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Guidelines

ESTRO clinical practice guideline: Stereotactic body radiotherapy for spine metastases

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ABSTRACT

Background and purpose: Recent progress in diagnostics and treatment of metastatic cancer patients have improved survival substantially. These developments also affect local therapies, with treatment aims shifting from short-term palliation to long-term symptom or disease control. There is consequently a need to better define the value of stereotactic body radiotherapy (SBRT) for the treatment of spinal metastases.
Methods: This ESTRO clinical practice guideline is based on a systematic literature review conducted according to PRISMA standards, which formed the basis for answering four key questions about the indication and practice of SBRT for spine metastases.
Results: The analysis of the key questions based on current evidence yielded 22 recommendations and 5 statements with varying levels of endorsement, all achieving a consensus among experts of at least 75%. In the majority, the level of evidence supporting the recommendations and statements was moderate or expert opinion, only, indicating that spine SBRT is still an evolving field of clinical research. Recommendations were established concerning the selection of appropriate patients with painful spine metastases and oligometastatic disease. Recommendations about the practice of spinal SBRT covered technical planning aspects including dose and fractionation, patient positioning, immobilization and image-guided SBRT delivery. Finally, recommendations were developed regarding quality assurance protocols, including description of potential SBRT-related toxicity and risk mitigation strategies.

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Conclusions: This ESTRO clinical practice guideline provides evidence-based recommendations and statements regarding the selection of patients with spinal metastases for SBRT and its safe implementation and practice. Enrollment of patients into well-designed prospective clinical trials addressing clinically relevant questions is considered important.

Introduction

Bone metastases are, together with lung and liver metastases frequent sites of tumor spread. More specifically approximately 18.8 per 100,000 cancer patients are diagnosed with de novo bone metastases per year [1]. The most common primary tumor types resulting in bone metastases are lung cancer followed by prostate cancer and breast cancer, where > 80% and > 50% of all metastatic patients have the bone system involved, respectively. Historically, overall survival (OS) was short in metastatic cancer patients with median survival rates of only 6 months, for the group as a whole, which was not different between patients with and without bone metastases [1]. Spine metastases in particular are associated with potentially serious consequences on patients' quality-of-life (QoL) such as pain, compression of the spinal cord or cauda equina and associated neurological deficits, spinal instability, pathological fractures and impairment of bone marrow [2,3].(See Tables 1–6).

Treatment of spinal metastases using conventional radiotherapy (CRT) is an evidence-based approach, supported by randomized phase III trials and recommended in international guidelines [34–38]. Based on randomized trials and *meta*-analyses, CRT achieves overall pain response rates of ~ 60% and complete pain response rates ranging from ~ 10–25% [39,40]. Conventional palliative external beam radiotherapy has traditionally been delivered with low radiation doses including 8 Gy in a single fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. A single fraction of 8 Gy is equivalent to fractionated radiotherapy with respect to pain response, but is associated with an increased rate of re-treatment, which is necessary in approximately 20% of patients [39,40].

In recent years, there have been substantial improvements in cancer diagnostics, local and systemic therapies for metastatic cancer, putting long-term OS within reach of more patients, including individual patient cohorts such as those with metastatic melanoma treated with immune checkpoint inhibition [41] or driver mutated non-small cell lung cancer (NSCLC) treated with targeted therapies [42]. This long-term OS of metastatic cancer patients has clinically relevant implications for the scope and practice of "palliative" radiotherapy: a) goals of treatment might change from short-term palliation to durable symptom management; b) potential late side effects of large-volume palliative radiotherapy might become relevant (e.g. in combination with targeted therapies); c) and durable local metastasis control might contribute to long-term freedom from disease progression or even cure in selected patients with oligometastatic patients [43,44]. These changing trends in our approach to the palliative patient has given rise to SBRT.

There is consequently a rational for the use of dose-escalated SBRT in appropriately selected patients with vertebral metastases, to achieve good and durable pain response, to prevent local metastasis progression and development of associated symptoms and complications and to contribute to a definitive metastases-directed treatment strategy in oligometastatic patients. Potential advantages of SBRT need to be balanced with a potential for increased toxicity after higher-dose radiotherapy, the increased requirements on staffing and equipment resources and the prolonged time interval until delivery of SBRT as compared to conventional radiotherapy.

This clinical practice guideline by the ESTRO society aims to summarize the evidence for the use of SBRT in patients with vertebral metastases and provide guidance for best-practice of spinal SBRT. Patients with symptomatic metastatic spinal cord compression (MSCC) and the reirradiation scenario were excluded from the scope of the guideline. This multidisciplinary guideline complements previous ESTRO guidelines with a dedicated focus on SBRT[37,45].

Table 1
Key question 1 recommendations, strength of recommendation and level of evidence.

	KQ 1 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients who are candidates to receive SBRT for painful vertebral metastases from solid malignancies, a baseline and post-SBRT pain assessment is recommended using either Brief Pain Inventory Index (BPI), Visual Analog Score (VAS) or Numeric Rating Scale (NRS).	Strong	High [4–9]
2.	For patients with painful vertebral metastases from solid malignancies, SBRT should be considered due to higher complete pain response rates in carefully selected patients who are not frankly unstable (SINS>12), who have no or minimal epidural disease (Bilsky 0–1), up to 3 contiguous vertebral segments in the radiation treatment volume and a prolonged life expectancy where durable local and control is also intended.	Conditional	Moderate [4–9]

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; BPI = Brief Pain Inventory Index; VAS = Visual Analog Scale; NRS = Numeric Rating Scale; NSAID = non-steroidal anti-inflammatory drug; SINS = spinal instability neoplastic score.

Methods

This guideline, its scope and the composition of the writing panel were approved by the ESTRO guideline committee. The multidisciplinary writing panel consisted of an international group of radiation oncologists (n = 10), all experts in the field of spinal SBRT, a spinal neurosurgeon (n = 1), medical physicists (n = 3), a radiation therapy technologist (n = 1) and two radiation oncology residents (n = 2). The writing panel was chaired by MG and FA.

Scope of the guideline

The scope and content of the guideline are summarized within four key questions:

1) What is the overall pain response rate, complete pain response rate and duration of pain response after SBRT for painful vertebral metastases? How does pain response after SBRT compare to conventional palliative radiotherapy?
2) What is the local control (LC) after SBRT for spine metastases? What is the role of spine SBRT in oligo-metastatic disease (OMD)?
3) What is the practice of spinal SBRT to optimize safety and efficacy according to available evidence?
4) What is the toxicity profile of spine SBRT?

Re-irradiation of vertebral metastases and symptomatic metastatic spinal cord compression were excluded from the scope of this guideline.

A systematic literature review formed the basis for this guideline and for answering the key questions [46]. The systematic review was

Table 2
Key question 2 recommendations, strength of recommendation and level of evidence.

	KQ 2 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients with vertebral metastases from solid malignancies, SBRT should be practiced with a prescription dose higher than the equivalent of 1x18Gy ($BED_{10} = 50\ Gy_{10}$). For de novo spine metastases, high dose spine SBRT practice includes 1x20Gy, 1x24Gy, 2x12Gy, 3x10Gy, and 5x7Gy. Based on these schemes there is an expectation of local control (LC) ranging from 80 to 90% at 1–2 years.	Strong	Moderate/expert opinion [6,10–13]
2.	For patients with painful vertebral metastases from solid malignancies meeting the eligibility criteria for spine SBRT, a fractionated approach using 2x12Gy is conditionally recommended as the preferred palliative SBRT dose and fractionation.	Conditional	Moderate [6]
3.	For patients with vertebral metastases from solid malignancies, single fraction SBRT with 16 or 18 Gy is not recommended as an alternative to conventional low-dose palliative radiotherapy (1x8Gy) if pain relief and/or quality of life are the primary treatment goals.	Strong	Moderate [10]
4.	For patients with vertebral metastases from solid malignancies, where local therapy for OMD is supported by disease-specific guidelines and/or the tumor board, then spine SBRT is recommended for the majority of eligible patients. In selected patients, more aggressive combined modality approaches involving (separation) surgery and SBRT may be needed to optimize LC and functional outcomes.	Strong	Expert opinion/ moderate [11,14–19]
5.	For patients with vertebral metastases from solid malignancies, when SBRT is performed in the context of concomitant targeted/immuno-therapy, a potential risk for unexpected and/or increased toxicity should be discussed between spine SBRT practitioners and medical oncologists.	Strong	Expert opinion [20,21]

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; Gy = Gray; BED = Biologically Effective Dose; LC = local control; OMD = oligometastatic disease.

performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [47]. The search was conducted in PubMed, Embase and Cochrane Library, the search period was January 2005-September 2021 and in addition, in April 2023 the RTOG 0631 study was added.

The following search terms and inclusion / exclusion criteria were used:

Search terms:

Table 3
Key question 2 statements and level of evidence.

	KQ 2 Statements	Level of Evidence (Refs)
1.	For patients with vertebral metastases from solid malignancies, very high dose single fraction spine SBRT (e.g. 1x24Gy) is associated with high rates of LC. However, the gains in local control should be balanced with a higher risk of vertebral compression fracture.	Expert opinion [11,14,22–25]
2.	For patients with vertebral metastases from solid malignancies, MRI is the preferred modality for assessing local control. CT and/or PET/CT are alternative modalities with the caveat that they are less sensitive for epidural disease. The possibility of post-SBRT imaging changes and pseudo-progression should be kept in mind. In selected patients tumor markers (e.g. PSA) may be used for follow-up.	Expert opinion [26,27]
3.	For patients with vertebral metastases from solid malignancies, spine SBRT practitioners should be alert for clinically relevant but less common toxicities, like plexopathy and myositis.	Expert opinion [19]

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; Gy = Gray; LC = local control; VCF = vertebral compression fracture; MRI = magnetic resonance imaging; CT = computed tomography; PET/CT = positron emission tomography–computed tomography; PSA = prostatic specific antigen;

- Stereotactic radiotherapy OR Stereotactic body radiotherapy OR Stereotactic ablative radiotherapy OR radiosurgery
- Spinal metastases OR spine metastases OR vertebral metastases

Exclusion criteria:

- Reviews, planning studies, study protocols, technology studies without reporting clinical outcome data (at minimum local control or pain control)
- Studies including a mixed group of previously irradiated and unirradiated patients were included only if outcomes regarding the previously unirradiated subset can be deciphered.
- Abstracts, case reports, studies with 5 or fewer patients, and reports not published in English were excluded.
- In cases of studies that were clearly updates of previous publications, the series with the longest follow-up was used.

The results of the systematic review formed the basis for recommendations and statements to answer the four key questions. The quality of evidence and strength of recommendations followed the methodology as proposed and published by the American Society for Radiation Oncology (ASTRO) (ASTRO METHODOLOGY GUIDE — V1: 5/2019).

All task force members except the n = 2 residents voted on all statements and recommendations, and consensus was defined as a minimum of 75% agreement. All task force members contributed to the final writing of the manuscript and approved the final version of the manuscript.

Key questions (KQ) and recommendations

KQ1: What is the overall pain response rate, complete pain response rate and duration of pain response after SBRT for painful vertebral metastases? How does pain response after SBRT compare to conventional palliative radiotherapy?

Based on the systematic review, pain response following spine SBRT was reported in 7 prospective and 28 retrospective studies: the overall and complete pain response averaged (non-weighted) over all studies were 83.2% and 43.5%, respectively [46].

Overall n = 5 randomized trials reported about pain response after SBRT as compared to CRT. The first was a randomized phase II trial

Table 4
Key question 3 recommendations, strength of recommendation and level of evidence.

	KQ 3 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	Patients with vertebral metastases of solid malignancies treated with SBRT should be appropriately positioned in a reproducible supine position. Above the cervical-thoracic junction (e.g. thoracic 4 vertebra and above), patient-specific rigid fixation is recommended (e.g. thermoplastic head and neck mask). Below the cervical-thoracic junction, near-rigid body immobilization, or no immobilization combined with intra-fraction positional verification/spine tracking, is recommended.	Strong	High [4,5,9,10,28]
2.	For patients with vertebral metastases of solid malignancies treated with SBRT, target and organ-at-risk volumes should be delineated on a simulation CT with slice thickness $\leq$ 1.5 mm, co-registered to T1 and T2 MRI series. Volumetric MRI images acquired in the radiotherapy treatment position are conditionally recommended.	Strong	High [4,5,9,10,28]
3.	For patients with vertebral metastases of solid malignancies treated with SBRT, the overall geometric treatment uncertainty should allow a GTV/CTV to PTV margin $\leq$ 3 mm. A minimum PTV margin of 1 mm is recommended.	Strong	Moderate [5,9]
4.	For patients with vertebral metastases of solid malignancies treated with SBRT, radiotherapy treatment should be performed using an intensity modulated delivery technique (i.e. fixed beam IMRT, VMAT, helical tomotherapy, robotic RT). The use of fast delivery techniques, such as using flattening filter free beams, is conditionally recommended.	Strong	High [4,5,9,10,28]
5.	For patients with vertebral metastases of solid malignancies treated with SBRT, a treatment planning strategy of prioritizing organ-at-risk sparing over target coverage should be utilized where the PTV is close to or overlaps with the critical organ-at-risk (i.e. spinal cord, cauda equina, oesophagus). A "cropped PTV" approach and planning organ-at-risk volume (PRV) safety margins is conditionally recommended in the planning optimization process only.	Strong	High [4,5,9,10,28]
6.	For patients with vertebral metastases of solid malignancies treated with SBRT, online image guidance procedures should be performed before each daily delivery session (e.g. using cone beam CT, stereoscopic $\times$ ray, in-room MR). Intra-fraction treatment verification imaging is conditionally recommended at least once during each treatment fraction. Six-degree of freedom (6DoF) patient positioning correction is conditionally recommended. When 6DoF is performed, verification imaging after pitch and roll corrections is conditionally recommended.	Strong	High [4,5,9,10,28]
7.	The start-up of an SBRT program for patients with vertebral metastases of solid malignancies should include radiation oncologist, medical physicist, and radiation therapist. Each SBRT case should be discussed in a multi-disciplinary setting, including medical oncologist, radiation oncologist, spine surgeon, and neuro-radiologist. The discussion with medical physicist and radiation therapist regarding the technical feasibility is conditionally recommended.	Strong	Expert opinion
8.	Each SBRT case should undergo patient specific quality assurance. All centers should audit their own SBRT technique and evaluate the positioning precision and accuracy of their equipment and this will inform center specific PTV margins.	Strong	Expert opinion

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; Gy = Gray; CT = computed tomography; MRI = magnetic resonance imaging; GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; IMRT = intensity-modulated radiation therapy, VMAT = volumetric modulated arc therapy, HT = helical tomotherapy; RT = radiotherapy; PRV = planning organ-at-risk volume; 6DoF = six degree of freedom.

comparing SBRT to CRT reported by Sprave et al.[4]. They evaluated pain response in a cohort of 55 patients treated with either 24 Gy in 1 SBRT fraction or 30 Gy in 10 CRT fractions. The primary endpoint was pain response at three months, defined as a decrease in pain of $>$ 2 points on the Visual Analog Scale (VAS). The authors reported a faster decrease in pain score in the SBRT arm at 3 months ($p = 0.01$), and while the difference in pain response rate at 3 months did not reach statistical significance (69.9% vs. 47.8%, $p = 0.13$) it was significant at 6 months (73.7% vs 35%, $p = 0.015$) in favor of SBRT. This trial was not powered appropriately but provided a benchmark for an appropriately designed and powered Phase 3 trial. The 6-month vertebral compression fracture rate was significantly higher in the SBRT arm at 28% vs 5% after CRT.

The Canadian Cancer Trials Group (CCTG) Symptom Control 24 (SC.24) phase II/III clinical trial [5] aimed to determine if the complete pain response rate was superior with SBRT vs. CRT, with the primary endpoint measured at 3 months post-treatment. The trial tested 24 Gy in 2 SBRT fractions (n = 114) vs. 20 Gy in 5 CRT fractions (n = 115). A statistically higher rate of complete pain response after 3 months in the SBRT arm (35% vs 14%, $p = 0.0002$) was observed, with a durable effect confirmed at 6-months follow-up (relative risk 1.24, $p = 0.0036$). Fracture rates were not different between both arms and no case of radiation induced myelopathy was observed. In a sub-cohort of this trial consisting of 137 of the randomized patients, from the Sunnybrook Health Sciences Center (Toronto, Canada), long-term local control, reirradiation and fracture outcomes were reported. Not only were long-term magnetic resonance imaging (MRI)-based local control rates superior in the SBRT vs. CRT arm with 2 year rates of local failure of 14.8% vs 35.6%, respectively ($p < 0.001$), the re-irradiation rates were also significantly lower (2.2% vs 15.8% at 1 year; $p = 0.002$) and the median time to re-irradiation was 22.4 months in the SBRT arm vs 9.5 months in the CRT arm [6]. However, amongst those with an iatrogenic fracture,

Table 5
Key question 4 recommendations, strength of recommendation and level of evidence.

	KQ 4 Recommendations	Strength of Recommendation	Level of Evidence (Refs)
1.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of spinal stability using the validated SINS score is recommended.	Strong	High [4,5]
2.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of surgical stabilization is recommended in case of intermediate instability (score 7–12) and especially instability (score 13–18) based on the SINS score.	Strong	Expert opinion
3.	For patients with vertebral metastases of solid malignancies, pre-SBRT assessment of epidural involvement using the validated Bilsky grade is recommended.	Strong	Moderate [29,30]
4.	For patients with vertebral metastases of solid malignancies, SBRT is not recommended in the situation of symptomatic MSCC (spinal cord or cauda equina).	Strong	High [4,5,7]
5.	For patients with vertebral metastases of solid malignancies, the following procedures are recommended to keep the risk of radiation induced myelopathy at a very low level: ● Appropriate imaging (volumetric T1/T2 MRI or alternatively CT myelography) for accurate localization of the spinal cord and/or thecal sac. ● Use of PRV concept for the spinal cord. ● Adherence to accepted dose constraints for the PRV spinal cord. ● Priority of the spinal cord dose tolerance over target volume coverage in inverse SBRT planning. ● High-precision SBRT delivery.	Strong	High [4,5,7]
6.	For patients with vertebral metastases of solid malignancies, it is recommended to prioritize adequate coverage of the GTV over sparing of nerve roots due to the low risk of radiation induced radiculopathy.	Strong	High [5,31]
7.	For patients with vertebral metastases of solid malignancies, the routine use of prophylactic treatment with steroids is not recommended due to the low risk of post-SBRT pain flare.	Conditional	Moderate [5,32,33]

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; SINS = spinal instability neoplastic score; MSCC = malignant spinal cord compression; MRI = magnetic resonance imaging; CT = computed tomography; PRV = planning-organ-at-risk; GTV = gross tumor volume.

the severity was greater in the SBRT cohort, with all grade 3 fractures observed in the SBRT cohort (n = 5).

A randomized trial using the "trials within prospective cohorts" (TwiCs) methodology compared various SBRT fractionations (18 Gy in 1 fraction, 30 Gy in 3 fractions, or 35 Gy in 5 fractions) to various CRT (8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions) for 110 patients. No benefit of SBRT was observed, with pain response at 3 months being the primary endpoint; however, the trial was not specific to spinal metastases, the dosing was non-standardized, and the trial was underpowered due to a high rate of dropout [7].

Table 6
Key question 4 statements and level of evidence.

	KQ 4 Statements	Level of Evidence (Refs)
1.	For patients with vertebral metastases of solid malignancies, fractionated SBRT is not associated with an increased risk of vertebral fracture when compared to CRT.	High [5,22]
2.	For patients with vertebral metastases of solid malignancies, single-fraction SBRT with doses > 20 Gy is associated with an increased risk of vertebral fracture as compared to CRT and compared to fractionated SBRT.	High [5,14,25]

Abbreviations: KQ = key question; SBRT = stereotactic body radiotherapy; Gy = Gray; CRT = conventional radiotherapy.

The randomized phase 3 NRG Oncology/ RTOG 0631 trial [8] compared single fraction SBRT (16 Gy or 18 Gy in 1 fraction to the involved vertebra) to CRT (8 Gy in 1 fraction to the involved vertebra and one vertebra above and below) to sites of painful spinal metastases (minimum baseline pain score of 5 using the 0 to 10 Numerical Rating Pain Scale). A total of 339 patients were randomized 2:1 between SBRT and CRT and no improvement in pain response (defined as a minimum 3 point drop in the VAS pain score) at 3 months was observed: 41.3% vs 60.5% favoring CRT. There were no differences in acute or late adverse effects between treatment arms including vertebral compression fracture, which was 19.5% after SBRT and 21.6% after CRT at 24 months. There were no cases with spinal cord complications reported at 24 months [8].

The ROBOMET phase III trial [48] has been reported in abstract form only, which randomized 126 patients with painful bone metastases 1:1 to 8 Gy single fraction CRT vs 20 Gy single fraction SBRT; primary endpoint was complete pain response at 1 months. Patients with complicated bone metastases were excluded and about one quarter of patients was treated for spine metastases. Complete pain response was not statistically significantly increased at one month (37% vs 25%) in the intention to treat analysis, whereas a significantly improved complete pain response was observed at 3 months in the per protocol analysis for the SBRT cohort (54% vs 31%; p = 0.048). No differences in toxicity, pain flare and quality-of-life were observed between treatment arms.

Few prospective studies assessed the long-term pain response rates after SBRT. A multi-center single arm non-randomized phase 2 study reported data on 63 painful metastases treated with SBRT in 57 patients with a median follow-up of 60 months [9]. An overall pain response rate of 82% was reported, including 31% of patients with complete response; minimal toxicity was observed with late grade 3 toxicity recorded in 4% of cases, and a favorable impact in terms of quality-of-life, with improved results remaining stable over time.

Ultimately, at present, we conclude that there is benefit of SBRT for appropriately selected patients who are not frankly unstable (SINS>12), who have no or minimal epidural disease (Bilsky 0–1), up to 3 contiguous vertebral segments in the radiation treatment volume and a prolonged life expectancy where durable local and control is also intended: SBRT offers higher rates of overall and complete pain response, better local control and a lower risk of reirradiation. Conversely, conventional radiotherapy is preferred over SBRT in patients with short-life expectancy, where only short-term pain control is intended, in patients unable to tolerate MRI or immobilization for SBRT, or patients in significant pain despite oral analgesia, who may not be able to tolerate waiting for MR and SBRT planning.

KQ2: What is the local control (LC) after SBRT for spine metastases? What is the role of spine SBRT in oligo-metastatic disease (OMD)?

A high local metastasis control (LC) is required for definitive local treatment of oligometastatic disease (OMD), and it follows that if spine SBRT has high LC, combined with acceptable toxicity and an objective means of response assessment, it will be a useful non-invasive treatment

option in OMD. A variety of SBRT schedules have been used to treat spinal oligometastases Based on the systematic review, local control rates of 80–95% are reported at 1–2 years (Fig. 1). Additionally, analysis of 1- and 2-year LC data (excluding reirradiation) indicates that higher prescription (total) dose is associated with higher LC. Results from a cohort of SC.24 patients demonstrated MRI-based LC of 93.9/85.2% at 1/2-years respectively [6]. A randomized phase III trial compared single fraction SBRT (24 Gy) with fractionated SBRT of 27 Gy in 3 fractions in 117 oligometastatic patients (56% spinal metastases) and reported improved local control after higher-dose single fraction SBRT [49]. Based on these and other data, a prescription dose greater than the equivalent of 1x18Gy/BED_{10} = 50 Gy_{10} is recommended for durable LC in oligometastatic patients. While a higher dose may increase LC, it can also increase the expected risk of vertebral compression fracture, especially when a single-fraction schedule like 1x24Gy is used; depending on factors like institutional ability to deal with such fractures, this may lead some practitioners to choose for fractionated SBRT schedule with 2–5 fractions [14,22,50].

In NRG Oncology/RTOG 0631 trial, a gap of 3 mm between spinal cord and epidural disease was mandated, whereas CCTG SC.24 only excluded patients with symptomatic spinal cord compression or cauda equina syndrome. Nonetheless, only 2% of the SBRT patients in CCTG SC.24 had high grade epidural disease (e.g. Bilsky grade 2 or 3; with an additional 41% having low grade) [51]. Because the probability of (durable) LC may be compromised by epidural disease in contact with the spinal cord [6], some centers have begun to practice spinal separation surgery followed by post-operative SBRT. Although this is an emerging trend, it requires the patient be subjected to an invasive surgical procedure and associated complications and may not be applicable in most clinical cases. The optimal management of high-grade epidural disease continues to evolve, and some centers have investigated dose escalation to the spinal cord constraint as a means to optimize outcomes for those in MSCC [52].

After spine SBRT, the combination of clinical follow-up and spine MRI scans (e.g. 3-monthly in year one and 3–6 monthly thereafter) has been used in clinical trials, and is supported by consensus recommendations (e.g. SPINO group) as the standard way of assessing patient and tumor outcomes and complications (e.g. vertebral compression fracture, the chance of which is highest in the 1st year) [26]. The presence of epidural disease is also best visualized using MRI. However, if factors such as available resources/financial limitations, overall disease status/comorbidity or patient preference do not facilitate such a schedule then follow-up is still recommended and various approaches may be considered (e.g. tumor marker-based when there is a suitable surrogate like prostatic specific antigen (PSA), with imaging on indication; or computed tomography (CT)-based imaging with additional MRI, and/or positron emission tomography/computed tomography (PET/CT), on indication). It should also be borne in mind that interpretation of post-SBRT images can be challenging with risks of over-reporting tumor progression/recurrence due to post-SBRT changes; in such situations metabolic imaging like fluorodeoxyglucose (FDG)- or prostate specific membrane antigen (PSMA)-PET may be helpful [53].

KQ3: What is the practice of spinal SBRT to optimize safety and efficacy according to available evidence?

The technology applied to radiation oncology is constantly evolving, and SBRT of the spine is an indication which may especially benefit from improve precision due to the close proximity of the target volume with critical serial organs at risk. Many currently available, and sometimes commonly adopted technologies were not available at the time of those prospective and randomized trials discussed in this guideline. Therefore, we provide best practice recommendations based on the available clinical evidence, meaning that their use is expected to re-produce the safety and efficacy of spinal SBRT in the existing retrospective and prospective evidence-base.

Spine SBRT is an MRI-based technique, and unless contraindicated, or in specific circumstances deemed unnecessary by the treating team, MRI should be used for target and organs at risk (OAR) (in particular spinal cord and cauda equina) delineation; CT myelogram may be used for delineation of the spinal cord and cauda equina in circumstances where metallic artifacts are interfering with the visualization. CTV is defined using anatomical concepts described by Cox et al.[54]. PET/CT can also be co-registered for target definition [55]. All spine SBRT plans should be optimized using a modulated treatment planning system. Dose calculations should be performed with a grid size < 1.5 mm, using a modern dose calculation algorithm (e.g. type C such as Monte Carlo, Acuros or if these are not available, type B models like Collapsed Cone) [56]. A suitable SBRT platform capable of delivering an intensity-modulated beam with appropriate image-guidance is essential to allow an end-to-end tolerance of<2 mm, and a limit for clinical target volume (CTV)-PTV expansion of ≤ 3 mm, in particular at the periphery of the target volume (i.e. farthest from the isocenter/spinal cord) where the impact of rotational deviations on target coverage is expected to be greatest [5]. Six degrees of freedom (6DoF) couches have become more broadly available and are expected to provide benefit for spine SBRT from both dosimetric and set-up perspectives [57,58], if there is availability in a center it should be used for spine SBRT, in particular for longer (>1 or 2 vertebrae)/irregularly-shaped planning target volume (PTV), or where the spinal cord changes direction (e.g. pitches) within the PTV. Given the potential for patient movement after 6D corrections, they should be combined with verification imaging, especially after large pitch and roll corrections (e.g. $> 1°$; including in patients with near-rigid immobilization). Finally, we emphasize that each step in the process should be appropriately quality assured. All these points contribute to keeping uncertainties sufficiently low.

To this end, the whole chain of treatment should be considered involving radiation oncologists, medical physicists, and radiation therapy technologists (RTT). Therefore, in addition to the technology, we emphasize the central role of education and training for the entire team performing spine SBRT. RTTs also have a central role to play in continually evaluating the optimal use and reproducibility of new rigid immobilization systems that may be used in spine SBRT.

KQ4: What is the toxicity profile of spine SBRT?

Vertebral compression fracture (VCF) is the most frequent adverse event after spinal SBRT and can lead to significant pain, spinal deformity, neurological deficit and in a few patients spinal instability or spinal cord compression requiring stabilization/decompression [59]. The incidence of VCF after spine SBRT has been described in two large multicenter analyses, reporting fracture rates ranging between 6% and 14% [14]. About half of all fractures were new, developing after SBRT whereas the other half were pre-existing but progressed after SBRT: this rate of newly developing fractures appears similar to.

CRT. However, (very) high dose single fraction SBRT ($\geq$20-24 Gy) in particular appears to be associated with increased fracture rates [14]. Other risk factors include pre-existing VCF, presence of lytic tumor and the associated extent of lytic disease, baseline pain, location in thoracic spine, a higher (e.g. > 8) pre-treatment Spinal Instability Neoplastic Score (SINS score), a Bilsky grade > 0, older age (e.g. > 55 years), female sex and type of primary tumor (e.g. lung tumor metastases higher, prostate cancer metastases lower) [14,25,60–67].

The reported risk of radiation myelopathy is consistently low and is primarily driven by the total radiation dose, dose-per-fraction, and history of previous spinal cord irradiation. In the de novo spine SBRT setting, the incidence of radiation myelopathy was reported to be 0.4% in a pooled analysis of>1,000 patients [68]. The most recent modelling analyses by the Hypofractionation Treatment Effects in the Clinic (HyTEC) reported [69] maximum point dose to the spinal cord (thecal sac used as planning organ-at-risk volume) of 12.4–14.0 Gy in 1 fraction, 17.0–19.3 Gy in 2 fractions, 20.3–23.1 Gy in 3 fractions, 23.0–26.2 Gy in 4 fractions and 25.3–28.8 Gy in 5 fractions to keep the risk under 5% [69].

Brachial plexopathy and lumbosacral plexopathy are late toxicities following spine SBRT and there are only limited published series

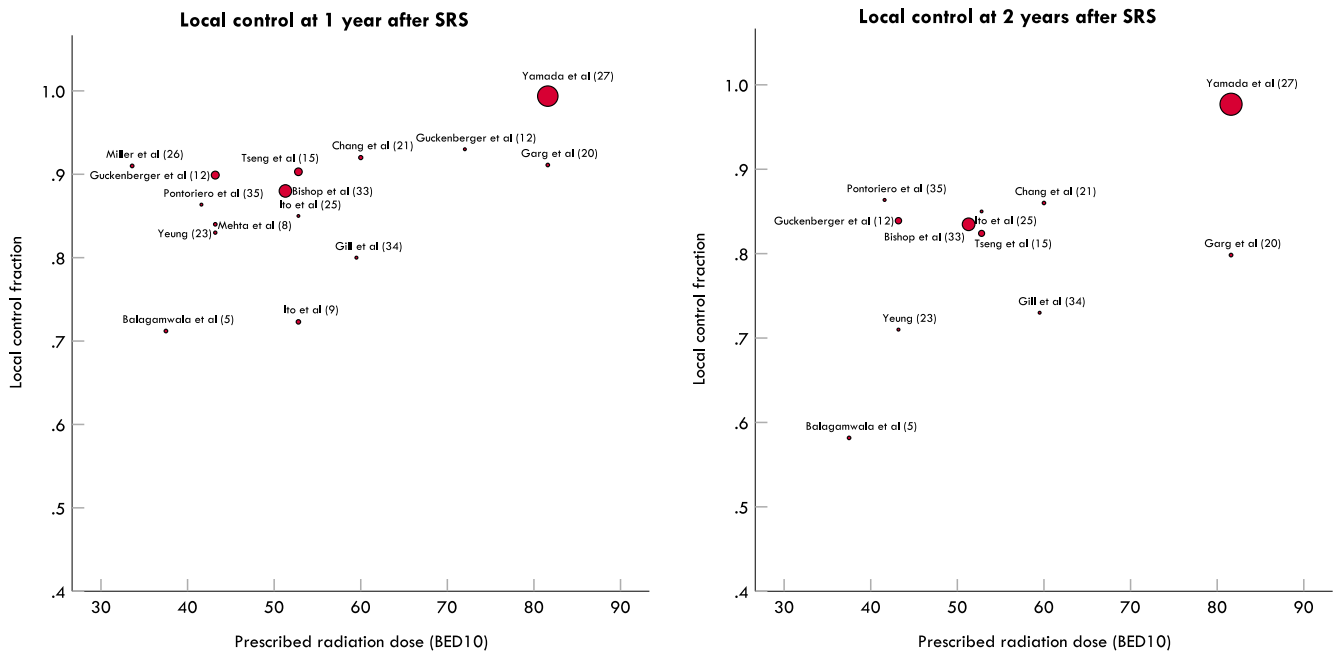

Fig. 1. Local control versus prescribed dose in biologically equivalent dose calculated with alpha/beta = 10. Studies with re-irradiation of the spine are excluded. Median follow-up time in months is denoted in parenthesis. The size of the dot is based on the numbers at risk at the evaluated time-point, a larger dot represents more patients.

reporting on SBRT-induced plexopathy [70–72]. In the large series by Stubblefield et al of 447 patients treated with single fraction SBRT (18–26 Gy) there were 14 events of plexopathy reported in 13 patients, at a median of 10 months post-SBRT [71]. The low incidence of plexopathy in the literature may be partly driven by the low number of cases that actually included the plexus in the target region. Patients should be appropriately counselled about this uncertainty [73].

A systematic review and *meta*-analysis of randomized trials reported a modest increase in acute pain flare after SBRT vs CRT, with rates of 43% vs 33% [32] and patients with renal primary, soft tissue involvement, Bilsky > 0, spinal instability neoplastic score > 6, and gross tumor volume > 8 cc were reported to be at increased risk [74]. Prophylactic treatment with steroids has been reported to minimize the risk of pain flare, but needs to be balanced with the associated risk of steroids [75].

While overall toxicity from spine SBRT is low, the combination of SBRT with novel and targeted therapies is an area where knowledge is rapidly evolving [20,21]. In such situations the etiology of the toxicity may be multifactorial, i.e. not just due to the radiation. Practitioners are recommended to discuss the potential for increased/unknown risks with the treating team (e.g. medical oncologist) and patient. Together with the treating medical oncologist a decision can be made whether to continue or temporarily stop the targeted/immune therapy at/around the time of the SBRT, and if the latter then for how long.

Conclusion and future directions

This clinical practice guideline by a multidisciplinary group of spine SBRT experts acting on behalf of the ESTRO society is based on a systematic review and was able to achieve consensus (at least 75% agreement) in all four key questions, resulting in a total of 22 recommendations and 5 statements concerning the use of spine SBRT for vertebral metastases. In the majority of cases, the level of evidence supporting the recommendations and statements was moderate or expert opinion, only, indicating that spine SBRT is still an evolving field of clinical research. Enrollment of patients into well-designed prospective clinical trials addressing clinically relevant questions is therefore considered important.

Conflict of interest statement

M Guckenberger: Research support: Varian, ViewRay, AstraZeneca, Advisory Board: AstraZeneca.

N Andratschke: Advisory board duties / speaker's duties for AstraZeneca, ViewRay Inc., Brainlab AG.

EORTC RTQA Chair, GHG Chair, SAKK Radio-oncology chair, ESTRO/SASRO member.

M Dahele: Research funding from Varian Medical Systems.

G Minniti: Compensation for speaker activity with BrainLab.

P Munck af Rosenschold: Collaboration agreement with Accuray Inc, US.

A Sahgal: Consulting for Varian, Elekta (Gamma Knife Icon), BrainLAB, Merck, Abbvie, Roche.

Vice President of the International Stereotactic Radiosurgery Society (ISRS).

Co-Chair of the AO Spine Knowledge Forum Tumor.

Past educational seminars (honorarium) for AstraZeneca, Elekta AB, Varian, BrainLAB, Accuray, Seagen Inc.

Research Grant: Elekta AB, Varian, Seagen Inc, BrainLAB.

Travel accommodations/expenses: Elekta, Varian, BrainLAB. Dr. Sahgal also belongs to the Elekta MR Linac Research Consortium and is a Clinical Steering Committee member, and chairs the Elekta Oligometastases Group and the Elekta Gamma Knife Icon Group.

WFAR Verbakel: has received research grants and travel expenses from Varian Medical Systems, outside the current work. Since May 1st 2023 employed by Varian Medical Systems.

F Alongi: Varian, Elekta, Brainlab: consultant/speaker honoraria/research funding.

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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Appendix KQ2. Data analysis behind Fig. 1

Data were used for further analysis when the local control estimate were calculated using the Kaplan-Meier estimator, censoring for death or lost to follow-up. Alternatively, cumulative incidence was derived treating death and lost to follow-up as competing risks. Data on histology of the primary tumor was evaluated qualitatively. In order to assess the impact of each data set, data was collected on the number of lesions as well as the median follow-up time of the study in question. Unless the authors stated the number of patients at risk at the 1- and 2-year time point this was estimated based on the number of lesions included in the study and the median follow-up. Finally, the data on the median prescribed radiation dose and the number of treatment fractions was collected. The actual details regarding dose prescription varied between studies and was not considered further in this analysis. The prescription doses were converted to a biological equivalent dose (BED) using an alpha/beta value of 10 Gy.

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