Critical Reviews in Oncology/Hematology 98 (2016) 147–158

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Spinal metastases: Is stereotactic body radiation therapy supported by evidences?

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Contents

ARTICLE INFO

Article history:
Received 24 September 2015
Received in revised form 1 November 2015
Accepted 4 November 2015

Keywords:
Spine metastases
SBRT
Dosimetry
Palliative radiotherapy
Local control
Toxicity

ABSTRACT

Stereotactic body radiotherapy (SBRT) is becoming widely adopted in the treatment of primary and secondary tumors. Spinal bone metastases are frequently discovered in cancer patients, and in the past have been usually treated with a palliative goal. Nevertheless, in some particular clinical settings, such as oligometastatic patients and/or those with a long life expectancy, spinal SBRT could be considered a valid therapeutic option to obtain long-lasting palliation and, when possible, with a curative goal.

This review aims to summarize available clinical and dosimetric data of published studies about spinal SBRT.

1. Introduction

Approximately one third of all cancer patients will develop bone metastases and approximately 70% will present metastases involving the vertebral column, most commonly at the thoracic and the

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http://dx.doi.org/10.1016/j.critrevonc.2015.11.002
1040-8428/

lumbar level (Van Oorschot et al., 2011). Back pain is the most common initial presenting symptom, often with associated neurological problems. Conventional fractionated radiotherapy (RT) has an historical role in the management of spine metastases and the most commonly used regimen of RT is 30 Gy in 10 fractions (De Bari et al., 2011). Nevertheless, a RTOG study evaluating different dose fractionation schedules in terms of frequency, promptness and duration of pain relief showed that more hypofractionated schedules were as effective as high dose protracted regimens (Tong et al., 1982). These data have been confirmed in several randomized controlled trials and subsequent meta-analyses conducted by Wu et al. and by Chow et al., both showing no significant differences in complete and overall pain relief between single and multi-fractions palliative RT for bone metastases, but also significantly higher re-treatment rates occurring in patients receiving single fraction regimens (Wu et al., 2003; Chow et al., 2012). The choice between the different schedules depends on several factors, including the clinical conditions of the patient and/or the local anatomy and/or some local organizational constraints (Koswig and Budach, 1999). However, single-dose treatments are usually preferred in patients with a limited lifespan and/or poor performance status or in case of long waiting lists of the treating centers (Lutz et al., 2007).

Recent advances in RT treatment planning and dose delivery allow radiation oncologists to deliver treatments with a long-lasting palliation potential (and sometimes also potentially curative) also to patients that would be traditionally candidates only to palliative systemic therapies, possibly at a reasonable price in terms of toxicity. Ideal candidates for these treatments are *oligometastatic* (i.e. those presenting 1–5 metastatic sites and also an active primary lesion) or, much better, *oligo*-recurrent patients (i.e. patients affected by 1–5 metastatic sites with a cured primary tumor) (Niibe and Chang, 2012).

A study by Jacobson et al. (2001) already showed that patients with bony oligometastases may have a prolonged survival time, passing from a median survival of 55 months for patients with 1 bone metastatic site to 22 months for those presenting $\geq$3 metastatic sites. Moreover, a curative approach to metastatic disease could potentially allow a durable tumor control, following the "seed and soil" and the "multiple steps cancer progression" theories (Chambers et al., 2002; Fidler, 2003).

Recently, stereotactic body radiation therapy (SBRT) has been introduced in the daily clinical practice in several RT centers, both in the treatment of small primary and secondary tumors and represent a local, non-invasive approach compared to surgery or other minimal-invasive options because of a lower rate of morbidity, lower costs, and the potential for delivering ablative treatments on an outpatient basis (De Bari et al., 2014a; Alongi et al., 2013, 2012; Ricardi et al., 2013). SBRT was introduced in the 1990s, as an extracranial application of the well-known radiosurgery approach using spatial coordinates to define the position to irradiate target with highly escalated radiation doses. Today, the concept is rapidly changing, and SBRT identifies a "philosophy" for treating cancer in the body not necessarily with spatial coordinates, but essentially prescribing high focused high total doses delivered in one or few sessions (Ricardi et al., 2013; Alongi et al., 2014). Moreover, the introduction over the last few decades, of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) techniques allowed clinicians to prescribe safely higher doses/fraction in few fractions. Several studies showed a reduction of toxicity rates in patients treated with IMRT compared to those treated with 3D-EBRT (Gomez-Millan et al., 2013; Bauman et al., 2012). Recently, more evolved forms of IMRT, such as volumetric modulated arc radiotherapy (VMAT) or helicoidal tomotherapy (HT), and robotic accelerators specifically designed for SBRT have been introduced in the clinical practice, showing initial promising dosimetric improvements compared to IMRT (Mellon et al., 2015; Dai et al., 2014; Peters et al., 2014; Atalar et al., 2012; Cendales et al., 2014) combined with substantially reduced treatment delivery times. Image guided radiotherapy (IGRT) allowed daily online and offline verification of the setup of the patients. Using IGRT, the treatment volume can be reduced by minimizing the size of the necessary margins to count for inaccuracies in target position and patient setup, with a consequent reduction of toxicity rates (Alongi and Di Muzio, 2009; De Bari et al., 2014b; Maund et al., 2014; Chen et al., 2014; Udrescu et al., 2012). Spine SBRT has been quickly adopted in the RT community (Pan et al., 2011), and available retrospective and prospective evidences are growing, both in terms of number of involved patients and in the quality of the studies (Wang et al., 2012; Ryu et al., 2003; Guckenberger et al., 2014).

This review aims to perform a descriptive summary of the available clinical data and dosimetric aspects of SBRT for spinal metastases.

2. Studies selection

Articles dealing with SBRT in the treatment of spinal metastases have been searched. The word "SBRT" or "stereotactic body radiotherapy" or "stereotactic body radiation therapy" AND "spinal metastases" or "metastases" were used to search articles in the PubMed database. Then, articles reporting data concerning issues other than the role of SBRT in the treatment of spinal metastases were excluded. Articles written in languages other than English and those presented only as abstracts at conferences proceedings were also excluded. Finally, 24 articles were selected (for a total of 2792 patients and 3454 metastatic lesions, see Table 1).

3. Clinical experiences: clinical outcomes and safety

3.1. Efficacy

The first report about SBRT for spinal metastases was published in 1995 by Hamilton et al. (1995). Authors used a prototypic device called extracranial stereotactic radiosurgery frame to deliver SBRT to treat 5 patients with metastatic spine neoplasms using a modified linear accelerator. This system had been presented by the same authors in a previous report (Hamilton and Lulu, 1995) and it was used both for immobilization of the patients, and for tumor localization and treatment. A median single fraction dose of 10 Gy (range: 8–10 Gy) was delivered, with a median normalization to 80% isodose contour (range: 80–160%). These five patients represent the first clinical application of SBRT for spinal targets. After a median follow-up of 6 months (range: 1–12), authors reported a single complication of esophagitis resolved with medical therapy in a patient treated for a tumour involving the C6-T1 segments. No radiographic or clinical signs of in-field progression were reported, but 2 patients died from systemic metastatic disease. The authors concluded that extracranial SBRT could be considered a therapeutic option, even in case of spinal cord compression. Since then, several articles have been published.

3.2. Clinical outcomes

Tables 1 and 2 summarize available data (Wang et al., 2012; Guckenberger et al., 2014; Gerszten et al., 2007; Sellin et al., 2015; Folkert et al., 2014; Mantel et al., 2014; Benzil et al., 2004; Chang et al., 2007, 2009, 2012; Choi et al., 2010; Gagnon et al., 2009; Sheehan et al., 2009; Zelefsky et al., 2012; Greco et al., 2011; Garg et al., 2012; Nguyen et al., 2010; Sahgal et al., 2009; Yamada et al., 2008; Klish et al., 2011a; Balagamwala et al., 2012; Schipani et al., 2012 ; Laufer et al., 2013a; Heron et al., 2012). In Table 1, the number

Table 1
Principal studies on spine SBRT (patients characteristics).

Author and publication year [reference]	Years of enrollment	Type of study	No. of patients (No. of lesions)	De-novo irradiations/reirrad. (pts)	SBRT Schedule [Gy]	Primary endpoints
(Benzil et al., 2004)	2001–2004	Case series	31 (35)	31/0	10–25 Gy/2–10 fx	Efficacy; Toxicity
(Chang et al., 2007)	NR	Phase I/II study	63 (74)	53/10	27–30/3–5 fx	Safety; effectiveness; patterns of failure
(Gerszten et al., 2007)	NR	Prospective data collection	393 (500)	156/344 (by lesions)	12.5–25Gy/1 fx	Efficacy; Toxicity
(Ryu et al., 2008)	2003–2006	Prospective study	93 (103)	93/0	18–24 Gy/1 fx	Efficacy; Toxicity
(Chang et al., 2009)	2002–2007	Retrospective study	129 (167)	76/53	16–39/1–5 fx	Efficacy; Safety
(Gagnon et al., 2009)	2002–2006	Prospective study	200 (274)	82/118	21–37.5/3–5 fx	Pain; quality-of-life
(Sheehan et al., 2009)	2004–2007	Retrospective study	40 (110)	40/0	10–24/1 fx	Efficacy; Safety
(Sahgal et al., 2009)	2003–2006	Retrospective study	39 (60)	14/25	24/3 fx	actuarial outcomes; dosimetric analysis
(Choi et al., 2010)	2002–2008	Retrospective study	42 (51)	0/42	10–30/1–5 fx	Efficacy; safety
(Nguyen et al., 2010)	2002–2007	Retrospective study (only CCRC metastases)	48 (55)	22/26	24 Gy/1 fx 27 Gy/3 fx 30 Gy/5 fx	Efficacy; Safety
(Greco et al., 2011)	2004–2007	Retrospective study	103 (126)	103/0	18–24/1 fx	LC
(Klish et al., 2011a)	2002–2007	Phase I/II study	58 (65)	58/0	18 Gy/1Fx 27 Gy/3 Fx 30 Gy/5 fx	To evaluate the rates of failure in adjacent and distant spine
(Chang et al., 2012)	2002–2008	Retrospective study	185 (185)	131/54	Mean radiation doses (EQD2, alpha/beta ratio 10 Gy) *De novo* irradiations: 50.7 Gy Re-irradiations: 51.1 Gy	LC
(Wang et al., 2012)		phase 1–2 study	149 (166)	70/79	27–30/3 fx	Efficacy; safety
(Zelefsky et al., 2012)	2004–2010	Retrospective study (only RCC metastases)	105 (105)	105/0	18–24/1 fx 20–30/3–5 fx	Local control; toxicity
(Garg et al., 2012)	2005–2010	phase 1–2 study	61* (63)	61/0	non-renal spinal metastases : 18 Gy/1 fx renal spinal metastases : 24 Gy/1 fx	Efficacy; Safety
(Balagamwala et al., 2012)	NR	Retrospective study	57(88)	39/18	8–16 Gy/1 fx	Efficacy; safety
(Schipani et al., 2012)	2005–2008	Retrospective study	124(165)	165/0	8 Gy/1 fx	Dosimetric analysis
(Heron et al., 2012)	2000–2008	Retrospective study	228(348)	246/102	Mean doses: 16.3 Gy/1fx 20.6 Gy/3 fx 23.8 Gy/4 fx 24.5 Gy/5 fx	Efficacy; safety
(Laufer et al., 2013a)	2002–2011	Retrospective study(post-surgery spinal metastases)	186(186)	186/0	24 Gy/1fx 18–36 Gy/5–6 fx 24–30 Gy/3 fx	clinical outcome
(Folkert et al., 2014)	2005–2012	Retrospective study(only sarcoma metastases)**	88(120)	108/12(lesions)	18–24/1 fx 24–36/3–6 fx	Efficacy; safety
(Mantel et al., 2014)	2004–2010	Retrospective study	32(36)	32/0	48.5–65/17–33 fx	Efficacy; safety
(Guckenberger et al., 2014)	2004–2013	Multicentric retrospective study	301(387)	301/0	10–60 Gy/ 1–20 fx	Safety and clinical outcome
(Sellin et al., 2015)	2005–2013	Retrospective study(only RCC metastases)	37(40)	37/0	24/1 fx 27/3 fx 30/5 fx	Overall survival;toxicity

of patients treated for a *de-novo* irradiation and those treated in the context of a re-irradiation is also detailed. These reports largely varied in terms of total dose, dose/fraction and/or delivery techniques and it makes any comparison difficult, both in terms of efficacy and safety. Moreover, studies are often characterized by a retrospective and single-institution nature, and the different endpoints

Table 2
Principal studies on spine SBRT (clinical outcomes).

Author and publication year [Reference]	Years of enrollment	FUP Months(range)	Local control (LC) and/or pain relief	Overall survival (OS)	Grade 3–4 Acute and late toxicity rates(pts)
(Benzil et al., 2004)	2001–2004	NR	Significant pain relief: 32/34	NR	None
(Chang et al., 2007)	NR	21.3	actuarial 1-year tumor progression-free incidence: 84%	NR	- Acute G3 nausea or vomiting: 2 - Acute G3 diarrhea: 1 - Acute G3 dysphagia and trismus:1; - Acute G3 noncardiac chest pain: 1. - No late G3-4 toxicity.
(Gerszten et al., 2007)	NR	21(3–53)	LC: 88%	NR	NR
(Yamada et al., 2008)	2003–2006	15(2–45)	LC: 90% Durable symptom palliation	NR	No G3–G4 acute/late toxicities
(Chang et al., 2009)	2002–2007	6	Pain relief in 91%	NR	NR
(Gagnon et al., 2009)	2002–2006	12(1–51)	Improvement of the mean pain scores(from 40.1 to 28.6 after SBRT, $P < 0.001$). Median LC *de novo* irradiations: 14.5re-irradiation: 10.5	NR	None
(Sheehan et al., 2009)	2004–2007	12.7 months(4–32)	LC: 82% Pain relief: 85%	Median OS:12.2 months(6–26)	One-year kyphosis progression: 73%
(Sahgal et al., 2009)	2003–2006	9	1-year LC: 85% 2-years LC: 69%	Median OS: 21 months2-years OS: 45%	No G3-4
(Choi et al., 2010)	2002–2008	7(2–47)	6-months LC:87% 1-year LC: 73%	6 months: 81% 1-year: 68%	G4 neurotoxicity: 1 (2%)
(Nguyen et al., 2010)	2002–2007	13.1(3.3–54.5)	1-year pain control: 52%.1-year LC: 82%	1-year OS: 72%	G3 Pain: 1 (2%)G3 anemia: (2%)
(Greco et al., 2011)	2004–2007	18(2–45)	Local relapse-free survival (LRFS): 64% LRFS HD (23–24Gy): 82% LRFS HD (18–20 Gy): 25%($p < 0.0001$)	NR	Acute G3 GI: 2 (1.9%) Late Esophageal stricture: 1 patient Late G3 peripheral neuritis syndrome : 3
(Klish et al., 2011a)	2002–2007	18(6–66)	Time to any spine failure: 9.7 months	Median OS: 30 months	NR
(Chang et al., 2012)	2002–2008	21.8	Median progression free time : 29.6 months *De novo* irradiations:26 months Re-irradiations:18 months *de novo* irradiations LC: 6- months: 95% 1-year: 89% 2-years: 90% Re-irradiations LC: 6- months: 96% 1-year: 81% 2-years: 79%	Median OS29.6 months *de novo* irradiations: 32.4 months re-irradiations: 20.7 months	No case of radiation myelopathy detected. Post-SBRT vertebral fracture: 6.5%
(Wang et al., 2012)		15.9(9.5–30.3)	1-year LC: 80.5% 2-years LC: 72.4% 6-months pain relief: 27.7%	1-year OS: 71.9% 2-years OS: 48.8%	- Acute G3 nausea or vomiting: 2 - Acute G3 diarrhea: 1 - Acute G3 dysphagia or trismus: 3 - Acute G3 noncardiac chest pain: 1 - Acute G3 neck pain: 1. - Acute G3 diaphoresis: 1 - Acute G3 fatigue:1 - No late G3-4 toxicity.
(Zelefsky et al., 2012)	2004–2010	12(1–48)	3-years LC: 44%. 3-years HD (24 Gy) LC: 88% 3-years LD (<24 Gy) LC: 21%		Acute G4 erythema:1 Post-SBRT vertebral fracture: 3.8%
(Garg et al., 2012)	2005–2010	19.7(1.2–52.1)	18 months LC: 88%	18 months OS: 64%	Late Neurologic toxicity: 2 One hemicord syndrome (11 months after treatment) One L5 radiculopathy (9 months after treatment)
(Balagamwala et al., 2012)	NR	5.4(0.3–38)	Median time to pain and duration relief were 0.9 months and 5.4 months respectively Radiographic progression free survival at 1 year: 71.2%	1 year -OS: 48.9%	Nausea and vomiting G3: 1

Table 2 (*Continued*)

Author and publication year [Reference]	Years of enrollment	FUP Months(range)	Local control (LC) and/or pain relief	Overall survival (OS)	Grade 3–4 Acute and late toxicity rates(pts)
(Schipani et al., 2012)	2005–2008	7(1–50)	LC: 92%At the time of the analysis Pain and/or neurological symptoms controlled in 114 patients (92%)	8(2–50)	None
(Heron et al., 2012)	2000–2008	12	2-years LC: 96% for multi-fractions group 2-years LC: 70% for single-fraction group	1-year OS: 63% for multi-fractions group 1-year OS: 46% for single-fraction group	Acute G3:1 in single-fraction group No G3–G4 in multi-fractions group
(Laufer et al., 2013a)	2002–2011	7.6(1–66.4)	Cumulative incidence of local progression at 1 year: 16.4%	NR	NR
(Folkert et al., 2014)	2005–2012	12.3(1–80.7)	1-year LC: 87.9%	1-year OS: 60.6%	- Acute dermatitis: 1 - Acute G3 fatigue: 1 - Acute G3 postoperative wound complication: 1 - G3 tracheoesophageal fistulae: 2
(Mantel et al., 2014)	2004–2010	20.3	1-year LC: 92% 2-years LC: 84% Pain free sites: 61%	Median OS:19.6 months 2- and 3- years: 41%	Progressive of new vertebral compression fractures: 22%
(Guckenberger et al., 2014)	2004–2013	11.8(0–105)	1-year LC: 89.9% 2-years LC: 83.9% Median time to local failure: 9 months (range: 1–55)	median OS: 19.5 months	Acute grade 3: 2 patients. Progressive of new vertebral compression fractures: 7.8%
(Sellin et al., 2015)	2005–2013	49(38.2–75.8)	LC: 57% Pain evaluationimproved: 12 patients stable: 8 patients worse: 9 patients	Median OS: 16.3 months	Progressive of new vertebral compression fractures: 27.5% Progressive kyphosis: 1 patient

(and adopted scores) which have been tested are other important limiting factors in the comparison of the results of these studies.

Gerszten et al. (2005) published the series with relative longest median follow-up (37 months). In their prospective evaluation of 60 lesions in 48 consecutive patients treated with CyberKnifeã for spinal metastases from RCC, 42/60 lesions had previously received EBRT. Mean delivered dose was 20 Gy (range: 17.5–25 Gy), in a single fraction. The volume of spinal cord and cauda equina exposed to ≤8 Gy ranged from 0.01 to 3 cm^3 (mean: 0.64 cm^3) and from 0.01 to 2.2 cm3 (mean: 0.65 cm3), respectively. With this dose limits, no radiation-induced toxicity occurred. Axial and radicular pain improved in 89% of patients treated for pain. There were 8 patients who were treated for a radiographically documented tumor progression: 7/8 patients showed a radiological tumor control. Looking at the overall population, 6 patients required open surgical intervention for a clinically demonstrated tumor progression after radiosurgery. In our opinion, two aspects of this series should be highlighted: a single-fraction spinal SBRT seems to be safe and to provide good, long term symptomatic responses, and it is also effective in tumors traditionally considered radio-resistant, as RCC and melanoma.

The same team lately published the largest series of spinal SBRT. The authors collected data of patients treated with a single-fraction SBRT as part of the management of metastatic spine tumors: 393 patients for a total of 500 lesions of histologically proven spinal metastases were treated using CyberKnifeã Image-Guided Radiosurgery System (Gerszten et al., 2007). Mean age was 56 years (range: 18-85 years). Lesion location included 73 cervical, 212 thoracic, 112 lumbar, and 103 sacral. Noteworthy, 344 lesions had previously undergone external beam irradiation (EBRT) using standard fractionation schedules (from 30 Gy in 10 fractions to 35 Gy in 14 fractions). Pain was the primary indication for spinal SBRT in 336 cases (67%). The maximum intratumoral dose ranged from 12.5 to 25 Gy (mean 20). Median follow-up was 21 months (range: 3–53 months). Spinal SBRT was found to be highly effective in decreasing pain, with an overall long-term improvement of pain in 86% of the patients, with some differences in terms of efficacy depending on primary histology. Indeed, this study showed a long-term pain improvement in 96% of breast cancer and melanoma patients, 94% of renal cell carcinoma patients (RCC) and 93% of lung cancer patients. Overall long-term tumor control was radiologically demonstrated in 90% of cases, with 100% of breast, lung, and RCC metastases, and 75% of melanoma metastases which were controlled, respectively. For previously irradiated lesions, overall long-term radiographic tumor control was 88% for all cases, with better results in breast (100%) and lung (100%) cancer patients and worst results in RCC (87%) and in melanoma (75%) patients. At a median follow up of 21 months (range, 3–53 months), there were no clinically neurologic signs attributable to radiation induced spinal cord toxicity. In two cases neurologic impairment was felt not to be due to radiation injury, but for tumor progression and subsequently spinal cord compression, as revealed imaging.

3.3. Feasibility

A possible concern about spinal SBRT is the feasibility, both in terms of accuracy in the delivery and in terms of tumor coverage and organs at risk constraints. This issue was addressed by a recent prospective Phase II multicentric trial (Radiation Therapy Oncology Group (RTOG 0631 trial) (Ryu et al., 2014). After an accreditation of 65 Institutions based on spine phantom dosimetry and IGRT compliance, 44 eligible patients with 1–3 spine metastasis and with a Numerical Rating Pain Scale (NRPS) ≥5 have been enrolled in this study. Prescription dose was 16 Gy delivered in a single fraction and the primary endpoint was the SBRT feasibility. Accuracy of image guided SBRT was in compliance with the protocol in 95%. Overall

compliance for other normal tissue constraints was per protocol in 74%. The target coverage and spinal cord dose constraint were in accordance with the protocol requirements in 100% and 97%. This study rigorously demonstrated the feasibility of spinal SBRT, and it is the basis for the ongoing randomized phase III RTOG 0631 trial, addressing the more clinical issue of pain relief and quality of life by comparing SBRT (single dose of 16 Gy) and standard EBRT (sigle dose of 8 Gy) (Available, 2015).

These good results in terms of feasibility and these high rates of agreement amongst the institutions performing spinal SBRT was already published in the study by Guckenberger et al. (2011) reporting the results of a survey about the methods of spine radiosurgery at five international institutions. Results of this survey showed a global good agreement amongst the participating Institutions in the pre-treatment clinical and technical procedures, but it also identified 3 major areas of uncertainty and disagreement: indications and contra-indications for spine radiosurgery, treatment dose and fractionation and tolerance dose of the spinal cord.

Lately it has been published an international report identifying key methodologies for safe implementation and credentialing of spinal SBRT (Gerszten et al., 2013): it was based on a questionnaire consisting of 24 items covering various aspects of institutional credentialing for spinal SBRT completed by 7 institutions. Despite some slight differences amongst the involved centers, authors showed a strong agreement in considering credentialing as an important component for safety and efficacy of spinal SBRT implementation.

3.4. Treatment of contiguous metastases

Another important issue is the treatment of contiguous sites of vertebral body metastasis using SBRT, because of the potential larger treatment volumes and consequent higher risk of toxicity.

Sellin et al. (2015) recently analyzed the outcomes of 37 consecutive patients (40 target volumes) undergoing de novo stereotactic radiosurgery for contiguous RCC metastases. The majority of the patients was treated with single fraction radiosurgery of 24 Gy; the maximum dose to any portion of the spinal cord was 10 Gy. Their study interestingly showed that local control significantly influenced the overall survival: patients presenting a local progression after spinal SRS had a worse overall survival compared to those with a locally controlled disease (HR 3.4, 95% CI 1.6–7.4, $p = 0.002$). Moreover, these authors described some important prognostic factors which could help in the selection of best candidates to spinal SBRT: at multivariate analysis, local progression after spinal SBRT, a diagnosis of metastasis <12 months after primary treatment for renal cell carcinoma, KPS score $\leq$70, and a progressive systemic disease at time of SBRT significantly influenced overall survival (respectively, HR 3.7, $p = 0.002$; HR 2.6, $p = 0.026$; HR 4.0, $p = 0.002$; and HR 13.2, $p < 0.001$). This study confirmed the efficacy of SBRT also to treat cancers traditionally considered to be radio-resistant, as RCC.

Another study confirming this potential of ablative doses of RT delivered with SBRT techniques was published by Folkert et al. (2014). Authors report data in terms of outcomes and toxicity for hypofractionated (HF) or single-fraction (SF) image-guided SBRT for spinal metastases from sarcomas. A total of 88 patient and 120 lesions were treated with HF (52 patients, 3–6 fractions; median dose, 28.5 Gy) or SF (68 patients, median dose: 24 Gy). The choice between HF and SF was based on prior irradiation to the same lesion (12/120 lesion had received a previous course of RT) or proximity to critical dose-limiting normal structures. Thirty-three out 120 lesions received surgery before SBRT, and 5/120 received it after SBRT. After a median follow-up of 12.3 months, the 1-year LC rate was 87.9% (CI95%: 81.3–94.5%). SF showed better results than HF, with a 1-years LC rate of 90.8% (CI, 83–98.6%) vs 84.1% (CI, 72.9–95.3%, $p = .007$). This better outcome was confirmed also at 18 months (88.2% versus 76.4%, $p = .007$) and at the multivariate analysis ($p = .030$, HR 0.345; CI, 0.132–0.901). Authors report a good toxicity profile, with one case of G3 acute dermatitis, one case of G3 chronic fatigue, one case of postoperative wound complication and 2 cases of tracheoesophageal fistulae. The authors stated that both the cases of tracheoesophageal fistulae occurred in patients treated with single-fraction IG-SRS to lesions in the upper thoracic spine, who presented also radiation recall esophagitis after the administration of doxorubicin and iatrogenic manipulation in the form of biopsy, dilation, or both.

The long term results of fractionated stereotactic body radiation therapy for spinal metastases have been reported by Mantel et al. (2014). Authors report data about the treatment of 36 spinal metastases (32 patients) treated with various fractionated regimens. The median treatment dose was 60 Gy (range, 48.5–65 Gy) given in a median of 20 fractions (range, 17–33). After a median follow-up of 20.3 months, pain-free and neurological symptoms free lesions were 61% and 86%, respectively. One- and 2-years local control was 92 and 84%, respectively. With this fractionated schedule, no G3-4 acute or late toxicity were reported. Compared to surgery, SBRT potential benefits are the short treatment time (which is also interesting as it reduces the delay for the beginning of systemic treatments), good local control rates and acceptable toxicity. Last but not least, SBRT should be strongly considered in the conditions of re-irradiation after a previous course of EBRT.

3.5. Toxicity

Regarding late toxicity, vertebral compression fracture and radiation-induced myelopathy are the most important issues to analyze.

3.5.1. Vertebral compression fracture (VCF)

In a multi-institutional analysis, Sahgal et al. (2013a) assessed the risk of VCF after spine SBRT, using the Spinal Instability Neoplastic Score (SINS) criteria. A total of 252 patients with 410 spinal segments treated with SBRT were included. After a median follow-up of 11.5 months, (range, 0.03–113 months), in 410 spinal segments, authors observed 57 fractures (14%). Forty-seven percent of the events were de-novo fractures and 53% were classified as fracture progression. Median time to VCF was 2.46 months (range: 0.03–43.0), with 65% of them occurring within the first 4 months. One- and 2-year cumulative incidences of VCFs were 12.3% and 13.5%, respectively. At multivariable analysis, dose/fraction (greatest risk for $\geq$24 Gy vs 20 to 23 Gy vs $\leq$19 Gy), baseline VCF, lytic tumor, and spinal deformity, resulted to be significant predictors of VCF.

In a previous retrospective monoinstitutional study, the same team reported data on 167 spine lesions (Cunha et al., 2012). Authors identified 19 VCFs (11%), with 12 de-novo fractures (63%) and 7 cases of fracture progression (37%). Mean time to fracture after SBRT was 3.3 months (range: 0.5–21.6), and 1-year fracture-free probability was 87.3%. Multivariate analysis confirmed that alignment ($p = 0.003$), lytic lesions ($p = 0.007$), lung ($p = 0.03$) and hepatocellular ($p < 0.0001$) primary histology, and dose per fraction of 20 Gy or greater ($p = 0.004$) were significant predictors of VCF.

Rose et al. (2009) evaluated 62 consecutive patients undergoing single fraction IG-IMRT at 71 sites for solid organ metastases. A single median dose of 24 Gy was delivered. Fracture progression was found in 27 vertebrae (39%). Multivariate logistic regression analysis showed that CT appearance, lesion location, and percent of vertebral body involvement independently predicted fracture progression. Lesions located between the 10th thoracic vertebra (T10) and the sacrum were 4.6 times more likely to fracture than lesions above T10 (95% CI, 1.1–19.7). Lytic lesions were 6.8 times

more likely to fracture than were sclerotic and mixed lesions (95% CI, 1.4 to 33.3).

3.5.2. Radiation-induced myelopathy

In spine SBRT setting, a dose limiting structure is obviously the spinal cord. Radiation tolerance of the spinal cord is a dose limiting factor in the treatment of many malignancies. The risk of injury increases with higher total dose and dose per fraction.

A report published by the American Association of Physicists in Medicine (AAPM) indicates to limit to 7 Gy, 12.3 Gy and 14.5 Gy the dose delivered to ≤1.2 cc of spinal cord in one, three and 5 fractions, respectively (Benedict et al., 2010). The same report recommend to limit to 10 Gy, 18 Gy and 23 Gy the dose delivered to ≤0.35 cc of spinal cord in one, three and 5 fractions, respectively. These recommendations were based on the constraints used in the University of Texas Southwestern and the University of Virginia (Timmerman, 2008; Dunlap et al., 2009).

A study by Sahgal et al. (2010) reported dosimetric data of 5 patients presenting a radiation induced myelopathy after SBRT to spinal tumors. These patients were compared to a group of 19 patients with no sign or symptoms of radiation myelopathy post-SBRT, and the doses received to the maximum point, 0.1-, 1-, 2-, and 5-cc volumes, were analyzed. Authors concluded that 10 Gy to a maximum point are safe for single-fraction SBRT, and 2Gy-Equivalent Dose of 30–35 Gy to the thecal sac also poses a low risk of radiation myelopathy (RM) (alpha/beta ratio for spinal cord = 2 Gy).

The same team lately published another report about 9 patients presenting a post SBRT RM, compared to 66 patients also treated with spinal SBRT and not-presenting post-treatment myelopathy (Sahgal et al., 2013b). In this paper, authors also presented a logistic regression model to estimate the probability of RM using the dose distribution for a given volume. Finally, they report a risk of RM ≥5% when limiting the thecal sac point maximum doses to 12.4 Gy in a single fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25.3 Gy in 5 fractions (alpha/beta ratio for spinal cord = 2 Gy).

In a Phase I/II study of single fraction SBRT for 61 patients with previously un-irradiated spinal metastases, the dose delivered to the target volume ranged between 18 and 24 Gy. Dose to 0.01 cc of the spinal cord and of the spinal cord +2 mm was limited to 10 Gy and to 12 Gy. Two out of 61 (3%) patients, presented neurologic deterioration attributed to radiation toxicity. One patient developed a hemicord syndrome, 11 months post-SBRT, while in the second case a L5 radiculopathy was found 9 months after the treatment (Garg et al., 2012).

In a retrospective study by Chang et al. (2012) clinical outcomes of 131 newly treated and 54 re-treated patients were reviewed and analyzed. Different fractionation schedules were used: to compare them, the biologically effective dose (BED) was applied. The linear-quadratic model was used to calculate the SBRT dose, then the dose was normalized to a 2-Gy equivalent dose (nBED, a/b = 2 Gy for spinal cord, a/b = 10 Gy for tumor). With regard to spinal cord, a mean equivalent 2-Gy maximum dose (Dmax) of 83.4 Gy (retreatment) and 48.7 Gy (initial treatment) were reported. The mean delivered radiation doses to tumor margin were 51.1 Gy (retreatment) and 50.7 Gy (initial treatment). At a median follow up of 28 months, no cases of radiation myelopathy were detected in both groups.

3.5.3. Oesophageal toxicity

Another important point to be discussed is the potential oesophageal toxicity of these treatments: the same report by AAPM indicates to limit to 11.9 Gy, 17.7 Gy and 19.5 Gy the dose delivered to <5 cc of oesophagus in one, three and 5 fractions, respectively. The maximal dose to 0.0035 cc (or less) should be limited to 15.4 Gy, 25.2 Gy and 35 Gy, delivered in one, 3 and 5 fractions, respectively (Benedict et al., 2010).

In a prospective Phase I/II study by Garg et al. (2012) after a mean follow-up of 20 months, 5/61 patients (8%) complained mild esophagitis. There were no cases of Grade 4 toxicity.

In a series of 55 spinal metastases from RCC, three schedules were adopted (24 Gy in a single fraction, 27 Gy in three fractions, or 30 Gy in five fractions). SBRT was delivered to 6 cervical, 26 thoracic and 23 lumbar metastatic lesions. No cases of Grade 3–4 toxicities were observed. Only one case of acute G2 esophagitis was recorded (Schipani et al., 2012). Unfortunately, no dosimetric data about the patients presenting oesophageal toxicity are reported by both these authors.

3.5.4. Flare pain

Another important side effect of spine SBRT is the flare pain. Depending on the studies, pain flare is defined as an increased pain at the treated site and/or an increase in analgesic intake, and/or the initiation of steroids.

In a recent study by Pan et al. (2014) the authors analyzed 193 patients enrolled in Institutional Phase I/II trials. Pain flare was observed in 23% of patients, after a median time of 5 days after the start of treatment (range, 0–20 days). The multivariate analysis showed that the only independent factor associated with pain flare was the number of treatment fractions (odds ratio = 0.66, $p = .004$), with an increased number of treatment fractions showing a protective effect, compared to single-fractions regimens.

In a study by Chiang et al. (2013) the incidence of pain flare was even higher, with 68.3% of patients (28 out of 41 patients) presenting pain flare, most commonly on day 1 after SBRT (29%, 8 of 28). Noteworthy, all the patients enrolled in this study were steroid-naïve. Indeed, the prescription of dexamethasone resulted in a significant decrease in pain scores ($p < .0001$). Significant predictors of pain flare were higher Karnofsky performance status ($p = .02$) and cervical ($p = .049$) or lumbar ($p = .02$) locations.

4. Contouring and dosimetric recommendation

Historically, in conventional RT, the target volume usually used for spinal irradiation was 1–2 vertebral bodies above and below the level of involvement, and this for three reasons: (1) to avoid missing the correct level in the absence of computed tomography (CT) simulation; (2) to take into account for the possibility of spread of disease to the adjacent levels; (3) to take into account for beam penumbra.

The critical issue of physician acceptance of smaller fields covering only the involved levels instead of larger standard radiation portals for solitary metastasis relates to improvements in image-guided RT techniques using on board imaging techniques such as kV X-ray, cone-beam CT, or helical tomotherapy and significantly improved setup accuracy derived from stereotactic setup techniques.

Globally, available studies used various target volumes definitions, and it should be taken into account when considering toxicity profiles and clinical results of the studies. Roughly, in most of the available studies, the PTV was defined as the GTV ±2–3 mm (Table 4). Isolated local failures of the un-irradiated adjacent vertebral bodies occur in <5% of patients with isolated spinal metastasis (Klish et al., 2011b).

In the experience by Sahgal et al. (2009) 60 metastases were treated. The GTV was contoured without any margin (i.e., GTV = PTV). For postoperative cases, gross residual disease was delineated as GTV and a margin was applied to encompass the surgical bed as potential areas at risk of microscopic disease (GTV + surgical bed = CTV).

Table 3
Contouring guidelines for gross tumor volume, clinical target volume and planning target volume in spinal stereotactic body radiation therapy (SBRT) according to International Spine Radiosurgery Consortium (Klish et al., 2011b).

Target volumes	Guidelines
GTV	a) Contour gross tumor using all available imaging. b) Include epidural and paraspinal components of tumor.
CTV	a) Include abnormal marrow signal suspicious for microscopic invasion. b) Include bony CTV expansion to account for subclinical spread. c) Should contain GTV. d) Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression.
PTV	a) Uniform expansion around CTV b) CTV to PTV margin $\leq$3 mm c) Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised d) Never overlaps with cord e) Should contain entire GTV and CTV

Abbreviations: CTV: clinical target volume; GTV: gross tumor volume; PTV: planning target volume.

Nguyen et al. (2010) defined the GTV as the gross disease delineated by MRI scans, the CTV as the entire involved vertebral body, including the superior and inferior endplates, but excluding the disc and posterior elements unless they were involved by the tumor.

Notewprthy, international guidelines have been finally published and are available for the target definition of spinal SBRT (Table 3) (Cox et al., 2012).

Looking at the fractionation schedules, the available data summarized in Table 1 show a very large heterogeneity in the number of fractions and in the dose/fraction. Roughly, spinal SBRT has been usually delivered in 1–3 fraction, with a total dose of at least 7–8 Gy in multi-fractions schedules and of at least 15 Gy in the single-fraction schedules (Table 1). Table 4 summarizes available target volumes definition and dosimetric constraints to the spinal cord in the published studies.

It should be noted that in the available studies, the constraints are often not reported, thus strongly limiting the possibility of looking for any correlation between the delivered dose and the toxicity. Gertzen et al. (2007) used a Dmax to the kidneys <2 Gy. Zelefsky et al. (2012), Greco et al. (2011), and Garg et al. (2012) optimized their plans using a general rule of maintaining the maximal dose (Dmax) inferior to 16 Gy for all the organs at risk nearest the PTV. In these studies, Greco et al. reported 2 cases of a acute G3 gastrointestinal toxicity, one case of late oesophageal stricture and 3 cases of late G3 peripheral neuritis, Zelefsky et al. one case of G4 acute erythema and Garg et al. reported one case of late G3 radiculopathy.

The exception to this lack of constraints is the article published by Folkert et al. (2014): authors summarized in a table all the constraints that they used for single fraction- and for multiple fractions treatment. Interestingly, authors established some rigorous constraints both for neurological (Spinal cord, cauda, brainstem, brachial plexus) and for not-neurological structures (larynx, oesophagus, heart, liver, kidney, stomach/bowel, rectum). Using these constraints, authors report only one case of G3 late wound complication. No other acute or late G3 side effects are reported by the authors.

5. Patients selection

One of the most challenging issues in this clinical setting, is the correct selection of patients candidates to potentially curative SBRT. Indeed, it could be easily argued that it is crucial to identify those who would really benefit of more intensive treatments and those who would be candidate only to palliative treatments.

Chao et al. (2012) generated a prognostic index based on the recursive partitioning analysis (RPA) for patients undergoing spinal SBRT. The authors used a Kaplan-Meier analysis to detect any correlation between survival and several clinical and technical features. Finally, time from primary diagnosis (< or >30 months) and the Karnofsky performance status (< or >70) resulted to be the most important parameters to be used to identify patients with better prognosis, and then most likely to benefit of spinal SBRT.

Laufer et al. (2013b) published the decision framework used at Memorial Sloan-Kettering Cancer Center to decide about the optimal treatment for patients with spinal metastases. This framework, called NOMS, is based on neurologic, oncologic, mechanical, and systemic parameters and incorporates the use of conventional radiotherapy, spinal SBRT, and minimally invasive and open surgical procedures. Following the NOMS decision algorithm, SBRT should be delivered in patients presenting: (1) A low epidural spinal cord compression score, a radioresistant tumor and without signs of vertebral instability; (2) As post-stabilization treatment, in patients with an high epidural spinal cord compression score, a stable vertebral structure, a radioresistant tumor and able to tolerate surgery; (3) As post-stabilization treatment, in patients with an high epidural spinal cord compression score, an unstable vertebral structure, a radioresistant tumor and able to tolerate surgery.

Recently, Tang et al. (2015) published a scoring system that stratifies patients based on a secondary analysis of overall survival of 2 mature Phase II prospective trials. They analysed 206 patients with a minimal follow-up of 3 years. Finally, they identified 4 subgroups of patients characterized by different prognosis, from excellent to poor. This prognostic index for spinal metastases (PRISM) was based on a multivariate Cox regression model. Five clinical variables (female sex, Karnofsky performance score >60, only one bone metastasis, low number of extra-osseous metastatic sites and an interval from initial diagnosis to detection of spine metastasis of more than 5 year) and two therapeutic variables (previous surgery at the SBRT site and a previous radiotherapy at the SBRT site) were found to be statistically predictive of good or excellent prognosis after SBRT.

6. Future perspectives

Currently, the most important randomized prospective trial is the RTOG 0631 Phase II/III study (Available, 2015). Primary objective of the phase II was to determine the feasibility of successfully delivering image-guided SBRT for spine metastases in a cooperative group setting. Primary objective of the phase III is to determine whether image-guided SBRT (single dose of 16 Gy) improves pain control (as measured by the 11 point of numerical rating pain scale) as compared to conventional external beam radiotherapy (single dose of 8 Gy).

Table 4
Definition of the clinical target volume (CTV) and planning target volume (PTV) in the published studies.

Author and publication year [Reference]	Volume definition	Dosimetric constraints to the PTVand to the spinal cord
(Benzil et al., 2004)	PTV = metastasis GTV	PTV covered by the 85–90% of the prescribed dose. Spinal cord: Dmax ≥ 50% of the prescribed dose.
(Chang et al., 2007)	CTV = entire involved vertebral body and any paravertebral component. In the case of no vertebral body involvement, only theparavertebral disease was delineated. PTV = not defined	PTV covered by the 80–90% of the prescribed dose. Spinal cord: Dmax ≥ 9 Gy.
(Gerszten et al., 2007)	NR	PTV covered by the 80% of the prescribed dose. Spinal cord: NR.
(Yamada et al., 2008)	CTV = the entire involved vertebral body PTV = CTV + 2 mm	100% isodose line to maximize the percentage of PTV that received 100% of the prescribed dose. Spinal Cord: Dmax 12–14 Gy
(Chang et al., 2009)	NR	NR
(Gagnon et al., 2009)	CTV = tumor evident from imaging plus a margin of tissueat risk for microscopic disease PTV = CTV	PTV covered by the 75% of the prescribed dose. Spinal cord: NR.
(Sheehan et al., 2009)	NR	PTV: NR Spinal cord contiguous with the spinal metastasis being treated: Dmax <10 Gy to 10% of the spinal volume
(Sahgal et al., 2009)	Not- operated cases : GTV = PTVpostoperative cases : GTV + surgical bed = CTV = PTV	PTV: NR Spinal cord: NR, but a retrospective analysis of the doses delivered to neurologic structures has been performed and reported.
(Choi et al., 2010)	lytic lesion: PTV = GTV Ill-defined lesions: PTV = GTV + 2–3 mm	PTV: NR Spinal cord: Dmax 70% of the prescribed dose. A retrospective analysis of the doses delivered to neurologic structures has been performed and reported.
(Nguyen et al., 2010)	GTV = lesion defined on MRI CTV = the entire involved vertebral body up to and including the superior and inferior endplates, excluding the disc and posterior elements unless they were involved with tumor. PTV = NR	CTV = covered by 90% of the prescribed dose. Spinal cord: Dmax 9–10 Gy.
(Greco et al., 2011)	CTV = the entire involved vertebral body PTV = CTV + 2 mm	PTV: covered by 100% of the prescribed dose. Spinal cord: Dmax <12 Gy.
(Klish et al., 2011a)	GTV = CTV CTV = the entire involved vertebral body, pedicles and posterior elements with posterior bone margin	NR
(Chang et al., 2012)	GTV = CTV PTV = GTV + 2–3 mm	PTV: covered by the 80–90% of the prescription dose. Spinal cord : Dmax ≤10 Gy. A retrospective analysis of the doses delivered to neurologic structures has been performed and reported.
(Wang et al., 2012)	GTV = vertebral lesion CTV = GTV + surrounding vertebral body (including superior and inferior endplates and any existing paraspinal component), along with all additional spinal structures deemed to be at risk for recurrence, such as the pedicle, lamina, and posterior elements. PTV = CTV	PTV: NR. Spinal cord : Dmax ≤10 Gy.
(Zelefsky et al., 2012)	CTV = the entire involved vertebral body PTV = CTV + 2 mm	PTV: covered by 100% of the prescribed dose. Spinal cord: Dmax <12 Gy.
(Garg et al., 2012)	GTV = tumor defined with MRI CTV = GTV plus contiguous marrow space or at-risk postoperative region PTV = CTV	PTV: mean dose 1 Spinal cord: Dmax <12 Gy.
(Balagamwala et al., 2012)	GTV = CTV = PTV CTV = entire vertebral body and/or posterior elements depending on tumor involvement and paraspinal and epidural disease No margins were added to CTV	PTV: minimum of 90% coverage of CTV by prescription dose Spinal cord: Dmax 14 Gy, less than 10% of spinal cord volume receiving ≥10 Gy Cauda equina: Dmax 16 Gy, less than 10% of cauda equina volume receiving ≥10 Gy
(Schipani et al., 2012)	GTV = CTV = PTV CTV = involved spine segment and the radiographically evident gross tumor involving epidural or paraspinal tissue	Spinal cord: 10Gy to 10% partial of spinal cord defined from 6 mm superior to 6 mm inferior to the target spine
(Heron et al., 2012)	GTV = tumor discernible on the relevant imaging study (CT and/or MRI) CTV = GTV + a margin of tissue at risk for microscopic extension PTV = CTV	In multi-fractions group: dose was prescribed to the 72% isodose line (range, 50–85%) In single-fraction group: dose was prescribed to the 80% isodose line (range, 70–95%) Spinal cord: NR
(Laufer et al., 2013a)	Preoperative MRI was used to delineate GTV which included intraosseous, epidural and paraspinal components CTV = GTV + an expansion of GTV to account microscopic tumor PTV = CTV + 2 mm	NR
(Folkert et al., 2014)	Planning contours were consistent with International Spine Radiosurgery Consortium consensus guidelines (Table 2).	PTV: covered by 100% of the prescribed dose. Spinal Cord: if single fraction treatments: 14 Gy (max point dose) or 12 Gy (max circumferential dose). If multiple fractions treatments: 21 Gy in 3 fractions (max point dose).

Table 4 (*Continued*)

Author and publication year [Reference]	Volume definition	Dosimetric constraints to the PTVand to the spinal cord
(Mantel et al., 2014)	GTV = tumor defined with MRI CTV = whole vertebra* PTV = NR	Median dose to the PTV = 60 Gy. Spinal Cord: NR.
(Guckenberger et al., 2014)	Multicenter restrospective study: target volume definition was not standardized between institutions, but it is reported in the article	Multicenter restrospective study: treatment planning and delivery techniques were not standardized between institutions, but they are described in the article.
(Sellin et al., 2015)	GTV = lesion defined on MRI CTV = the entire involved vertebral body up to and including the superior and inferior endplates, excluding the disc and posterior elements unless they were involved with tumor. PTV = NR	CTV = covered by 80–90% of the prescribed dose. Spinal cord: Dmax 9–10 Gy.

Dose constraints to organs at risk (OARs) other than spinal cord are usually not reported in the considered articles. A more detailed description of the few studies reporting constraints to the OARs is reported in the text of the article.

* In this study, the majority of the treatments (26/36) used a simultaneous integrated boost (SIB) concept, where the involved parts of the vertebrae were treated with escalated irradiation doses (median: 60 Gy, range: 48.5–65.0 Gy) and uninvolved parts of the vertebrae with conventional doses (median: 40 Gy, range: 30.0–56.0 Gy).

Abbreviations: NR = Not Reported; GTV = gross tumor volume; CTV = clinical target volume; PTV = Planning Target Volume; Dmax = maximal dose.

Recently, the results of the phase II have been published: they showed the feasibility and an accurate use of SRS to treat spinal metastases, with rigorous quality control, in a cooperative group setting (Ryu et al., 2014). The planned RTOG 0631 phase III component will proceed to compare pain relief and quality of life between SRS and external beam radiation therapy.

If the Phase III will reach the primary endpoint, the results of this study could change the practice in the therapeutic approach of patients with spinal metastases. Up to now, 217 out 395 planned patients have been enrolled (Available, 2015).

7. Conclusions

Spinal SBRT as emerging practice has been shown to be a feasible option in the treatment of spinal metastases in properly selected patients. Nevertheless, no randomized trials comparing SBRT with conventional RT in terms of pain and tumor control are available. Moreover, and there is still no consensus for the optimal treatment schedule. Preliminary data indicate local control rates exceeding those obtained with conventional RT.

The ability to deliver ablative doses in the spine also challenges traditional viewpoints on the role of surgery for spinal metastases, and will reshape not only how we select patients for surgery, but what surgery should be performed.

Although, compared to surgery and to other local approaches, including, radiofrequency ablation, cryosurgery etc, the non-invasiveness of SBRT represents a really attracting feature in the panorama of local treatment options, prospective studies with standardized outcome measures to make accurate conclusions, and ultimately, randomized studies to prove superiority of SBRT to other local options are required.

In summary, although only retrospective and some phase I-II studies are available, SBRT seems to be a promising technique for isolated or few spinal metastases. In particular, it should be probably considered as a standard approach in some clinical situations, such as re-treatments, or when a more “curative” dose would be delivered, such as in patients with a long life expectancy and/or in oligometastatic settings. Ongoing prospective studies will definitively establish its role in the treatment of spinal metastases.

Conflict of interest

None declared.

Funding

None declared.

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