTOG 0915 trial randomized patients to a single fraction of 34 Gy (BED$_{10}$ 149 Gy), n = 39 *versus* 12 Gy × 4 (BED$_{10}$ 106 Gy), n = 45. After a median follow-up of four years for all patients and six years for those alive at the time of analysis, grade 3 toxicity rates were comparable between arms (2.6 *versus* 11.1 % respectively). No difference in 5-year LC (89.4 *versus* 93.2 % respectively) nor survival was reported [15]. The second trial by Singh et al. included 98 patients randomized to 30 Gy × 1 (BED$_{10}$ 120 Gy) *versus* 20 Gy × 3 (BED$_{10}$ 180 Gy). After a median follow-up of 4.5 years, no difference in grade 3 thoracic toxicities (16 *versus* 12 % respectively) nor LR was described [16]. These results are consistent with other prospective trials assessing the efficacy of one to three fraction-SBRT for peripheral tumors [14,17]. The application of SF-SBRT for lung tumors is not a general consensus and is limited by the technical constraints, the expertise of treatment centers, and the lack of long-term data. However, in well-selected situations, this regimen is as an interesting alternative to MF-SBRT regimens, but deserves further investigation [18].

On the other hand, few series have reported the outcomes of SF-SBRT for central tumors, whereas MF-SBRT has been associated with a high risk of ≥ grade 3 toxicities [19]. Le et al. conducted a phase 1 dose-escalation study assessing SF-SBRT for NSCLC (n = 21) or solitary lung metastases (n = 11). Patients received doses from 15 to 30 Gy/fraction with CyberKnife. Twenty patients received a total dose of 25 Gy and only two a total dose of 30 Gy. For NSCLC lesions, the 1-year LC was dose-dependent (91 % for dose >20 Gy and 54 % for dose <20 Gy). All late toxicities occurred at doses >20 Gy and the majority were in central or large tumors [20]. Ma et al. have reported the outcomes of 42 patients treated with SBRT for central tumors (11 with 26–30 Gy/1 and 31 with 50–60 Gy/5). The 1-year LC was 100 % for the SF-SBRT group and 96 % for MF-SBRT group. The grade ≥3 toxicity rate was similar between groups, although the only grade 4 toxicity (bronchopulmonary hemorrhage) occurred in the SF-SBRT group [21]. In a series of 66 patients with oligometastatic lung tumors, Osti et al. observed similar LC and toxicities between patients having central (n = 49 targets, dose of 23 Gy × 1) or peripheral lesions (n = 54 targets, dose of 30 Gy × 1) [22]. In summary, the scarcity of data on SF-SBRT for central tumors does not encourage its application.

● Primary renal cell carcinoma (RCC)

Although nephrectomy remains the standard of care for localized renal tumors, SBRT has gradually emerged as a viable alternative for inoperable patients or unresectable tumors. There is a strong radiobiological rationale for the use of SBRT for renal cancer, as some studies have shown that renal tumors are more radiosensitive to high doses per fraction. In addition, the possibility of combining irradiation with immunotherapy appears promising. Numerous studies with varying patient profiles and SBRT regimens have confirmed the efficacy and safety of this treatment. In 2014, Pham et al. were the first to report the results of a prospective phase 1 dose-escalation trial where 20 patients with inoperable primary RCC received SBRT of 26 Gy in a single fraction (for tumors <5 cm) or 42 Gy in three fractions (for tumors ≥5 cm). Treatment was delivered with a 3-dimensional conformal technique. After a median follow-up of 6 months, 60 % of patients presented with grade 1–2 toxicity (mainly nausea, chest wall pain and fatigue) but no grade ≥3 toxicity was observed [23]. Using the same fractionation regimen in function of tumor size, Siva et al. reported prospective results of 37 patients. After a median follow-up of 24 months, LC and OS were 100 % and 92 % respectively. Only one patient (3 %) had a grade 3 toxicity [24]. In another prospective study, 40 patients (with 45 tumors, mixed histology) were treated with 25 Gy in a single fraction with CyberKnife. After a median follow-up of 9 months, LC rate was 98 % and 19 patients were in complete remission. No grade ≥3 adverse event was reported and renal function remained stable [25]. A multicentric pooled analysis from the International Radiosurgery Oncology Consortium for Kidney (IROCK) reported the outcomes of 223 patients treated by either a single (n = 118; median dose 25 Gy) or multiple fractions (n = 105; median dose 40 Gy, median number of fractions: 4). Local control at 2 and 4 years was 97.8 %, with no significant difference between the SF- and MF-SBRT. Only three patients presented with grade ≥3 bowel toxicity. There was no difference in mean renal function change at last follow-up according to the fractionation (-6.1 mL/min and −4.9 mL/min for the single and the multi-fractionation respectively, p =.66). On multivariate analysis, tumor size and MF-SBRT were associated with worse PFS and cause-specific survival [26]. Despite lack of prospective data, SF-SBRT appears as a viable therapeutic alternative for RCC.

● Prostate cancer

Because of the improvement in radiobiological knowledge and technical capabilities in recent years, fractionation in the radiotherapy of prostate cancers has been drastically reduced such that hypofractionation is now a standard of care. In particular, the use of SBRT in five to seven fractions has shown high LC rates with favorable toxicity profiles, despite a relatively short median follow-up [27]. Few publications have evaluated the effectiveness of a SF-SBRT for prostate cancer. The PRO-SINT phase 2 trial randomized 30 patients with intermediate-risk cancer

Table 1
SF-SBRT for lung oligometastatic disease (selected studies with >50 patients).

Author, year	Design	Inclusion criteria	Population (patients/tumors)	Single fraction regimen	Median follow-up	Toxicity rate	Local control rate	OS
Hof, 2007	retrospective	≤4 cm diameter	61/71	12–30 Gy	14 months	5 % G3	1-year 89 %, 2 years 74 %, 3 years 63 %	1-year 78.4 %, 2-years 65.1 %, 3-years 47.8 %
Filippi, 2014	retrospective	1 to 5 metastasis, ≤5 cm diameter	67/90	26 Gy	24 months	12 % late G3	1-year 93 %, 2 years 88 %	1-year 85 %, 2 years 71 %, 1-year CSS 90 %, 76 % at 2 years
Siva, 2021	randomized phase 2	1 to 3 peripheral metastasis, ≤5 cm diameter	90/133	28 Gy/1 *vs* 48 Gy/4	36.5 months	1-year 5 % *vs* 3 % One G5 event in the multifraction arm	1-year 93 % *vs* 95 % 3-years 64 % *vs* 80 %	1-year 95 % *vs* 93 %, 3-years 81 % *vs* 67 %

Abbreviations: OS: Overall Survival.

to receive 24 Gy in one fraction or 45 Gy in five fractions. No androgen deprivation therapy was allowed. To minimize toxicities and to improve quality in treatment delivery, a Foley catheter was inserted (for intrafractional motion management) and an endorectal balloon was used (to limit the prostate motion). The PTV consisted of the prostate gland with a 2-mm margin except at the interfaces with OARs (0-mm margin). Toxicities and quality-of-life endpoints (evaluated with the IPSS and EPIC scores) were comparable between arms with no grade ≥2 adverse event. At median follow-up of 36 months, PSA declined to <0.5 ng/mL similarly in both arms [28]. The ONE-SHOT phase 1/2 trial evaluating the efficacy and safety of a single fraction of 19 Gy (with urethrasparing) for low- and intermediate-risk prostate cancer is currently recruiting [29]. The enthusiasm for the development of single-fraction regimens must be weighed against data from the High-Dose-Rate (HDR) brachytherapy experience, where single-session treatments have shown disappointing results. Morton et al. have compared a 19 Gy single fraction to 27 Gy in two fractions for 70 patients with low- to intermediate-risk prostate cancer. Although toxicities were comparable, the 5-year biochemical disease-free survival was significantly lower in the single fraction arm (73.5 % *vs* 95 %, p =.001). The cumulative incidence of biopsy proven local failures was also higher is the single fraction arm (29 % *vs* 3 %, p < 0.001) [30]. These arguments suggest that at present, SF-SBRT should not be offered outside of clinical trials for prostate cancer.

• Pancreatic cancer

SBRT is currently a standard of care for pancreatic tumors, whether to improve resectability (borderline tumors) or increase LC (locally advanced tumors (LAPC)). One of the main arguments in favor of the development of short course treatments is the reduction of the chemotherapy-free interval, because pancreatic cancers have been shown to have micro-metastatic spread even at early stages. In a phase I dose-escalation trial, Koong et al. were the first to report the results of a single fraction of 15 to 25 Gy for patients with LAPC. No ≥ grade 3 gastro-intestinal toxicity was reported. All patients who received 25 Gy (n = 6) achieved LC until death or last follow-up [31]. The same authors later published the results of this 25 Gy regimen for 77 patients, of whom 96 % received a gemcitabine-based chemotherapy. While the LC rates were 91 % and 84 % at 6 and 12 months respectively, 25 % of patients had grade ≥2 late toxicity [32]. Since then, several studies have shown that the use of hypofractionated regimens led to high LC rates while maintaining acceptable toxicity. Pollom et al. published one of the largest studies comparing a SF (25 Gy) *versus* a MF regimen (25 Gy in five fractions) for 167 patients with unresectable pancreatic adenocarcinoma (of whom 87.5 % received chemotherapy). After a 7.9 months median follow-up, there was no difference in LC or OS rates between groups. However, there were almost three times more grade ≥2 digestive toxicity in the single arm (HR = 3.01; 95 % CI 1.3–6.9; p =.005) [33]. With these results, the utilization of SF-SBRT has definitely

stopped in favor of MF-SBRT, which is currently recommended by ASTRO for borderline resectable and LAPC.

Metastases

• Spinal metastases

There is extensive literature describing the effectiveness of SBRT for spinal metastases. The use of this technique developed early, as the immobility of the target did not require complex motion management software. There is no established consensus on dose and fractionation, and no randomized study has directly compared SF- to MF-SBRT in terms of local control. In a large retrospective series of 228 patients (348 lesions), Heron et al. reported significantly higher rate of and earlier 1-year pain control in the SF group (100 % *vs* 88 %, p =.003) but the MF group achieved greater local tumor control at 2 years (96 % *vs* 70 %, p =.001) with less need for retreatment [34]. On the other hand, Singh et al. compared SF-SBRT, MF-SBRT and conventional RT in the SAFFRON meta-analysis for 4911 spinal metastases (3237 patients): SF-SBRT had superior 1-year LC compared to conventional RT (93 % *vs* 81 %, p =.007) with no difference between conventional RT and MF-SBRT (p =.86). For SF-SBRT, a 4.7 % benefit in LC was seen for each 10 Gy_{BED10} dose escalation, at the cost of increased vertebral collapse fracture (VCF) *versus* MF-SBRT (19.5 % *vs* 9.6 %, p =.039). However, no correlation between dose and VCF rates was found [35]. Particular attention should likely be paid to the dose delivered with a SF regimen, as some studies have indicated a significant risk of VCF with a single dose ≥20 Gy. Sahgal et al. analyzed 252 patients (410 spinal metastases), showing that the dose per fraction was correlated with the VCF rate in multivariate analysis (HR of 5.3 for doses ≥24 Gy and 4.9 for doses between 20 and 23 Gy *versus* ≤ 19 Gy). Nearly-two thirds of VCF occurred within the first 4 months after SBRT, suggesting the need for close follow-up. Other well-documented criteria are associated with the risk of VCF independent of the delivered dose and must be considered in the choice of fractionation: baseline VCF, lytic disease, and spinal instability [36,37]. The Spinal Instability Neoplastic Score (SINS) may be a useful predictive tool, as a high SINS [7–12] was significantly associated with a fivefold risk of VCF [38].

• Oligometastatic disease

A single fraction regimen is particularly attractive for oligometastatic patients (classically defined as having less than five metastases), as they have been shown to have favorable oncologic outcomes, justifying the development of therapeutic intensification strategies with curative intent. Several phase 2 randomized trials have reported survival benefits with the addition of SBRT to the standard of care for oligometastatic patients [39,40]. While there is a growing interest in metastasis-directed therapy (MDT) strategies, SF-SBRT regimens offer several advantages in terms of patient convenience, reduction in the duration of interruption

Table 2
SF-SBRT for liver oligometastatic disease.

Author, year	Design	Inclusion criteria	Population (patients/tumors)	Single fraction regimen	Median follow-up	Toxicity rate	Local control rate	Median OS (months)
Herfarth, 2004	phase I/II	≤6 cm	37/60	14–26 Gy	15.1 months	no G3	68 % at 18 months	25
Goodman, 2010	phase I	≤5 metastasis, ≤5 cm	26/40	18–30 Gy	17 months	no G3	77 % at 12 months	28.6
Habermelh, 2013	retrospective	∅	90/138	median 24 Gy (17–30)	21.7 months	no G3	87 % at 6 months 70 % at 12 months 59 % at 18 months	24.3
Meyer, 2016	phase I	≤5 metastasis	14/17	35–40 Gy	2.5 years	no G3	100 % at FUP	2-y: 78 %

Abbreviations: OS: Overall Survival.

of systemic therapies, and optimization of hospital resources.

Sogono et al. have reported the results of a large retrospective study including 371 patients with 494 extracranial oligometastases (one to five) treated by SF-SBRT. The median follow-up was 3.1 years. The 5-year OS and PFS were 55 % and 14 %, respectively, and the 5-year cumulative incidence of local failure was 8 %. The toxicity profile was favorable with 3 % grade 3–4 treatment-related adverse events. Interestingly, it was observed that the median time to onset of systemic treatment was 2.1 years (3.5 years after exclusion of prostate cancer patients). Locoregional relapse was found to be the second most frequent pattern of failure after distant recurrence, suggesting the probable importance of combining treatment of the primary tumor with MDT [41].

- Lung metastasis

Several studies have focused on SF-SBRT for lung oligometastases [42–44] (Table 1). The recent phase 2 SAFRON II trial randomized 90 patients with one to three peripheral lung metastases to a single session of 28 Gy or 48 Gy in four fractions. The 1-year grade ≥3 adverse events rate was similar between groups (<5%). No differences were observed between the two arms for freedom from local failure, OS or DFS, which begs the question of single-fraction regimens for future trials. Translational data demonstrated that both regimens could induce systemic immune activation [44].

- Liver metastasis

A number of studies have evaluated SF-SBRT for liver oligometastases [45–48] (Table 2). Several phase 1 dose-escalation trials have shown the feasibility of treating liver metastases with a dose range of 14–40 Gy. Patients most frequently had metastases of colorectal origin with a limited number (≤5) and size (≤6 cm). LC rates at 12–18 months were 70–80 % overall, without dose-limiting toxicity. In the series by Goodman et al., two patients with tumors located in the porta hepatis presented with late grade 2 digestive toxicities (duodenal ulcers) suggesting the importance of patient selection, favoring multifractionation in case of proximity to the OAR [46]. Habermehl et al. reported the largest retrospective study of 138 intrahepatic tumors of 90 patients treated with a single fraction of 17–30 Gy (median dose 24 Gy). After a median follow-up of 21.7 months, patients achieved good LC rates (87 % and 70 % at 6 and 12 months respectively) and a favorable toxicity profile (no grade ≥3 toxicity) [47]. The phase 1 dose-escalation trial from Meyer et al. evaluated the highest tolerated dose of 40 Gy for 7 patients without achieving dose-limiting toxicities. It is important to note that this trial included highly selected patients: tumors had to be located outside of the central liver zone, corresponding to a 2-cm expansion around the portal vein along its course up to the intrahepatic bifurcation [48].

Medico-economic and organizational impact of SF-SBRT

The development of SF-SBRT regimens addresses a real need as the indications for RT in oncological management keep on increasing. The improvement of systemic therapies, in particular immunotherapy, has also led to increased patient survival, thus increasing the incidence of metastatic relapses. In addition, better definition of the oligometastatic status in recent years has led to a growing number of MDT strategies. Single-fraction regimens therefore facilitate access to treatment machines (from the hospital resources perspective) while limiting patient transfers (from a patient convenience perspective) and reducing treatment cost (from the service provider perspective).

The medico-economic advantage of SBRT over other focal therapies is well documented [49]. For intracranial lesions, several studies have shown favorable cost analyses of SBRT compared with surgery [50,51]. The same finding has been reported for lung tumors. Wolff et al. compared the cost-effectiveness of SBRT *versus* video assisted thoracic surgery for operable stage 1 NSCLC. The quality adjusted life years (QALY) was slightly superior for SBRT (5.86 *vs* 5.81 respectively). In addition, average discounted lifetime costs were >8000 euros higher for surgery [52].

Very few studies have compared the cost-effectiveness of SBRT regimens according to their fractionation. Boyce-Fappiano et al. conducted a time-driven activity-based cost analysis of several RT schemes (30 Gy/ 10 with 3D-conformational and intensity-modulated techniques, 27 Gy/ 3 MF-SBRT and 18 Gy SF-SBRT) for spinal metastases. SBRT techniques incurred lower technical costs compared to 3D and IMRT (driven by a decreased staff time and LINAC costs) but higher personnel costs driven by increased physician and physicist time in simulation, planning and treatment delivery. When SBRT schemes were compared, the single session led to a 17 % total costs reduction and therefore to a favorable resource use profile [53]. The progressive development of single session treatments will necessarily imply a reflection on its mode of reimbursement such that financial considerations do not constitute an obstacle to its generalization.

Discussion

The current context of the SARS-CoV 19 pandemic strongly encouraged the use of hypofractionation with the aim of maintaining treatment quality while limiting the risk of contamination. At the extreme end of the spectrum, SF-SBRT allows safe delivery of ablative doses for highly selected cases. In the setting of high dose per fraction, the question of the choice of fractionation remains closely linked to the balance between the probability of tumor control and toxicities to the surrounding tissues. Intracranial lesions were the first to benefit from the development of single session RT (SRS). Based on the experience from intracranial tumors, several criteria can help in determining the best choice of fractionation, such as tumor volume, proximity to OARs, and tumor histology. However, their applicability to mobile extracranial lesions may be hampered by technical concerns. Although technological improvements allow for more precise identification of the target, uncertainties regarding intra-fraction tumor motion remain, which may raise oppositions against SF-SBRT. Several techniques in development may offer greater safety for SF-SBRT. Spacers that serve to increase the distance between the target and the OAR (especially for prostate and pancreatic tumors) is one possible solution. Another is the development of MRI-guided RT that will help ensure continuous monitoring of the

Locations	Single dose regimen	Supporting evidence in the literature
Brain	20 to 24 Gy	high
Lung (peripheral tumors)	30–34 Gy	high
Spine	16 to 24 Gy	moderate
Kidney	25-26 Gy	moderate
Liver mets	14 to 40 Gy	insufficient
Pancreas	15 to 25 Gy	insufficient
Prostate	19–24 Gy	insufficient
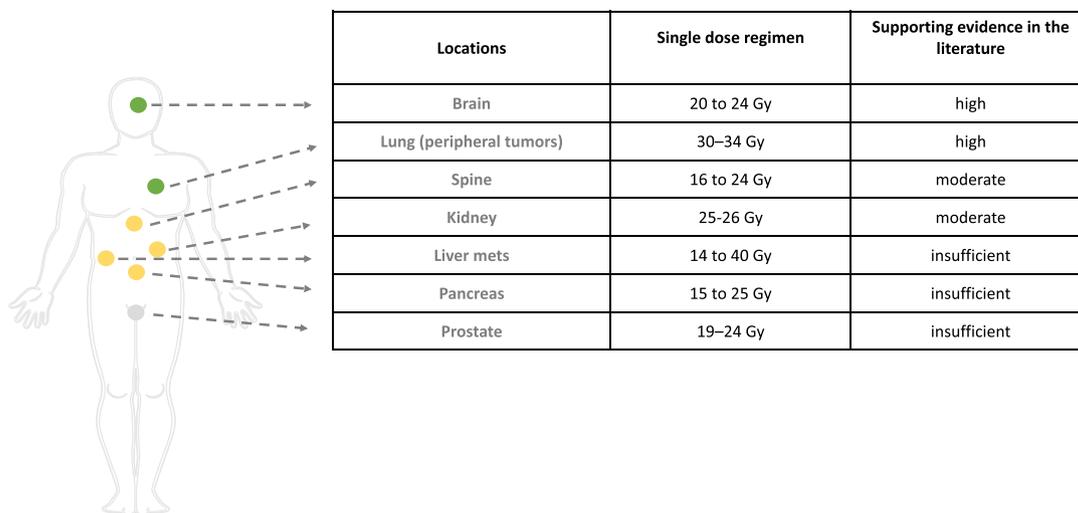
Fig. 2. SF-SBRT for intra-and extracranial targets: what level of evidence?

Table 3
Recruiting studies assessing single fraction SBRT.

Trial	design	site	patients	single fraction	multifraction	main objective
RTOG 1503 (FASTRACK II)	single arm phase II	renal cell carcinoma	70	26 Gy (<4cm)	42 Gy/3 (>4 cm)	local control
NCT04427228 (MIGRAINE)	randomized phase II	brain metastases for patients with immunotherapy	74	18–20 Gy (according to size)	3 × 9 Gy	radionecrosis rate
NCT02608866	randomized phase II	spine	68	16 Gy	3 × 8 Gy	toxicity
NCT03028337	randomized phase II	pre-irradiated spine mets	80	dose according to spinal cord and cauda equina	3 × 9 Gy	1-year local control
NCT03294889 (ONE-SHOT)	single arm phase I-II	prostate adenocarcinoma	45	19 Gy	∅	toxicity, biochemical PFS

target during treatment thus permitting margin reduction, a necessary condition for dose escalation within the target volume while sparing the adjacent structures.

The literature evaluating SF-SBRT regimens for extracranial targets is sparse and quite heterogeneous. Here, we have presented the main available data in tumor localizations for which the technique has been most explored and thus having a selection of analyzable publications. It should be emphasized that direct comparison of treatment regimens has not been possible among the studies because of the heterogeneity in the techniques, prescription isodoses, dose per fraction, and total dose prescribed. Overall, SF-SBRT in peripheral lung primary tumors have the highest level of evidence, with two phase II randomized trials, having prompted some societies to endorse this regimen in the context of the pandemic. For other localizations, the level of evidence is lower and thus prudence is advised. Several retrospective series have reported the feasibility of SF-SBRT for renal tumors, but comparative studies remain necessary. Data regarding single fraction for prostate cancer is clearly preliminary and do not allow its use outside of clinical trials (Fig. 2). The experience of HDR brachytherapy in prostate cancer calls for caution, due to the inferiority of the SF scheme in terms of biological and local control in a comparative trial. To guarantee maximum safety for SF-SBRT, it is necessary to establish strict protocols and trained teams with specific skills on SBRT should oversee these treatments.

Continued improvement in patient survival due to improvements in systemic therapies is leading to increased consideration of the relevance of focal therapies. For oligometastatic cases, the question of treating involved sites remains open and is the subject of several ongoing comparative trials in various histologies. SF-SBRT is one focal treatment option for the primary tumor as well as for metastatic lesions. Its utilization would likely therefore increase, permitting improved access to resources and potentially improving quality of life of patients. The possibility of treating several lesions during the same session is already envisioned by some companies with the development of the positron emission tomography (PET)-LINAC [54]. This Biology-guided Radiation Therapy (BgRT) uses PET emission as pseudo fiducials markers, allowing real-time tracking of the target and therefore margin reduction. Another possible advantage would be the decreased dependence on motion management algorithms and software. Finally, the development of novel irradiation modalities such as FLASH-RT, which consists of the delivery of an ultra-high dose-rate ($\geq$40 Gy/s in a very short time period, may also circumvent the problem of tumor motion.

Several studies evaluating the safety and the efficacy of SF-SBRT are recruiting (Table 3). In particular, the question of the most appropriate fractionation in combination with immunotherapy is currently being evaluated, since pre-clinical data have suggested a negative impact of high single dose in promoting immunogenicity.

Conclusion

The choice of fractionation in SBRT must be subjected to a rigorous assessment of the benefit/risk ratio. Single fraction RT appears to be the dogma for some radiation oncologists considering RT as a "pseudo-surgical" focal treatment. Whereas SF-SBRT is a standard of care for eligible intracranial lesions, robust data for widespread generalization to extracranial localizations are lacking. Concerns hindering its routine utilization include technical constraints of managing intra-fraction target motion to spare OARs, as well as physical and radiobiological uncertainties. Studies comparing different fractionations and evaluating the combination of SF with new systemic therapies (in terms of efficacy and safety) are needed. The radiation therapy community should

encourage the development of this regimen to improve both patient comfort and tumor control while reducing the socio-economic impact of treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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