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Recommendations for stereotactic body radiation therapy for spine and non-spine bone metastases. A GETUG (French society of urological radiation oncolgists) consensus using a national two-round modified Delphi survey

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ABSTRACT

Background and purpose: The relevance of metastasis-directed stereotactic body radiation therapy (SBRT) remains to be demonstrated through phase III trials. Multiple SBRT procedures have been published potentially resulting in a disparity of practices. Therefore, the french society of urological radiation oncolgists (GETUG) recognized the need for joint expert consensus guidelines for metastasis-directed SBRT in order to standardize practice in trials carried out by the group.

Materials and methods: After a comprehensive literature review, 97 recommendation statements were created regarding planning and delivery of spine bone (SBM) and non-spine bone metastases (NSBM) SBRT. These statements were then submitted to a national online two-round modified Delphi survey among main GETUG investigators. Consensus was achieved if a statement received $\geq$ 75 % agreements, a trend to consensus being defined as 65–74 % agreements. Any statement without consensus at round one was re-submitted in round two.

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Results: Twenty-one out of 29 (72.4%) surveyed experts responded to both rounds. Seventy-five statements achieved consensus at round one leaving 22 statements needing a revote of which 16 achieved consensus and 5 a trend to consensus. The final rate of consensus was 91/97 (93.8%). Statements with no consensus concerned patient selection (3/19), dose and fractionation (1/11), prescription and dose objectives (1/9) and organs at risk delineation (1/15). The voting resulted in the writing of step-by-step consensus guidelines.
Conclusion: Consensus guidelines for SBM and NSBM SBRT were agreed upon using a validated modified Delphi approach. These guidelines will be used as per-protocole recommendations in ongoing and further GETUG clinical trials.

Introduction

The prevalent use of functional imaging for disease assessment and the improvement of life expectancy driven by recent therapeutic advances make urological cancer patients more likely to be in an oligometastatic state at the time of diagnosis (synchronous) or recurrence (metachronous).[1,2] The relevance of metastasis-directed stereotactic body radiation therapy (SBRT) has been prospectively assessed in phase II randomized studies.[3–5] Aside from excellent local control with limited toxicity, the level of evidence for oncological benefits remains low.[6,7].

SBRT is often proposed to target oligometastases in the field of castration-sensitive prostate cancer or to treat metastases from renal cell carcinoma in order to postpone initiation or change of systemic therapies.[3,4,8] By inducing presentation of cancer antigens to the immune system, SBRT is also believed to stimulate a tumor-targeted immune response (bystander and abscopal effects) and to improve the therapeutic efficiency of immunotherapies (STAR effect).[9–11] In addition, a new era of therapeutic indications proposes the use of SBRT for pain relief for multimetastatic patients, as opposed to standard palliative irradiation.[12] Nevertheless, inclusion of patients in large phase III trials is still warranted to better understand the true benefits of metastasis-directed SBRT.

A large number of SBRT procedures has been published with significant differences in terms of delineation, dose prescription, fractionation and dose objectives, potentially resulting in a disparity of practices.[13] As approximately-one-third of cancer patients will develop bone metastases, of which 70 % will experience spinal metastases[14], the French society of urological radiation oncolgists (GETUG) recognized the need for joint expert consensus guidelines for metastasis-directed SBRT in order to guarantee a consistent practice in ongoing and further clinical trials carried out by the group.

Using a modified Delphi approach [15], a representative panel of GETUG experts was interviewed to assess the level of consensus regarding recommendations for all aspects of SBRT in spine bone metastases (SBM) and non-spine bone metastases (NSBM).

Materials and methods

Building of a first proposal of statements by a GETUG task force

A GETUG task force of six radiation oncologists and four medical physicists specialized in the treatment of urological malignancies and SBRT was created. Three members of the task force (FV, PG, DP) conducted a Pubmed search for relevant English-language articles, published within the last 10 years and providing practical recommendations for treatment planning and delivery of bone metastasis-directed SBRT. Other members of the task force were asked to add to the list of publications as they deemed necessary. Following article selection, the task force conducted a literature review session to decide the main steps for planning bone metastasis-directed SBRT. Conclusions were summarized in a written document and a list of 97 recommendation statements was edited to be submitted to GETUG investigators through a two-round modified Delphi survey. These statements were structured around seven main topics: patient selection, treatment preparation (patient immobilization and imaging modalities), target volume delineation, dose and fractionation, modality of prescription and dose objectives, organs at risk, image guided radiation therapy (IGRT).

Respondents

The main active investigators of GETUG clinical trials were contacted by e-mail to answer the survey. If the participants felt it appropriate, they could forward the survey to the member of their department with a higher expertise in SBRT. Respondents were encouraged to answer the survey in collaboration with a physicist. Physicians who accepted to respond to the first round were invited to the second round and were offered authorship.

Two-round modified Delphi survey

To assess the consensus level for each of the 97 statements, an online questionnaire was generated using the Google Form plateform (Google, Alphabet Inc, Mountain View, USA) and was used to conduct a two-round survey through a modified Delphi approach.[15] Prior to the first round, the document summarizing the task force literature review was sent to all respondents.

In round one, respondents were asked to rate their degree of agreement for each statement using a 7-point Likert scale. Answers were grouped as follow: disagreement including answers “strongly disagree” and “disagree” (votes 1–2), neutral (votes 3–5), agreement including answers “agree” and “strongly agree” (votes 6–7). Participants were encouraged to explain their disagreement in a free text box. Statements with 75 % agreement (votes 6–7) were considered to have met consensus and those statements were not redistributed for ranking in a second round [15].

In round two, the results from the first round were shared. Respondents were then asked to reevaluate each statement that had not achieved consensus in round one. At this point, to ensure a consistent interpretation of the statements, any statement that had been identified as unclear was slightly reworked and accompanied by an explanation. For a limited number of statements, the Likert scale was replaced by close-ended response options.

At the end of round two, statements with < 75 % agreement were considered to have failed to achieve consensus. Nervertheless, statements with 65–74 % agreement were considered to have achieved a trend to consensus.

Results

Twenty-nine radiation oncologists were asked to participate. Twenty-one (72.4 %) completed the first round survey. The same 21 also completed the second round. The invitation to round one was sent April 5th, 2021 and votes for round two closed October 10th, 2021.

Of the 97 recommendation statements submitted to vote, 75 achieved consensus at round one. The 22 remaining statements were submitted to revote and 16 of them achieved consensus at round two making a total rate of consensus of 94 % (91/97). Among the 6 remaining statements that failed to achieve consensus, 5 achieved a trend to consensus (statements 12, 19, 53, 71, 79) and 1 lacked any sort

of consensus (statement 7).

Content of each statement and the corresponding voting from the two-round survey are presented in Table 1. Statements that achieved consensus are in bold. Organs at risk dose constraints put to vote are presented in Table 2. The voting resulted in creation of step-by-step consensus guidelines for SBM and NSBM SBRT that can be found in Supplementary Material 1.

Discussion

We used a two-round survey through a modified Delphi approach to develop consensus guidelines regarding SBRT for treatment of SBM and NSBM [15]. A high rate of consensus allowed for the creation of a comprehensive list of recommendations from patient selection to treatment planning and delivery. These guidelines will be used as per-protocole recommendations to ensure a consistent approach for investigators' practice in ongoing and further GETUG trials, the final objectives being to encourage adoption of trials protocols, improve inclusion rates and limit major deviations.

Interestingly, among the six statements that did not achieve consensus, half were related to patient selection. Agreement was notable for defining the oligometastatic state as a maximum of five metastases - eventhough 24 % of experts would lower the limit to three - and for offering metastasis-directed ablative therapies to metachronous oligometastatic patients. On the contrary, a majority of experts considered that current knowledge does not allow for routinely offering that option to synchronous oligometastatic patients. These results underscore variations in the interpretation of the oligometastatic status that can be perceived through different perspectives. First, a biological perspective that makes the oligometastatic status an intermediate position between a localized and fully disseminated disease, hopefully still accessible to cure if treated early and aggressively to avoid wider spread.[16] Second, a pragmatic clinical perspective that seeks less ambitious but still major improvements in patient outcomes including time to disease progression, time before initiation or change of systemic treatments, avoidance of adverse symptoms related to local progression and improvement in quality of life [3,4]. Third, a rigorist approach based on the benefit-risk equation that promotes decision founded only on a high-level of scientific evidence.

Actually, the relevance of metastasis-directed ablative therapies remains to be demonstrated. SBRT has been mainly reported through retrospective series, as well as a limited number of small phase II randomized studies.[3–5] Aside from excellent local control and good tolerance, it appears that overall survival could be improved and the need for starting a new systemic treatment postponed.[6,7] Nevertheless, inclusion of patients in large phase III trials is still highly warranted. Moreover, the oligometastatic state encompasses a vast variety of clinical situations. The "de novo" oligometastatic disease can be synchronous or metachronous depending if it is diagnosed at the time or long after the primary cancer diagnosis. The "repeat" oligometastatic disease happens after prior history of oligometastatic disease. The "induced" oligometastatic disease is a polymetastatic disease that was once controlled for a varying length of time under systemic therapies and finally progresses in a limited number of sites.[1,2] All these situations should be separately assessed in clinical trials.

Experts reached consensus on the need for a 3 mm minimum GTV-to-spinal cord distance to allow adequate dose fall off. If this distance is too short, agreement for proposing an inaugural mini-invasive spinal cord separation surgery before SBRT achieved a trend to consensus making it a validated option.[17] Obviously, access to such a highly specialised approach is limited due to its technicity and should be considered with caution in the view of the benefit-risk balance when treating asymptomatic metastatic patients.

Delivering SBRT after stabilisation surgery or kyphoplasty appeared consensual for SBM. Responses were indeed more disparate regarding the acceptance of delivering SBRT to NSBM after osteosynthesis. This is explained by the lack of evidence for the safety of that approach with concern regarding potential cancer cells spread in the medullary space of a tubular bone.

Statements for treatment preparation were consensual especially for the need to provide setup intrafraction accuracy $\leq$ 1 mm/1° for SBM and $\leq$ 3 mm/2° for NSBM. Thus, a customized immobilization device is mandatory except if an image-guided tracking robotic system that provides minimal residual intra-fraction error is used. Of note, after round two, experts agreed on the use of a diagnostic MRI (as opposed to a dedicated MRI acquired in the treatment position) for treatment planning as long as it is<3-week-old. This is a practical approach reflecting the fact that most departments still don't have dedicated access to MRI. In rare cases, when the patient has a contraindication to MRI and on the condition that the spine metastasis does not reach the edges of the spinal canal, it seems acceptable to use the spinal canal as a surrogate for planning organ at risk volume (PRV) of the spinal cord or the cauna equida.

Experts agreed on relying on edited consensus contouring guidelines regarding target volume delineation for SBM SBRT.[18–20] Notably, the irradiation should not be restricted to the macroscopic disease but should include full vertebra segments to account for microscopic spread. Such recommendations were so far only based on experts opinions but were recently reinforced by the report by Chen et al. of an improvement in local control.[21] As a counterpart for NSBM, GETUG experts proposed to apply a 3–5 mm margin around the gross target volume (GTV) while keeping that extension inside the cortical bone (unless the tumor extends into surrounding soft tissues). This proposal is in accordance with recently published recommendations by Nguyen et al.[22].

Regarding SBM SBRT, a highly anticipated challenge arises due to the close vicinity of the clinical target volume (CTV) and some organs at risk (OARs) such as the spinal cord and the oesophagus for instance. This is even more challenging when margins are applied to create the corresponding PTV and PRVs that can then overlap. Drawing on SABR UK guidelines [23], the GETUG experts agreed on the generation of an intermediate target volume called "restricted PTV" (labelled PTV!) defined as the PTV minus the spinal canal and any area of PTV/PRVs overlap. The final treatment planning approval will then rely on the adequate coverage of PTV! by the prescription isodose. This coerces the planning system to lower dose distribution in specific areas of PTV - consented limited areas of local underdosage - with sharp dose gradient to adequately avoid major OARs. Nevertheless, in respect with ICRU guidelines, the final dose reporting will provide an information on the dose actually delivered to PTV.

A broad spectrum of dose fractionation schedules have been published [13] GETUG experts agreed on the following in order of priority: 30 Gy in 3 fractions of 10 Gy, 27 Gy in 3 fractions of 9 Gy, 35 Gy in 5 fractions of 7 Gy and 30 Gy in 5 fractions of 6 Gy for both NSBM and SBM including after prior surgery. A single dose of 24 Gy reached a trend to consensus for treating SBM from primary renal cell carcinoma with respect to its radioresistant status and the richness of its neovascularization. Ultrahigh-dose single-fraction irradiation has been shown to cause the translocation of acid sphingomyelinase (ASMase) from intracellular compartments to the plasma membrane where it hydrolyses sphingomyelin, generating ceramide, a proapoptotic messenger. As ASMase is abundant in endothelial cells, the tumor neovascularization is particularly responsive to ultrahigh-dose single-fraction.[24–26].

Recently, a phase III trial established a better local control after metastasis-directed SBRT (mainly bone metastases) using a single fraction of 24 Gy versus 27 Gy in 3 fractions, resulting in less distant metastatic progressions with no increase in toxicity.[27] Although exciting, these results should not yet be broadly applied as they were achieved in a highly selected population treated in a center of excellence with limited follow-up and as ultrahigh-dose single-fraction SBRT might cause serious long-term side effects.[28].

In order to allow for the generation of a sharp dose gradient, GETUG

Table 1
Results of the two-round survey (statements that achieved consensus are bolded).

Statements	n	Round	Agree	Neutral	Disagree	Consensus
Patient selection						
1. To offer SBRT to an oligometastatic patient, his life expectancy must be ≥ 6 months	21	1	**80.9 %**	19.1 %	0 %	**Yes**
2. To offer SBRT to an oligometastatic patient, his WHO performance status must be ≤ 2	21	1	**85.7 %**	14.3 %	0 %	**Yes**
3. For PET-avid primary tumors (prostate adenocarcinoma, urothelial carcinoma), the oligometastatic state must be attested by PET-CT and not only using conventional imaging (CT-scan, bone scan)	21	1	**85.7 %**	14.3 %	0 %	**Yes**
4. The oligometastatic state is defined by a maximum of 5 metastases total	21	1	**76.2 %**	0 %	23.8 %	**Yes**
5. The oligometastatic state is defined by maximum of 3 metastases total	21	1	23.8 %	0 %	76.2 %	No
6. Published data support the use of SBRT for treatment of metachronous oligometastases	21	1	71.4 %	23.8 %	4.8 %	No
	21	2	**85.6 %**	9.6 %	4.8 %	**Yes**
7. Published data support the use of SBRT for treatment of synchronous oligometastases	21	1	38.1 %	23.8 %	38.1 %	No
	21	2	28.6 %	9.6 %	61.8 %	No
8. Published data support the use of SBRT for pain relief for multimetastatic patients in the field of palliative care	21	1	38.1 %	38.1 %	23.8 %	No
	21	2	76.2 %	14.3 %	9.5 %	**Yes**
9. For SBM, GTV must be ≤ 5 cm	21	1	85.7 %	9.5 %	4.8 %	**Yes**
10. For SBM, a maximum of 2 contiguous vertebrae can be treated simultaneously	21	1	95.2 %	4.8 %	0 %	**Yes**
11. For SBM, the GTV-to-spinal-cord distance must be ≥ 3 mm in order to allow adequate dose fall off	21	1	66.7 %	33.3 %	0 %	No
	21	2	95.2 %	0 %	4.8 %	**Yes**
12. If the GTV-to-spinal cord distance is not sufficient, a spinal cord separation surgery (i.e. the epidural part of the tumor is resected without significant vertebral body resection) can be proposed before SBM SBRT	21	1	38 %	52.4 %	9.6 %	No
	21	2	66.6 %	9.6 %	23.8 %	No (trend)
13. The Spinal Instability Neoplastic Score (SINS) scoring system must be used to evaluate vertebral mechanical instability before SBM SBRT.	21	1	90.5 %	9.5 %	0 %	**Yes**
14. A SINS score > 7 requires a neurosurgical advise to discuss pre-SBRT vertebral stabilization	21	1	85.7 %	14.3 %	0 %	**Yes**
15. SBM SBRT after kyphoplasty or vertebral osteosynthesis is safe	21	1	66.7 %	33.3 %	0 %	No
	21	2	90.5 %	9.5 %	0 %	**Yes**
16. For NSBM, the Mirels scoring system should be used to assess the risk of post-SBRT fracture	21	1	61.9 %	33.3 %	4.8 %	No
	21	2	85.7 %	9.5 %	4.8 %	**Yes**
17. For NSBM, a Mirels score ≥ 9 requires orthopedic advise for bone stabilization surgery	21	1	76.2 %	23.8 %	0 %	**Yes**
18. For NSBM, ≥30 % circumferential cortical infiltration requires orthopedic advise for bone stabilization surgery	20	1	90 %	10 %	0 %	**Yes**
19. As no evidence exists for safety of SBRT after NSBM osteosynthesis, indication for bone stabilization surgery precludes the use of SBRT	21	1	33.4 %	42.8 %	23.8 %	No
	21	2	71.4 %	14.3 %	14.3 %	No (trend)
Treatment preparation (immobilization and imaging modalities)						
20. A customized immobilization device is mandatory (except if an image-guided tracking robotic system that provides minimal residual intra-fraction error is used)	21	1	95.5 %	0 %	4.8 %	**Yes**
21. The treatment planning will be performed on a planning CT-scan (≤2mm slice thickness) without contrast	21	1	85.6 %	9.6 %	4.8 %	**Yes**
22. For SBM, accuracy of ≤ 1 mm translational and ≤ 1° rotational setup errors must be ensured	21	1	95.2 %	4.8 %	0 %	**Yes**
23. For SBM, the planning CT-scan should cover at least 2 vertebrae above and below PTV	21	1	95.5 %	4.8 %	0 %	**Yes**
24. For SBM, the imaging modalities used for the treatment planning must include a spine MRI (≤3mm slice thickness) with contrast	21	1	90.4 %	9.6 %	0 %	**Yes**
25. For SBM, the MRI should at least include axial T2-weighted (for spinal cord identification) and gadolium-enhenced T1-weighted (for GTV localization) sequences	21	1	76.2 %	23.8 %	0 %	**Yes**
26. For SBM, an automatic planning-CT/MRI rigid registration (focused on the region of interest) must be performed followed by a carefull medical validation before starting volumes delineation	21	1	85.6 %	9.6 %	4.8 %	**Yes**
27. For SBM, It is highly recommended but not mandatory for the spine MRI to be acquired in the treatment position using the patient's customized immobilization device	21	1	61.9 %	33.3 %	4.8 %	No
	21	2	80.9 %	14.3 %	4.8 %	**Yes**
28. For SBM, as an option, a diagnostic spine MRI (i.e. not acquired with the patient's customized immobilizaton device) can be used but must be<3-week-old	21	1	71.4 %	28.6 %	0 %	No
	21	2	95.2 %	0 %	4.8 %	**Yes**
29. For NSBM, accuracy of ≤ 3 mm translational and ≤ 2° rotational setup errors must be ensured	20	1	90.4 %	9.6 %	0 %	**Yes**
30. For NSBM, the planning CT-scan should cover at least 10 cm above and below PTV and include the metastatic bone in it's entirety	21	1	85.7 %	14.3 %	0 %	**Yes**
31. For mobile targets (eg. ribs), a 4D-planning CT-scan must be performed	21	1	90.5 %	9.5 %	0 %	**Yes**
32. For NSBM, a bone MRI and/or a PET-CT can be registered (optional) to the planning-CT to help for the delineation of GTV	21	1	90.5 %	9.5 %	0 %	**Yes**
33. For NSBM, if a planning-CT/MRI registration is performed, a diagnostic MRI (i.e. not acquired with the patient's customized immobilization device) can be used if<3-week-old	21	1	90.5 %	9.5 %	0 %	**Yes**
Target volume delineation						
34. For SBM, GTV = macroscopic disease as assessed on planning (CT) and diagnostic (MRI+/- PET) imaging	21	1	100 %	0 %	0 %	**Yes**
35. For SBM, GTV must include epidural and paraspinal tumor expansion	21	1	90.4 %	9.6 %	0 %	**Yes**
36. For SBM, after debulking surgery: GTV = residual macroscopic disease only	21	1	80.8 %	9.6 %	9.6 %	**Yes**
37. For SBM, CTV = GTV + anatomical sections of the vertebra at risk for microscopic spread	21	1	100 %	0 %	0 %	**Yes**
38. For SBM, CTV delineation should follow guidelines for vertebral [Cox et al. IJROBP 2012;83(5):e597-605] and sacral [Dunne et al. Radiother Oncol. 2020;145:21–9] metastases	21	1	95.2 %	4.8 %	0 %	**Yes**
39. For SBM, CTV with a "donut" shape should be avoided	19	1	68.4 %	31.6 %	0 %	No
	21	2	85.6 %	4.8 %	9.6 %	**Yes**
40. For SBM, after debulking surgery: CTV = residual GTV + preoperative bony and epidural extent of the disease + adjacent sections of the vertebra at risk for microscopic spread [Redmond et al. IJROBP 2017;97(1):64–74] .	21	1	95.2 %	4.8 %	0 %	**Yes**
	21	1	90.4 %	9.6 %	0 %	**Yes**

(*continued on next page*)

Table 1 (*continued*)

Statements	n	Round	Agree	Neutral	Disagree	Consensus
41. For SBM, after debulking surgery, a preoperative-MRI/postoperative-planning-CT registration is highly recommended to help for the delineation of CTV						
42. For SBM, PTV = CTV + 1–2 mm (institution-dependant)	21	1	95.2 %	4.8 %	0 %	**Yes**
43. For SBM, PTV will be partially amputated to create a volume called "restricted PTV" (labelled PTV!) in order to coerce the inverse planning system into decreasing the dose distribution in areas of close vicinity between PTV and major OARs (e.g. PTV! = PTV minus the spinal canal and any area of PTV/PRVs overlap)	21	1	100 %	0 %	0 %	**Yes**
44. For SBM, the final treatment planning approval (dose objectives achievement) must rely on the adequate coverage of PTV! – following SABR UK guidelines	21	1	28.6 %	0 %	71.4 %	No
	21	2	95.2 %	0 %	4.8 %	**Yes**
45. For SBM, PTV (and not PTV!) must be used for dose reporting – following ICRU guidelines	21	1	85.7 %	14.3 %	0 %	**Yes**
46. For NSBM, GTV = macroscopic disease as assessed on planning (CT) and diagnostic (MRI+/- PET) imaging	21	1	95.2 %	4.8 %	0 %	**Yes**
47. For NSBM, GTV must include extra-bone and medullary tumor expansions	21	1	95.2 %	4.8 %	0 %	**Yes**
48. For mobile targets: ITV = sum of each GTV from the different phases of a 4D planning CT	21	1	95.2 %	4.8 %	0 %	**Yes**
49. For NSBM, CTV = GTV (or ITV) + 3–5 mm	21	1	85.7 %	14.3 %	0 %	**Yes**
50. For NSBM, CTV must be manually adjusted to be kept inside the cortical bone (unless the tumor expanses in surrounding soft tissues)	21	1	90.5 %	9.5 %	0 %	**Yes**
51. For NSBM, PTV = CTV + 3–5 mm (institution-dependant)	21	1	100 %	0 %	0 %	**Yes**
Dose and fractionation						
52. For SBM, In case of multiple fractions, the treatment must be delivered every other day	21	1	80.9 %	14.3 %	4.8 %	**Yes**
Statements	**n**	**Round**	**Agree**	**Neutral**	**Disagree**	**Consensus**
53. For SBM from primary renal cell carcinoma (radioresistant), 24 Gy in 1 fraction is a valid treatment option	21	1	61.9 %	33.4 %	4.8 %	No
	21	2	71.4 %	4.8 %	23.8 %	No (trend)
54. For SBM from primaries other than renal cell carcinoma, multiple fractions should be favored	21	1	85.7 %	4.8 %	9.6 %	**Yes**
55. For SBM, 30 Gy in 3 fractions (10 Gy/fraction) is a valid prescription scheme	20	1	90 %	5 %	5 %	**Yes**
56. For SBM, 27 Gy in 3 fractions (9 Gy/fraction) is a valid prescription scheme	21	1	85.7 %	9.5 %	4.8 %	**Yes**
57. For SBM, 35 Gy in 5 fractions (7 Gy/fraction) is a valid prescription scheme	21	1	85.7 %	14.3 %	0 %	**Yes**
58. For SBM, 30 Gy in 5 fractions (6 Gy/fraction) is a valid prescription scheme	21	1	66.7 %	23.8 %	9.5 %	No
	21	2	95.2 %	0 %	4.8 %	**Yes**
59. For SBM, after debulking surgery the same prescription schemes as the ones mentioned above should be used	20	1	85 %	10 %	5 %	**Yes**
60. For NSBM, multiple fractions should be favored over ultrahigh-dose single-fraction	21	1	80.9 %	14.4 %	4.8 %	**Yes**
61. For NSBM, the same prescription schemes as the ones used for SBM can be used	21	1	90.4 %	4.8 %	4.8 %	**Yes**
62. For NSBM, it is possible (option) to deliver the treatment every day instead of every other day as long as a gap of 24 h between two fractions is provided.	21	1	52 %	38 %	10 %	No
	20	2	100 %	0 %	0 %	**Yes**
Prescription and dose objectives						
63. The "prescription dose" is defined as the dose deemed to enclose an optimal percentage of the volume of PTV (ideally 95 % of PTV)	21	1	95.2 %	4.8 %	0 %	**Yes**
64. The treatment planning should promote a significant dose heterogeneity within PTV with an increase in dose beyond 107 % of the prescription dose	19	1	73.7 %	0 %	26.3 %	No
	21	2	95.2 %	0 %	4.8 %	**Yes**
65. The maximum dose can reach up to:						
– 107 % of the prescription dose	19	1	26.3 %	0 %	73.7 %	No
	21	2	0 %	0 %	100 %	No
– 130 % of the prescription dose	19	1	73.7 %	0 %	26.3 %	No
	21	2	100 %	0 %	0 %	**Yes**
– 140 % of the prescription dose	19	1	57.9 %	0 %	42.1 %	No
	21	2	85.8 %	0 %	14.2 %	**Yes**
– 150 % of the prescription dose	19	1	10.5 %	0 %	89.5 %	No
	21	2	14.3 %	0 %	85.7 %	No
– 160 % of the prescription dose	19	1	0 %	0 %	100 %	No
	21	2	4.8 %	0 %	95.2 %	No
66. As an option, a simultaneous integrated boost technique can be used to confine the maximal dose inside GTV	21	1	47.6 %	38.1 %	14.3 %	No
	21	2	90.5 %	9.5 %	0 %	**Yes**
67. For SBM, main dose objective for PTV is as follow: ≥95 % PTV should receive ≥ 100 % of the prescription dose	21	1	90.5 %	9.5 %	0 %	**Yes**
68. For SBM, if required for the respect of OARs dose constraints, PTV dose objective can be lowered to ≥ 90 % PTV should receive ≥ 100 % of the prescription dose, provided that ≥ 98 % GTV receives ≥ 21 Gy in 3 fractions or ≥ 23 Gy in 5 fractions [Bishop et al. IJROBP 2015;92(5):1016–26.]	21	1	80.9 %	19.1 %	0 %	**Yes**
69. Fot SBM from primary renal cell carcinoma (radioresistant) it is mandated that ≥ 98 % GTV receives ≥ 18 Gy in 1 fraction, 24 Gy in 3 fractions or 30 Gy in 5 fractions [Wang et al. IJROBP 2017;98 (1):91–100]	21	1	76.2 %	23.8 %	0 %	**Yes**
70. For NSBM, main dose objective for PTV is as follow: ≥95 % PTV should receive ≥ 100 % of the prescription dose	20	1	95 %	5 %	0 %	**Yes**
71. For NSBM, PTV dose objective should not be lowered (motive: GTV to PTV disctance is narrow)	21	1	52.3 %	38.1 %	9.6 %	No
	21	2	66.6 %	0 %	33.4 %	No (trend)
Organs at risk						
72. Neurological OARs (brainstem, spinal cord, cauna equida, plexus) are delineated using the axial T2-weighted MRI sequence	21	1	95.2 %	4.8 %	0 %	**Yes**
73. For neurological OARs (brainstem, spinal cord, cauna equida, plexus), dose constraints will be applied to a PRV	21	1	90.5 %	9.5 %	0 %	**Yes**
74. The same margin as the one used from CTV to PTV is applied around neurological OARs (brainstem, spinal cord, cauna equida, plexus) to create their corresponding PRV	21	1	95.2 %	4.8 %	0 %	**Yes**
75. The thecal sac as assessed on MRI can be used as a surrogate for spinal cord PRV or cauda equina PRV	21	1	80.9 %	14.3 %	4.8 %	**Yes**
76. In rare cases, when the patient has MRI contraindication and on the condition GTV does not reach the edges of the spinal canal, it is acceptable to use the spinal canal as a surrogate for spinal cord or cauna equida PRV	21	1	76.2 %	23.8 %	0 %	**Yes**

(*continued on next page*)

Table 1 (*continued*)

Statements	n	Round	Agree	Neutral	Disagree	Consensus
77. The esophagus is a serial OAR potentially in close vicinity with PTV. Thus, a margin should be applied around the esophagus to create a PRV.	21	1	76.1 %	4.8 %	19.1 %	**Yes**
78. PRV is not mandated for OARs other than neurological structures or esophagus	21	1	57.1 %	23.8 %	19.1 %	No
	21	2	81 %	0 %	19 %	**Yes**
79. When emerging via the intervertebral foramina, a root of a brachial or sacral plexus cuts throughout PTV						
-To avoid major PTV underdosage, that root will not be delineated so that no dose constraint will be applied to it	21	1	57.1 %	0 %	42.9 %	No
	21	2	9.5 %	0 %	90.5 %	No
-That root will be delineated as part of the corresponding plexus and PTV underdosage will be allowed to provide the respect of the same dose constraints as for the plexus	21	1	42.9 %	0 %	57.1 %	No
	21	2	19 %	0 %	81 %	No
-That root will be delineated as a single volume in order to avoid the maximal dose to be delivered in that area but without compromising adequate dose delivery to PTV (no undertreatment)	21	2*	71.5 %	0 %	28.5 %	No (trend)
80. Brainstem dose constraints (see Table 2)	21	1	95.2 %	4.8 %	0 %	**Yes**
81. Spinal Cord dose constraints (see Table 2)	21	1	90.4 %	9.6 %	0 %	**Yes**
82. Cauda Equina dose constraints (see Table 2)	21	1	95.2 %	4.8 %	0 %	**Yes**
83. Plexus dose constraints (see Table 2)	20	1	95 %	5 %	0 %	**Yes**
84. Esophagus dose constraints (see Table 2)	21	1	95.2 %	4.8 %	0 %	**Yes**
85. Large Vessels dose constraints (see Table 2)	21	1	80.9 %	14.3 %	4.8 %	**Yes**
86. Skin dose constraints (see Table 2)	21	1	76.2 %	14.3 %	9.6 %	**Yes**
Image Guided Radiation Therapy (IGRT)						
87. The use of IGRT with online correction is required for every fraction	20	1	95 %	5 %	0 %	**Yes**
88. Orthogonal kV images provide adequate positioning precision only if using the Cyberknife© image guided tracking system or the Exatrac© system	20	1	90 %	5 %	5 %	**Yes**
89. For SBM SBRT, the ability to correct any displacement with a 6-degree of freedom couch is required	21	1	90.4 %	9.6 %	0 %	**Yes**
90. KiloVoltage cone beam CT (kV-CBCT) must be taken before every fraction for inaugural positioning (does not apply to Cyberknife©)	19	1	84.2 %	10.6 %	5.2 %	**Yes**
91. In the case of coplanar beam plans, the use of kiloVoltage cone beam CT (kV-CBCT) provides enough precision for patient positioning. The use of the Exactrac® system is optional (does not apply to Cyberknife©)	21	1	85.6 %	4.8 %	9.6 %	**Yes**
92. In the case of non-coplanar beam plans, as the use of kiloVoltage cone beam CT (kV-CBCT) is not possible, patient positioning must be checked using adequate on-board imaging such as the Exactrac® system (does not apply to Cyberknife©)	21	1	95.2 %	4.8 %	0 %	**Yes**
93. Patient positioning control must be repeated after any couch displacement	19	1	89.4 %	10.6 %	0 %	**Yes**
94. Intrafraction patient positioning controls are not mandatory if the treatment is fast (<2 min)	19	1	84.2 %	15.8 %	0 %	**Yes**
95. Post-fraction kV-CBCT is optional	19	1	94.7 %	5.3 %	0 %	**Yes**
96. Couch shifts must be applied in case of > 1 mm translational or > 1° rotational setup error for SBM SBRT	19	1	78.9 %	15.8 %	5.3 %	**Yes**
97. Couch shifts must be applied in case of > 1 mm translational or > 1° rotational setup error for NSBM SBRT	21	1	90.4 %	9.6 %	0 %	**Yes**

SBRT: stereotactic body radiation therapy; SBM: spine bone metastases; NSBM: non-spine bone metastases
* Third option added at the time of the second round

Table 2
Organs at risk dose constraints.

Organs at Risk	1 fraction	3 fractions	5 fractions
Brainstem*	D0.1 cc < 15 Gy D1cc < 10 Gy	D0.1 cc < 23.1 Gy D1cc < 18 Gy	D0.1 cc < 31 Gy D1cc < 26 Gy
Spinal Cord*	D0.1 cc < 14 Gy D0.35 cc < 10 Gy D1.2 cc < 7 Gy	D0.1 cc < 21.9 Gy D0.35 cc < 18 Gy D1.2 cc < 12.3 Gy	D0.1 cc < 30 Gy D0.35 cc < 22.5 Gy D1.2 cc < 14.5 Gy
Cauda Equina*	D0.1 cc < 16 Gy D5cc < 14 Gy	D0.1 cc < 24 Gy D5cc < 21.9 Gy	D0.1 cc < 32 Gy D5cc < 30 Gy
Plexus*	D0.035 cc < 17.5 Gy D3cc < 14 Gy	D0.035 cc < 24 Gy D3cc < 22.5 Gy	D0.035 cc < 32 Gy D3cc < 30 Gy
Esophagus*	D0.035 cc < 16 Gy D5cc < 11.9 Gy	D0.5 cc < 25.2 Gy D5cc < 21 Gy	D0.5 cc < 34 Gy D5cc < 27.5 Gy
Large Vessels	D0.035 cc < 37 Gy D10cc < 31 Gy	D0.5 cc < 45 Gy D10cc < 39 Gy	D0.5 cc < 53 Gy D10cc < 47 Gy
Skin	D0.035 cc < 26 Gy D10cc < 23 Gy	D0.5 cc < 33 Gy D10cc < 30 Gy	D0.5 cc < 39.5 Gy D10cc < 36.5 Gy

* Dose constraints must be applied to the planning organ at risk volume (PRV).

experts agreed that the prescription dose should be prescribed on the isodose line that encompasses ≥ 95 % of PTV and that the dose distribution inside PTV should be kept heterogeneous beyond 107 % and up to 140 % of the prescription dose. As an option, a simultaneous integrated boost technique can be used to keep the maximal dose inside GTV. Anticipating the need for acceptance of minor deviations and in accordance with Bishop et al. recommendations, GETUG experts agreed that, if required for the respect of OARs dose constraints, when delivering SBM SBRT the dose objectives can be lowered to ≥ 90 % PTV receives ≥ 100 % of the prescription dose providing that ≥ 98 % GTV receives ≥ 21 Gy in 3 fractions or ≥ 23 Gy in 5 fractions [29]. In the case of SBM from primary renal cell carcinoma, ≥98 % GTV should receive ≥ 18 Gy in 1 fraction, 24 Gy in 3 fractions or 30 Gy in 5 fractions [30]. For NSBM SBRT, lowering PTV dose objectives didn't reach the same consensus but remains an option depending on clinical situations. Although criticizable, we sense that the acceptance of minor deviations is a pragmatic view that provides a satisfactory balance between effectiveness and risk.

As SBRT is often proposed to asymptomatic long-term survivors, it is consensual that complications threatening major vital functions as well as quality of life must be avoided. As such, GETUG experts agreed for the application of a margin around the spinal cord, brachial/sacral plexus and oepsophagus to generate a PRV on which dose constraints will apply. This choice can differ from other reports, some authors considering that treatment delivery is accurate enough so that dose constraints should be applied to OARs with no margin [31] when others put security first and promote generation of PRVs [32,33].

As roots of the brachial plexus (anterior rami of C5-T1 spinal nerves) or the sacral plexus (anterior rami of L4-S4 spinal nerves) leave the spinal canal via the intervertebral foramina, it may happen that they run throughout PTV. Enforcing rigorous dose constraints to these substructures may then lead to major PTV underdosage. Neither the proposition of omitting the delineation of those roots nor the proposition of applying to them the same dose constraints as for the plexus were

validated. A trend to agreement was observed for delineating the roots as single volumes and to avoid delivering hot spots (maximal dose) to them without compromising the adequate coverage of PTV.

GETUG experts agreed that the use of daily image-guided radiation therapy with online setup correction is required. High precision orthogonal 2D kV images such as Cyberknife© image guided tracking robotic system or ExacTrac© system are considered adequate for pre-treatment and intra-fraction positioning control.[34,35] In case of coplanar fields, the use of kiloVoltage cone-beam CT (kV-CBCT) provides enough precision for pre-treatment positioning as well. Aware that the risk of significant intra-fraction movements increases with treatment duration, experts agreed that pausing treatment for intra-fraction kV-CBCT re-assessment is not mandatory as long as the fraction lasts<2 min.[36] Post-treatment kvCBCT is optional.

GETUG experts call for couch shifts to be applied for any $>$ 1 mm translational or $>1^{\circ}$ rotational setup error for both SBM or NSBM. The ability to acquire a 6-degree of freedom (DOF) positioning verification and to correct any displacement with a 6-DOF couch is required for SBM SBRT.

Current indications of metastasis-directed SBRT remain limited to selected oligometastatic patients [37]. Ongoing clinical trials are likely to enhance those indications in the future [38–40] and recent developments tend to position SBRT as a more palliative treatment as well. Sahgal et al. proposed to extend indications to the setting of pain relief for SBM, irrespective of the total tumor burden unless patient life expectancy is $>$ 3 months. Complete pain response was improved using SBRT compared to conventional radiotherapy [12]. Whilst not yet considered practice-changing, these results pave the way for an exponential increment in therapeutic applications raising the question of risk-taking in generalizing a treatment that is anything but trivial [41]. As more accidental exposures are expected, the radiation oncology community faces the great challenge of generalizing a highly precise technique without compromising patients' safety [42]. We therefore believe that providing expert group consensus guidelines using a rigorous methodology is of major interest. However, the main limitation remains the low level of evidence available in the literature, many of the studies being retrospective with limited population. Thus, many of the statements remain at the expert opinion level.

Conclusion

Consensus guidelines covering the main aspects of planning and delivery of SBRT for the treatment SBM and NSBM were provided using a validated two-round survey modified Delphi approach. These guidelines will be used as per-protocole recommendations to standardize investigators' practice in ongoing and further clinical trials carried out by the GETUG.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.08.006.

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