Clin Transl Oncol (2016) 18:342–351
DOI 10.1007/s12094-015-1383-y

CLINICAL GUIDES IN ONCOLOGY

Spanish Society of Radiation Oncology clinical guidelines for stereotactic body radiation therapy in lymph node oligometastases

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Received: 14 July 2015 / Accepted: 8 August 2015 / Published online: 2 September 2015

Abstract Data in the literature support the existence of a state of limited metastases or oligometastases. Favorable outcomes have been observed in selected patients with such oligometastases that are treated with local ablative therapies, which include surgical extirpation, stereotactic body radiation therapy (SBRT), and radiofrequency ablation. The role of SBRT in the setting of lymph node oligometastases is still emerging but the early results for local control are promising. However, the biggest challenge is to identify patients who will benefit from treatment of their oligometastatic disease with local aggressive therapy. Patients are initially categorized based upon examination of the initial biopsy, location, stage, and previous treatments received. Appropriate patient management with SBRT requires an understanding of several clinicopathological features that help to identify several subsets of patients with more responsive tumors and a good tolerance to SBRT. In an effort to incorporate the most recent evidence, here the Spanish Society of Radiation Oncology presents guidelines for using SBRT in lymph node oligometastases.

Keywords Lymph node oligometastases · SBRT · SABR · Adenopathies · Radiosurgery

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Introduction

Lymph node metastases are one of the main routes of tumor spread. Its incidence after curative treatment is very variable, from 7 % in prostrate tumors up to 15–20 % in colorectal and gynecological tumors [1–4].

Recurrence in abdominal lymph nodes is considered, according to the type and location of the tumor, to be advanced metastatic disease and the treatments offered in this situation are usually systemic, that is why only recently radiotherapy has only been offered as a palliative treatment. However, two theories, supported by an increasingly extensive clinical evidence, are changing this concept.

The first theory refers to the spectrum of tumor natural histories and was proposed in 1995 by Hellmann and Weichselbaum [5]. They described an intermediate state of metastatic disease that they termed oligometastases and defined as the situation in which a patient presents a limited number of synchronous or metachronous metastases (fewer than five), with the primary tumor either controlled or not. Subsequently, Niiebe et al. [6] built on the concept and proposed the situation of oligorecurrence as the appearance of metachronous metastases/recurrences, in one or many organs, with the primary tumor under control. In patients with oligometastases or oligorecurrence, local control (LC) of the lesions results in an increase in survival and in the progression-free interval, delaying the initiation of systemic treatments, as demonstrated in studies on lung and liver oligometastases. The concept of oligo progression, which refers to the situation of disease progression in a limited number of locations after an initial response to systemic treatment, should also be added to these theories. This oncological situation is particularly common after the use of targeted pharmaceuticals and is a problem that can be resolved by applying a combination of systemic as well as local treatments, such as stereotactic body radiation therapy (SBRT), which is capable of eradicating disease that does not respond to pharmacological treatment [7]. Currently surgery and radiotherapy, specifically SBRT, are two ablative treatment options in patients with oligometastatic disease, with LC rates equivalent to or higher than 80 % for most studied sites (including lung, liver, and adrenal glands) [8]. SBRT has also been shown to increase the overall survival (OS) rate in several different studies for brain metastases [9, 10].

The second theory relates to the immunological effect of radiotherapy. Besides outstanding LC, SBRT also improves control of the disease outside the irradiated volume by stimulating the T lymphocyte mediated immune response, which promotes the eradication of micrometastases [11, 12].

SBRT is an advanced radiotherapy technique that is characterized by the administration of very high doses of radiation with ablative intent (a biologically effective dose, BED, of more than 100 Gy), with hypofractionated schemes of one to six fractions and doses greater than or equal to 7.5 Gy per fraction. This implies a high conformation (a conformation index less than 1.5) and high dose gradients in order to deliver the maximal dose to the tumor while protecting critical organs and healthy surrounding tissues. To reach this level of precision the treatment is administered using image guidance for each fraction (image guided radiation therapy, IGRT) with online correction and using a precise immobilization system that ensures intrafraction stability [13]. There is extensive experience in the field for both primary and secondary lung and liver lesions using these techniques.

Although there is less experience in treating lymph node oligometastases with SBRT, several series have recently been published in which control rates higher than 60 % were achieved with minimal toxicity [14], in several diverse types of tumor including gynecological, prostate, colorectal, and gastric carcinoma and in diverse locations including retroperitoneal, pelvis, upper abdomen, and groin [15–22].

Methodology for obtaining a Spanish Society of Radiation Oncology guideline on stereotactic body radiation therapy for lymph node metastases

To date there is no national consensus regarding the use of SBRT in patients with oligometastases, i.e. the optimal dose and number of fractions, the prescription dose, or dose limits for critical organs. Despite this, SBRT is a technique whose use is undergoing a period of expansion due to the growing number of indications. Therefore, the Spanish Society of Radiation Oncology (SEOR) was encouraged to find a guideline on the use of this technique in different locations: lung, liver, spine, and lymph node.

This report was produced after carefully reviewing a selection of the literature on the topic. A selection of different specialists with experience in the treatment of lymph node metastases with SBRT performed a search in March 2015 on PubMed, http://www.clinicaltrials.gov, and the Web of Knowledge, using a combination of the following terms: oligometastases, lymph node metastases, adenopathies, stereotactic, radiotherapy, metastases, radiosurgery, SBRT, and SABR). Following the search and also reviewing the papers cited in the selected articles, we identified 62 papers published in English, including both

retrospective and prospective studies. We excluded duplicates or studies reporting a non-oligometastatic disease.

Studies were only eligible if the dose per fraction was 6 Gy or higher for a total dose of more than 24 Gy, or 5 Gy per fraction for a total dose of more than 45 Gy. Studies were also excluded if fewer than seven patients were reported or if the median follow-up was less than 12 months. Thirty-two studies on oligometastatic and/or oligo-recurrent disease met all previous criteria for this review, and, eventually, 25 focused on SBRT/SABR.

Indications and patient selection

According to the panel, SBRT on lymph node metastases indicated for patients with:

- Prostate or colorectal origin, among other histologies.
- A previously treated primary tumor and an apparent complete local response.
- More than 2 years from diagnosis of the primary tumor to the metastatic recurrence. In these cases an increase in OS has been demonstrated [16, 17].
- In a maximum of three locations (with 4–5 widely disseminated sites) [18].
- Radical treatment of all the lesions should be possible. Both through metastasectomy and/or by SBRT, inability to radically treat all the locations compromises survival [19–22].
- The guideline proposed by the SEOR for SBRT is to use one of two dose schemes per fraction, according to the medical criteria and depending on the tolerance of the surrounding structures: either six fractions of 7.5 Gy or three fractions of $\geq$10 Gy. Better results are associated with higher doses, even though a dose limit has not yet been determined; control local cannot be gained with SBRT with doses that are too low, and therefore these patients are treated with palliative intent following standard schemes and doses. IGRT may be required to reach the dosimetric objectives.
- Lymph nodes should have a diameter of 5 cm or less. Increased size compromises LC and is a factor for worse prognosis; an abdominal nodule gross tumor volume (GTV) of 17 cm^3 or less, predicts disease-free survival (DFS), and each additional 1 cm^3 GTV is associated with a 1 % worse DFS [23].
- An Eastern Cooperative Oncology Group (ECOG) performance status higher than 2 or a Karnofsky index higher or equal to 70 %.
- Life expectancy greater than 3 months.
- Normal bone marrow function.
- Informed consent

Exclusion criteria:

- It is very important to exclude any patients with a high-risk histology, whose outcomes are very poor, for example patients with small-cell carcinoma or Ewing sarcoma.
- The presence of brain metastases before inclusion, either untreated or still uncontrolled with treatment.
- Concomitant chemotherapy [24], given that there are no data that support increased tumor control [25] and that there is a possibility of increased toxicity. Chemotherapy should be suspended at least 3 weeks before SBRT [15]. Prior treatment with chemotherapy, or concomitant hormonotherapy, are not exclusion criteria [26], although in the case of the former it is a poor prognostic factor [27] and the role of the latter is still being determined [28].
- Lesions that directly contact the gastro-intestinal tract: the minimum distance is should be at least 6 mm [29].

Diagnostic tests and extensions required

The workup and extension study results are essential for diagnosis of oligometastatic lymph node relapse and to establish an SBRT treatment indication. In the context of a known primary tumor and the occurrence of a lymph node metastases susceptible to local treatment, a histologically-confirmed diagnosis is not considered necessary.

The study prior to SBRT lymph node metastases treatment should include:

- A clinical history and complete physical examination.
- A complete analytical series, including hematology, biochemistry with a hepatic profile, kidney function, and tumor markers, depending on the primary tumor.
- An abdominopelvic contrast CT and a magnetic resonance imaging (MRI) scan: these allow the detection and location of the metastases, determination of their relation with risk organs as well as allowing the size to be established. They also are part of the extension study, helping to discard the presence of metastases in other locations. MRI image fusion with a radiation therapy simulation CT allows better delineation of the GTV. An MRI is especially recommended in the case of pelvic metastases.
- A bone scintigraphy scan is used to discard the presence of blastic bone metastases, especially in tumors of prostatic origin. Its application must be evaluated depending on the availability of other imaging tests such as PET-CT.
- PET/PET-CT with ^{18}F-fluorodeoxyglucose (FDG) provides metabolic information about the lesions detected with other imaging tests and completes the extension study. Its introduction in recent years has significantly

improved the selection of patients for SBRT treatment. SBRT studies on lymph node metastases from colorectal, gastric, or gynecological cancers, include PET-CT with FDG in the staging in addition to standard tests for each pathology [30–34]. The panel recommends its routine inclusion in the extension study for candidate patients for SBRT, both to establish a treatment indication and to delimit the target volumes. Moreover, knowledge of the maximum standardized uptake value (SUVmax) of the lymph node before radiotherapy can be useful as a prognostic factor which could potentially allow more personalized treatment, depending on the risk of relapse [35].

- PET/PET-CT with choline (11C-choline or 18F-choline) allows recurrent disease (lymph node, visceral, or bone metastases) to be detected in patients with biochemical recurrence and is included in the extension study in most work published on the use of SBRT in primary prostate-origin cancer [23, 36–38]. It is also of great help in delimiting the GTV. The sensitivity of the test seems to be related to the levels of prostate-specific antigen (PSA) and its kinetics (PSA velocity and doubling time) [39, 40]. Although the cutoff values are still controversial, PSA values higher than 1 ng/ml, a velocity higher than 2 ng/ml/year, and a doubling time less than 6 m, increase the sensitivity of the test [41].
- Whole body diffusion MRI and hybrid PET-MRI with choline are recently introduced tests for prostate cancer staging with promising results but they are still in the investigative phase. Their use depends on their availability in each center [41, 42]. Others tracers such Ga68 PSMA PET/CT have a promising future in the detection of prostate cancer metastases but this technique is under implementation in Europe [43, 44].

Clinical protocol

Requirements for planning stereotactic body radiation therapy

The requirements for planning SBRT in these locations have been described in several reports such as the 101 from the American Association of Physicists in Medicine (AAPM) [45]. The main objective is the acquisition of a series of images to calculate the dose for the most reproducible position (with the best movement control possible), which the patient will occupy during the treatment. Therefore, given the elevated dose gradient used in SBRT, precise delimitation of the patient's anatomy and a clear visualization of the target volume location is required during administration of the treatment. In general, CT is the main imaging technique used to plan SBRT and is the basis for the planning calculations. MRI or PET/CT images can be fused with this initial image, if possible using the same immobilization system, in the latter case bearing in mind any possible co-registration uncertainties, meaning that PET/CT currently provides more directional information rather than a high resolution of the lesion being treated.

The simulation CT should extend at least 5–10 cm above and below the treatment area. In the case of non-coplanar treatment it must be longer than 20 cm. All organs at risk should be included within these limits in a way that they can be properly considered within the dose/volume calculations. The cut size can vary between 1 and 3 mm in the majority of cases. In the cases of a previously irradiated area, the prior radiotherapy should be taken into account for the SBRT planning (Fig. 1).

Immobilization

The degree of immobilization required for SBRT is related to the imaging system used to verify the treatment. These systems, including the current guided tomography systems integrated into cone beam accelerators, reduce but do not eliminate the need for adequate immobilization.

Historically, in order to minimize many of these possible variations, the first SBRT techniques used the same philosophy as radiosurgery: use of a robust frame that served as a coordinate axis, even though this did not guarantee that the internal structures were in the position calculated.

The current availability of IGRT has made the use of these body frames as a fiducial system obsolete. Therefore, the main aim of the immobilization system must be the creation of a stable and reproducible patient position. To do this there are distinct solutions on the market that can also integrate into robotic treatment tables that allow corrections to be made in all six axes.

In the case of treatment of abdominal or pelvic lymph metastases, the position of the intestinal loops must also be taken into account and so it is recommended, that a CT scan be performed after at least 6 h of fasting to maintain an empty rectum and bladder, similar to how the treatment itself must be performed.

The definition of the structures, as described in reports 50 and 62 from the International Commission on Radiation Units and measurements (ICRU [46, 47]), are based on the GTV, clinical target volume (CTV), internal target volume (ITV), planning target volume (PTV), and organs at risk (OARs). Margins must be determined for each lymph node, or other location, based on the mobility of the structure being treated and on the OARs. Based on the above, the mobility of adenopathies at the paraaortic level has been

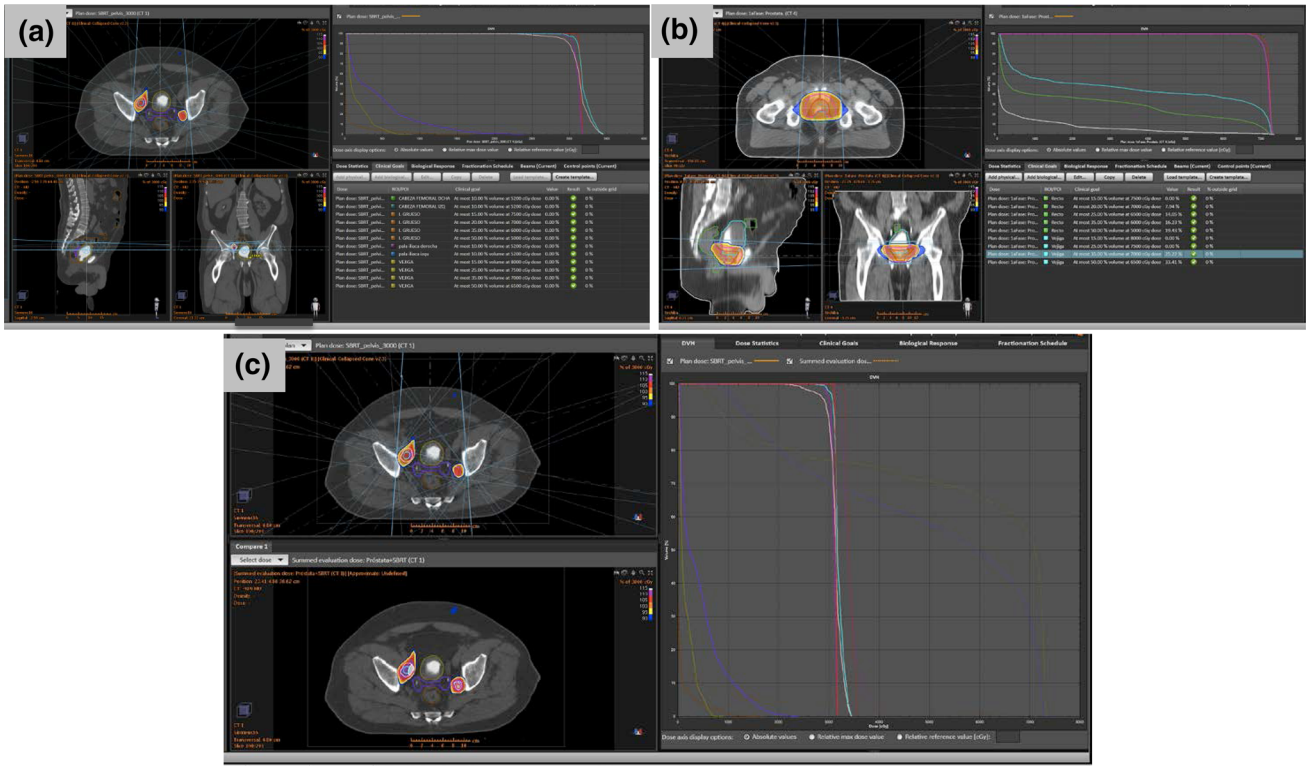

Fig. 1 SBRT planning for a patient with lymph node oligorrecurrence after radiotherapy for prostate bed using fusion and deformable registration of dose. **a** SBRT planning, **b** Previous treatment of the prostate fossa, **c** fusion and deformable registration of dose from new and old treatment

estimated by Wysocka et al. [48] as an average of 3.8 mm craniocaudal displacement, and which was less on other axes. In this way, based on Bignardi et al. [15], and assuming that the IGRT set up margin with techniques such as cone beam Kv CT (CBKvCT) is close to 0, we can establish a GTV the same as the CTV, with a craniocaudal PTV margin of 6 mm, and of 3–4 mm on the anteroposterior and lateral levels. If motion control is available, an ITV can be created from the CTV and a PTV margin based on the uncertainty of the table in the position used, which is usually around 2 mm in most systems. Given that the vast majority of treatments are administered as intensity-modulated radiation therapy (IMRT), ICRU report 83 [49] recommendations must be followed in these cases.

The SBRT-SG considers that each center should implement the immobilization system most suitable for the IGRT technique, provided that the recommendations we highlight here are met (Table 1).

Selecting the fractioning divisions and timing

Various fractionation schemes are described in the literature, which range between single doses of 24 Gy to schemes of 10 fractions of 5 Gy [50, 51]. To date we do not have any clear results that demonstrate the benefit of one type of dose or fractioning over another, although the best published results were obtained with higher doses per fraction. A phase III clinical trial led by the Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Pisa is currently underway, which is comparing schemes of single doses of $\geq$21 Gy, to hypofractionated doses of three 9 Gy fractions for different types of metastases, including from the lymph node [52]. While there is no clear scientific evidence for the dose threshold required to control metastases, the aim is to administer the highest dose per fraction that does not compromise the OARs. To do this, the tolerance dose limits described in the 101 report by AAPM are recommended.

It is crucial to note the importance of following the same methodology when prescribing doses, given the heterogeneity of the sample group, both in terms of the calculation systems/algorithms used in different treatment units, and in individual patient pathology, location, and histology. The proposed prescription should be the dose that encompasses at least 95 % of the PTV.

The different fractionations for recurrent cancer limited to the lymph nodes only are used. The series and their results are described in the Table 2.

The guideline proposed by the SEOR for SBRT is to use one of two dose schemes per fraction, according to the

Table 1 Key points for SBRT for lymph node oligometastases

The selection of local therapy should involve interdisciplinary discussion among surgeons, radiologists, radiation oncologists, and medical oncologists, as well as patients
Data in the literature suggest a favorable outcome in patients with prostate or colorectal primary tumors
Primary tumors should be in locoregional complete response
Karnofsky performance status should be 70 or more and life expectancy greater than 3 months
Patients with a few lymph node metastases (up to three) would benefit from SBRT
Lymph nodes should have a diameter of 5 cm or less, with a gross tumor volume up to 17 mL, since those measures are related to improved local control
The guideline proposed by the SEOR for SBRT is to use one of two dose schemes per fraction, according to the medical criteria and depending on the tolerance of the surrounding structures: either six fractions of 7.5 Gy or three fractions of $\geq$10 Gy
Data suggest that patients that present with oligometastatic lymph nodes more than 2 years after treatment of the primary tumor have higher odds of longer overall survival
The inclusion of these patients within a clinical trial is highly recommended

medical criteria and depending on the tolerance of the surrounding structures: either six fractions of 7.5 Gy or three fractions of $\geq$10 Gy.

Acute secondary effects and their evaluation

The side effects described in the literature for SBRT treatments for lymph node metastases depend on the location, target volume, the OARs, and the dose per fraction administered. Salama et al. [18] describe three cases of grade 3 (G3) gastro-intestinal toxicity after administering three fractions of 8 Gy for paraaortic adenopathies in the last 3 months of the treatment. The other series for pelvic adenopathies do not describe toxicity that reaches G2. Bae et al. [53] define the maximum dose (Dmax) as a better predictor of G3 gastro-intestinal toxicity for schemes of three fractions: they describe a probability of 5 % with a Dmax higher than 35 Gy and of 10 % with a Dmax higher than 38 Gy. Multivariate analysis discarded a prior history of gastro-intestinal ulcers as an independent risk factor. In his first series, Rwigema et al. reported a patient who developed a colovesicular fistula at 20.9 months in the setting of local tumor progression. The bowel volume that received 20 Gy (V20 Gy) was 26.9 mL, and the overall mean bowel V20 Gy achieved was 16 Gy for an approximate volume of 22.9 mL. This group also reported one patient with G2 proctitis at 13 months after SBRT.

The recommendation for SBRT is that toxicity data should be collected on a monthly basis after finishing the treatment, and in the follow-up visits every 3–4 months, and then every 6 months thereafter. LC can be evaluated with CT/MRI (preferably, using the same method used to provide the initial diagnosis) at 3, 6, 12, 18, and 24 months. In patients where PET-CT was performed before SBRT, the metabolic response should be evaluated with PET-CT at 6 and 12 months. In this case the PET response criteria in solid tumors (PERCIST) criteria should be used to evaluate the response [54]. In some cases, for example prostate cancer, PSA levels can be used as a guide for selecting the timing of imaging tests.

The scales used should be the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0 [55]) or the criteria stated by the Radiation Therapy Oncology Group (RTOG [56, 57]).

Results on the effectiveness of SBRT for lymph node metastases

A recent review of 38 articles on lymph node metastases treated with SBRT, that included 7 reviews and 31 patient series (20 retrospective and 11 prospective), with a total of 636 treated adenopathies, differentiated the results at the level of effectiveness into two subgroups:

Exclusive lymph node relapse

- LC was higher than 80 % in all cases.
- Relapse pattern: predominantly out of the treatment field, especially in the form of a distant metastases or regional adenopathies.
- 10 % of the patients presented with regional adenopathies, accounting for 50–80 % of all the progressions.
- Progression-free survival (PFS) at 3 years was higher than 20 %, and was higher in gastro-intestinal tumors.
- OS was in the region of 93.3 % at 2 years and 71.4 % at 3 years.

Oligometastases

- LC: 61–67 % at 1 year, 53–88 % at 2 years, 64–98 % at 3 years, 73–82 % at 4 years, and 57 % at 5 years.
- An association between LC and higher doses was established.

Table 2 The different fractionations for recurrent cancer limited to the lymph nodes only

References	No. of patients	Follow up (months)	Treatment	Location	Outcome	Toxicity grade ≥3 (no. of patients)
Bignardi et al. [15]	19	12	7.5 Gy × 6	Abdomen	LC at 24 mo: 77.8 % 2-year PFS 19.7 %. Patterns of failure: 2 pts local + distant; 2 pts only regional 7 pts distant PD 2-year OS: 93.3 %	1
Jereczek-Fossa et al. [36]	14	19	10 Gy × 3	Pelvis Retroperitoneal	LC: 100 % 8 NED, 4 AWD, 1 alive with biochemical failure, 1 died for other cause Clinical PD in 5 pts after mean 12.7 mo No in-field PD Distant PD in 2 pts Regional PD in 3 pts	0
Choi et al. [34]	30	15	33–45 Gy in 3 fr (11–15 Gy/fr) SBRT as boost: 13 Gy	Retroperitoneal	4-year OS 50.1 %; median survival rate not reached 4 year LC: 67.4 % 4 year PFS: 45 % Relapse in 11 pts: locoregional alone 4 (13.8 %), distant alone 3 (10.3 %), locoregional + distant 2 (6.9 %), recurrence at vaginal stump in 2 pts	1
Kim et al. [31]	7	26	Median 48 Gy (range 36–51 Gy) in 3 fr (16 Gy/fr)	Retroperitoneal	3-year-OS 71.4 %,	Local recurrence in 1 pt at 13 months after SBRT; regional recurrence in 1 pt; distant failure in 4 pts; 1 pt NED at 26 months
Casamassima et al. [39]	25	29	SBRT 30 Gy in 3 fr, (10 Gy/fr) in 18 pts; 24 Gy boost in 3 fr in 7 pts after Whole-pelvis RTE	22 Pelvic and/or para-aortic, 3 mediastinal	3-year OS: 92 % Progression in 10 pts:2 pts bone—8 pts LN (all out of field) (complete regression in 13 pts) 3-year DFS 17 % 3-year LC 90 %	0
Salama et al. [18]	61		8 Gy × 3	Multiple body sites	2 years PFS: 33 % 1 year OS 82 % 2 years OS: 57 %	1
Alongi et al. [63]	25	195 days	45 Gy in 6 fr (7.5 Gy/fr)	28 Abdomino-pelvic LN	Overall response rate 82 % (at median follow-up)	0
Jereczek-Fossa et al. [23]	69	20	11 Gy × 3 For 8 pts (9 %) SBRT as boost Re-irradiation 20 lesions (21 %)	94 Abdomino-pelvic LN	3-year LC: 64.3 % 2-year PFS: 20 % (dominant pattern of failure: out-field) 3-year OS: 49.9 %,	3
Corvò et al. [61]	33	28	Median 35 Gy in 5 fr (7 Gy/fr) 1 fr/week	36 Abdomino-pelvic LN	LC in 30 pts (83 %); 16 pts died at median follow-up (6 pts local PD, 10 pts distant PD)	0
Bonomo et al. [27]	26	4.6	Most common 36 Gy in 3 fr (12 Gy/fr)	32 Abdomino-pelvic LN	Freedom of local PD: 100 %. LC 90.9 % in pts with prostate histology. Distant PD in 8 pts (25 %)	0

Table 2 continued

References	No. of patients	Follow up (months)	Treatment	Location	Outcome	Toxicity grade ≥3 (no. of patients)
Rwigema et al. [62]	38	19	40 Gy in 4/5 fr	Gastrointestinal	CR/PR: 32/39 %	1
				Genitourinary	1 year LC 100 %	
				Gynecological	2 years LC 95.2 %	
				Breast	1 year OS: 75 %	
				Lung	2 years OS: 89 %	

Location, outcome and toxicity

EBRT external beam radiotherapy, *OS* overall survival, *PFS* progression-free survival, *G* grade, *BC* biochemical control, *LC* local control, *PD* progression disease, *CR* complete response, *PR* partial response, *NED* no evidence of disease, *AWD* alive with disease, *Fr* fractions

- The predominant pattern was progression outside of the field of treatment.
- Regional progression was described in 36 % of the patients, including all metastatic sites.
- In prostate or colorectal-origin metastases the majority of the relapses limited to the lymph node level were associated with higher PFS with respect to other relapses.
- OS: 80 % at 1 year, 50–65 % at 2 years, 22–60 % at 3 years, 13–28 % at 5 years.
- The existence of an initial advanced primary tumor is associated with lower OS.
- Lymph node metastases in the head and neck as a locoregional relapse is associated with lower OS with respect to other metastatic locations with this origin [58].

Follow-up for SBRT-treated lymph node metastases

The follow-up protocol in these cases has not yet been established. The aim is to evaluate the response and toxicity caused by the treatment.

Local failure can be defined as an increase in the tumor size over the follow-up period or the development of new lesions in the radiation field. The appearance of new lesions outside of the radiation field can be defined as a regional failure, and the appearance of new lesions outside of the organ should be treated as metastases [14]. Other authors [27] recommend that the World Health Organization (WHO) criteria should be followed [59, 60]: complete response (CR) indicates that no macroscopically visible tumor is present; a partial response (PR) indicates a greater than 50 % reduction in tumor volume; stable disease (SD) indicates a less than 50 % decrease in tumor volume; and progressive disease (PD) indicates a more than 25 % increase in tumor volume.

Conclusions

Even though the data are still not sufficient to be able to routinely recommend SBRT, the high LC and OS rates observed after SBRT in patients with oligometastatic lymph node disease justifies continued exploration of strategies for ablative dose delivery within research protocols.

The currently available studies suggest that the best candidates for this approach are those without high comorbidity, with complete local primary tumor response (better prostate or colorectal cancers), who have relapsed in a maximum of three locations (diagnosed with current imaging techniques) not exceeding 5 cm on the longest

axis (or are less than 17 mL [34]) at least 2 years after local treatment.

According to currently available clinical experience, subjects with an aggressive disease histology or in those where it is not possible to reach safe ablative doses for every lesion, would not been good candidates for SBRT.

Treatment planning with SBRT for lymph node metastases should use the imaging tests which provide the best visualization of the lesion in order to contour it (CT with/without MRI and/or PET, etc.), as well as immobilization systems that guarantee stabilization of the target volume position and treatment reproducibility in each session. The availability of IGRT is essential for completion of SBRT. Use of ITV is also recommended for reducing the treatment volume and for its potential to reduce toxicity.

Patients must be followed-up using appropriate imaging techniques according to the primary tumor histology, which must be similar to those used for diagnosing the oligometastases, using WHO or PERCIST criteria. Toxicity data should be collected using measurements such as the CTCAE v4.0 scale.

Further prospective studies must be carried out in order to establish clear criteria that allow patients in which the oligometastatic disease can be managed exclusively with SBRT to be distinguished from those who would better benefit from conventional external beam radiotherapy, SBRT associated with systemic treatments, surgery or systemic treatments alone.

Acknowledgments The authors wish to thank the Provincial Hospital of Castellón Foundation for their assistance in the development of this manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Informed consent This is a guideline, based on a review of clinical studies, but it is not a research study with patients.

Research involving human participants and/or animals This is a guideline, based on a review of clinical studies, but it is not a research study with human participants and/or animals.

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