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SBRT for lung oligometastases: Who is the perfect candidate?

Pierina Navarria, Fiorenza De Rose, Anna Maria Ascolese*

Radiotherapy and Radiosurgery Department, Humanitas Clinical and Research Center, Rozzano (Milano), Italy

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ABSTRACT

Aim: To analyze the literature data about lung oligometastatic patients who underwent SBRT with regard to doses, fractionation, outcomes, response assessment and prognostic factors, trying to define "the right patient" for the local treatment.

Background: "Oligometastatic disease" is defined as a state in which metastases are limited in number and site and characterized by unusual cancer biology and behavior. In this setting local therapy could have a potential curative role. Recently, technological advances in Radiation Oncology permitted the introduction of Stereotactic Body Radiation Therapy (SBRT), a novel treatment modality that delivers ablative dose of radiation to the extra-cranial sites with high precision using single or a small number of fractions.

Materials and methods: We performed a literature search using Medical Subject Heading terms "stereotactic body radiation therapy" and "lung metastases", considering a period of 10 years.

Results: Many non-randomized studies have shown that SBRT for lung oligometastases is safe and effective, with local control rates of about 80%. To date SBRT represents an alternative and competitive option in patients with lung oligometastatic disease who refuse surgical treatment or unsuitable for surgery. Based on published studies, SBRT might have major benefit for a patient with breast histology, disease-free interval ≥12 months, control of the primary tumor, small lesions, limited number of lesions and higher radiation dose delivered.

Conclusions: Well-designed collaborative trials are necessary to draw final conclusions. To date, the discussion within a multidisciplinary team becomes crucial to perform a careful patients' selection in the setting of oligometastatic disease.

* *Corresponding author at*: Istituto Clinico Humanitas, Cancer Center, Via Manzoni 56, 20089 Rozzano (Milano), Italy. Tel.: +39 0282247307; fax: +39 02248509.

E-mail address: fiorenza.de_rose@humanitas.it (F. De Rose).

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1. SBRT for lung metastases: state of the art

Literature data suggested the existence of "oligometastatic disease" as a state in which metastases are limited in number and site. Firstly in 1995, Hellman and Weichselbaum[1] described this state characterized by unusual cancer biology and behavior. In relation to different clinical and biological factors several authors stratified oligometastatic patients in three subgroups in which various therapeutic approaches can be used.[1–3] The first one includes de novo oligometastatic patients who initially present with limited metastases; the other one includes *induced* oligometastatic patients who present with limited metastases as result of systemic therapy; and the third one includes *recurrent* oligometastatic patients who present with limited metastases as subsequently developed after treatment of initial loco-regional disease. In this matter, the emerging data are that local therapy could have a potential curative role.

The lung is the main site of metastatic disease from the most solid tumors. Surgical resection has been recommended in carefully selected patients.[4] Anyway, there are no prospective randomized controlled trials evaluating the role of surgery in the management of these patients. However, the five-year survival rates are satisfactory, 30–65% in different studies.[4–6]

Recently, the technologies improvement changed the role of Radiation Therapy from palliative to curative treatment for lung oligometastatic patients. Stereotactic Body Radiotherapy (SBRT) allowed precise delivery of high radiation dose, defined as "ablative dose", with maximum sparing of normal tissue. To date, several papers have published on SBRT above all in stage I non-small-cell lung cancer[7,8] and more recently also in lung oligometastatic patients. Heterogeneous retrospective and few phase I–II prospective studies were published with patients with different solid tumors, various sites of metastatic disease (above all lung and liver) and different total dose and schedule. In some series the local control rate is more than 90%. Rusthoven et al. treated 63 lung lesions and reported local control rate of 96% at 2 years.[9] In our previous report 2-year local control rate was 89% in 118 lung lesions.[10] Based on these encouraging data, SBRT represents a valid alternative local therapy in patients unsuitable for surgery.

The big ongoing question is if and what a lot the best local approach might affect survival. Besides, the identification of patients with true oligometastatic disease is not too easy; so, another important issue is what kind of patient can have a major benefit from SBRT.

In this review we analyzed the literature data about lung oligometastatic patients who underwent SBRT. We considered the following points: prescribed total dose, employed fractionation, clinical outcomes, treatment response and prognostic factors. Besides we tried to identify "the right patient" for the proper local treatment. We performed a literature search using Medical Subject Heading terms "stereotactic body radiation therapy" and "lung metastases", considering a period of 10 years.

2. SBRT: generality and radiobiological advantages

The American Society of Radiation Oncology (ASTRO) defines SBRT as external beam radiotherapy used to deliver a high therapeutic dose of radiation, very precisely, to an extracranial target within the body. The features of this technique are: the use of a limited number of fractions (up to 5), high targeting accuracy, rapid dose fall-off gradients and maximum normal tissue sparing.[11] The radiobiological advantages of SBRT are the greater potential cell kill and the engaging of sphingomyelin-based endothelial mechanism of tumor control related to the high dose per fraction. In advance, the use of a limited number of fractions can lead to a potential reduction of the deleterious effect of tumor proliferation that may occur during a longer course of radiotherapy. Various dose-fractionation models have been proposed to predict the effectiveness of radiotherapy doses and fractionation regimens. The most widely used is the linear quadratic model, which models cell kill from both double-stranded and potentially repairable single-stranded DNA breaks. However, it overestimates cell kill at high doses per fraction (e.g., the doses used in SBRT), because there is proportionally more lethal damage to DNA and less sublethal damage.[12] The generalized linear quadratic model has been suggested to incorporate the conversion of sublethal to lethal DNA damage at high doses per fraction more accurately. Another model, the universal survival curve, incorporates both the linear quadratic and multi-target models and can thus predict cell kill at both high and low doses per fraction.[13] Ablative radiotherapy doses (i.e., those that destroy all living tissue in an area) need to have a higher biologically effective dose (BED) than do most conventionally fractionated regimens. BED is a measure of the effectiveness of different dose fractionation regimens, to allow comparison of different doses or doses per fraction. No definition of the doses needed for ablative radiotherapy is universally accepted. Multiple fractionation schemes have been employed, ranging from 24 to 60 Gy in one to five fractions. Anyway, regimens resulting in a biologically effective dose larger than 100 Gy ($\alpha/\beta = 10$ Gy) would be deemed ablative.[14] More recently, some reports identified an active role of radiotherapy in an immune-mediated mechanism. This mechanism, defined as abscopal effect, is a response in non-irradiated metastases and seems to be enhanced by the association of systemic immune modulators. The first preclinical experiences suggested that fractionated radiotherapy would better induce this interesting mechanism. Only preliminary data have been published on abscopal effects after hypofractionated radiotherapy, but further evidences are needed.[15,16] However, this effect might become particularly relevant in the treatment of oligometastatic disease where the potentiating of an immune response could be particularly efficacious.

3. Technical requirements for SBRT

SBRT process requires a coordinated team effort between the radiation oncologist, the medical physicist, the medical

dosimetrist, and the radiation therapist. Protocols for Quality Assurance (QA) should be implemented to monitor and assure proper functioning of the SBRT external beam delivery unit, the image guidance system as well as all other imaging devices used for SBRT and the image-based 3D and/or intensity-modulated treatment planning system.[11]

Because of the high radiation doses delivered, SBRT requires very high confidence in target localization to limit the amount of damage to surrounding normal tissues. Because of the complex target motion of extracranial structures, however, the treating physician must be able to take into account and manage daily setup variability and intrafraction motion in a way that allows for highly targeted therapy. This also requires modern delivery systems with the ability to shape the prescription isodose with a high degree of conformality. During the CT simulation process, immobilization is necessary. There are multiple reproducible systems that provide the necessary immobilization—many of which are institution specific—such as body frames, vacuum molds, abdominal compression techniques, and thermoplastic devices. Such immobilization strategies limit the effects of respiratory motion by restricting chest wall rise and diaphragmatic excursion using an abdominal pressure pillow. Alternatively, respiratory gating can be used to track the patient's range of motion throughout respiration and deliver treatment only during the chosen phase of the respiratory cycle.[17] Given potential changes in the internal location of mobile tumors relative to external frames, frame-based methods are generally supplemented with some form of pretreatment image guidance to confirm proper tumor relocalization. Frameless stereotactic uses the fiducials that are registered immediately before or during the targeting procedure.[11] In the management of lung and liver tumors, four-dimensional CT scans or fluoroscopic motion studies are conducted to provide accurate planning target volume (PTV) measurements. For tumors with avidity for positron emission tomography (PET), FDG-PET imaging is often performed with the patient in a body mold to improve the accuracy of delineating the tumor. Daily treatment image guidance is essential to ensure proper localization, reduce setup variability, and ensure that there is not a geographic miss for each fraction. Most commonly, this involves kilovoltage or megavoltage CT guidance for the delivery of each fraction. Cone beam CT refers to the incorporation of the imaging system into the linear accelerator. A CT machine on rails takes advantage of a shared tabletop for both CT imaging and a linear accelerator. All major manufacturers of linear accelerators currently produce delivery systems incorporating CT guidance. A variety of other systems with shared principles but different methods and technologies are in use for SBRT as well, including the Novalis BrainLAB system, TomoTherapy system, and Accuracy, Inc., CyberKnife system. The goal of dependable and reproducible immobilization, motion management, and image guidance is to restrict necessary PTV margins yet ensure the desired coverage of the CTV. There is no consensus on required PTV margins, which are typically institution specific and depend on an understanding of interfractional and intrafractional variability for a given delivery system and disease site. Treatment planning usually involves three-dimensional conformal radiotherapy (3DCRT) with multiple beam arrangement, often non-coplanar, or intensity-modulated radiotherapy (IMRT) to produce distributions with a very rapid fall-off. For all techniques, the goal is to limit the volume of normal tissue receiving the prescription dose.[17]

4. Outcome evaluation in relation to total dose and fractionation

4.1. *Single fraction*

From 2004 to 2014 six retrospective studies have been published on SBRT delivered in single fraction, three of them were phase I–II prospective studies (Table 1).

Wulf et al. published their results related to patients with oligometastatic disease. Twenty-five out of 51 metastatic lesions were small peripheral lesions treated with single fraction of 26 Gy, the other patients received a total dose of 30 Gy or 36 Gy/3 fractions. Mean clinical target volume (CTV) was 32 cc (range 1–155). At a median follow-up of 9 months (range 2–37), no local failure was observed in the single-dose group and 5/51 (10%) local recurrence/progression was seen in patients who underwent three-fractions SBRT. The authors showed a relationship between a single fraction compared with three fractions. The 1-year actuarial local control rate for the 51 metastases was 80%.[18] Fritz et al. reviewed data from 58 patients, 25 with pulmonary metastases (31 lesions) and 33 with early stage lung cancer. Lung metastases had a median CTV of 6 cc (range 2.8–55.8) and the prescribed dose to isocenter was 30 Gy in single fraction. After a median follow-up of 22 months (range 6.8–63), the local control rate of metastatic lesions was 87%.[19] Hof and colleagues analyzed data from 61 patients with 71 pulmonary metastases. Most of patients had primary lung tumor and initially a single metastasis (67.2%), with median CTV of 10 cc (range 1–53). The total prescribed dose was 24–26 Gy in the majority of patients. After a median follow-up period of 14 months the actuarial overall survival at 1, 2, 3 years was 78.4%, 65.1%, and 47.8% respectively. The authors evidenced a better local tumor control in patients with smaller tumor volumes, solitary metastases (not developing during the follow-up) and no primary colorectal cancer.[20] More recently, Ricardi et al. published our series of selected patients with 1–3 lung lesions, maximum diameter of 5 cm, ECOG 0–1, absent or controlled extra-thoracic disease and an adequate pulmonary function. Most of patients received a total dose of 26 Gy in single fraction or 45 Gy in 3 fractions. Median CTV was 3.3 cc (range 0.2–19). They achieved 2-year local control rate and Overall Survival of 89% and 66.5% respectively with median follow-up of 20.4 months (range 3–77.4). Data analysis confirmed smaller CTV (<3.3 cc) and single lesion as favorable prognostic factors for survival. No significant differences were observed between single fraction and hypofractionated group.[21] An update of this series of patients homogeneously selected and treated with single dose SBRT was published by the same Institution on February 2014. After a median follow-up time of 24 months, 1–2 years actuarial LC rates were respectively 93.4% and 88.1%, while OS rates at 1 and 2 years were 85.1% and 70.5%, respectively. On multivariate analysis, a disease-free interval longer than 24 months was close to significance for a benefit in Cancer-Specific Survival.[22] Osti et al. analyzed data from selected patients with 1–5 lung

Table 1 – Studies on single fraction.

	Study year	No. of patients	No. of lung lesions	Primary site	Dose	LC	Toxicity
Wulf et al.	2004	41	51	All (mostly from lung cancer)	26 Gy (25/51) (30–36 Gy/3 fr)	1-year actuarial LC 80%	G2 (pneumonitis) 3%
Fritz et al.	2006	25	31	All (mostly lung or rectal tumor)	30 Gy	22-months LC 87%	G1 (dermatitis) 16%
Hof et al.	2007	61	71	All (mostly from lung cancer)	24–26 Gy	1–2–3 year local prgogression-free-rate 88.6% – 73.7% – 63.1%	G3 (pneumonitis) 5%
Ricardi et al.	2012	61	77	All (mostly from lung cancer)	26 Gy (51/77) (45 Gy/3 fr)	2-year LC 89%	G3 (pneumonitis) 1.6% G2 3.3%
Osti et al.	2013	66	103	All (mostly lung, rectal or breast tumor)	23 Gy (central) 30 Gy (peripheral)	1–2 year LC 89.1%, 82.1%	G3 (pneumonitis) 3%
Filippi et al.	2014	67	90	All (mostly lung or rectal tumor)	26 Gy	1–2 year actuarial LC 93.4%, 88.1%	G2-3 (lung) 11.9% Chest wall tox 8.9%

metastases, maximum tumor diameter smaller than 50 mm, controlled extra-thoracic disease with a limit of 2 sites, adequate pulmonary function and ECOG performance status of 0–1. After a median follow-up time of 15 months (range, 3–45 months), local control rates at 1 and 2 years were 89.1% and 82.1% and overall survival rates were 76.4% and 31.2%. The authors showed a trend toward better local tumor control for smaller tumor volumes (<10 cc) and a statistically significantly improvement of LC rate for metastases from NSCLC, colon, and breast cancer than for other tumors like melanoma, renal cell carcinoma, and sarcoma (radioresistant histologies).[23]

4.2. *Hypofractionated stereotactic radiotherapy*

Fifteen studies on hypofractionated stereotactic radiotherapy were selected, as shown in Table 2 (patients with pulmonary and other sites of metastases) and Table 3 (selected patients with only lung metastases).

4.2.1. *SBRT for different lesion sites*

Wersall et al. published data from 58 patients with primary and metastatic renal cell carcinoma. They treated 162 lesions, most of them were pulmonary metastases (72.4%). Most common prescribed dose was 30/40 Gy in 3 fractions, varied from 10 Gy per 4–5 fractions to 15 Gy per 3 fractions related to diameter of the lesion. Total regression of treated lesions (30%) was observed mainly for small lung metastases with mean CTV between 28.2 cc and 53.5 cc; no change or partial regression was recorded for lesions with mean CTV between 67.1 cc and 113.7 cc. Local control rate of 90% was observed with a median follow-up time of 37 months (range 7–80 months).[24] A similar study was published by Svedman et al. on lung metastases exclusively from renal-cell carcinoma. Sixty-three out of 82 lesions were pulmonary metastases and most common total dose was 40 Gy in 4 fractions. They obtained a local control rate of 98% and a median survival of 32 months with a follow-up time of 52 months (range 11–66). The authors justified these excellent results in relation to different biology of renal cell carcinoma; in which induction of immune response or production of angiogenesis inhibiting substance could play an important role.[25] Milano et al. reviewed data collected prospectively from 293 metastatic lesions in 121 patients. Most of the primary tumors were breast or colorectal cancer. One hundred and three out of 293 lesions (35%) were pulmonary metastases, with median gross tumor volume (GTV) of 3.7 mm (range 0.08–101.8). Median prescribed dose was 50 Gy in 10 fractions. The 2-year and 4-year tumor LC rates were 77% and 73% respectively. Larger GTV, liver lesions and metastases from primary gastro-intestinal cancer were correlated to poor disease control. On the other hand, breast cancer patients had better survival and local control rate.[26,27] Other experiences confirmed the same data about survival and prognostic factors.[28–31]

4.2.2. *SBRT for only lung metastases*

Norihisa et al. treated 34 patients for 43 lesions with maximum diameter of 4 cm. The primary site of disease was controlled and there were no other organs involved. The total dose of 48 Gy in four fractions was escalated to 60 Gy in five fractions for 16 patients, with median overall treatment time of 12 days. The majority of the lesions had a tumor diameter less than 3 cm (91%). After a median follow-up time of 27 months (range 10–80 months), they observed the 2-year overall survival (OS), local control (LC) and progression-free survival (PFS) of 84.3%, 90% and 34.8% respectively. No significant differences were found between two different dose levels. Survival difference was significant and only related to disease-free interval (DFI), with greater OS in a subgroup with DFI more than 3 years.[32] A similar experience was reported by Rusthoven and colleagues. They enrolled 38 patients with one to three lung metastases, most of them from colorectal cancer. The total dose was safely escalated from 48 to 60 Gy. Median GTV was 4.2 mL (range 0.2–52.3). The 2-year LC and OS were 96% and 39% respectively, with median follow-up time of 15.4 months (range 6–48). This poor OS rate could be explained because the majority (82%) of treated patients had one or more unfavorable prognostic features as 3 thoracic lesions, extra-thoracic disease, disease-free interval less than 36 months, or 2 prior chemotherapy regimens for metastatic disease.[9] Also Oh et al. published their results on 57 patients with lung oligometastases (a total of

Table 2 – Studies on hypofractionated SBRT for different lesions' sites.

	Study year	No. of patients	No. of lung lesions	Primary site	Dose	LC	Toxicity
Wersall et al.	2005	58	117/162	Renal-cell carcinoma (RCC)	30–40 Gy/3 fr/1 week	Median follow-up of 37 months LC 90%	G3 (pneumonitis) in 5 pts
Svedman et al.	2006	30	63/82	RCC	40 Gy/4 fr/every second day	Median follow-up of 52 months LC 98%	G1-2 90% G5 (lung) 3.3% (one pt)
Milano et al.	2008/2012	121	103/293	All (mostly breast and colorectal)	50 Gy/10 fr/over two weeks	2–4 year LC 77%, 73%	G3 (lung) in one pt
Kang et al.	2010	59	18/78	Colorectal carcinoma	39–51 Gy/3 fr	3-year LC 66%	G1-2 (lung) in 6 pt (46%)
Inoue et al.	2010	41	22/60	All (mostly lung)	35 Gy/4 fr	3-year LC 80%	Intercostal neuralgia in one pt
Salama et al.	2011	61	41/113	All (mostly lung)	24–48 Gy/3 fr (3 radiation doses separated by >48 and <192 h)	2-year LC 66.7%	G3 (fatigue) in 2 pt G3 (lung) in one pt G3 (neurologic) in one pt
Stinauer et al.	2011	30	39/53	Melanoma and RCC	40–50 Gy/5 fr 42–60 Gy/3 fr (fractions could be given on consecutive days or separated with intervening days)	18-months actuarial LC 88%	G3 (hypoxia) in one pt G3 (pneumonitis) in one pt

67 lesions). Total dose was 50/60 Gy delivered in 5/4 fractions. The 3-year LC and the 2-year OS were 94.5% and 59.7% after median follow-up time of 21 months (range 3–107). Tumor size (<2.5 cm in 87% of patients) was a favorable prognostic factor while presence of extra-thoracic disease or metastases from liver and colorectal cancer were correlated with a worse prognosis.[33] More recently, Inoue et al. published results from 87 patients and 189 treated lesions. The most common dose fractionation was 48 Gy/4 fractions/4 days. The 2-year OS and LC rate were 47% and 80%, respectively. Breast cancer patients had a better local control compared with pulmonary metastases from intestinal cancers.[34] Navarria et al. reported data from 76 oligometastatic patients with 118 lung lesions. Following a schedule of risk-adapted dose prescription, they received total dose of 48 Gy in 4 fractions for peripheral lesions, 60 Gy in 8 fractions for central lesions and 60 Gy in 3 fractions for peripheral lesions with diameter $\leq$ 2 cm. All patients had controlled primary tumor, long-term of progression disease (longer than 6 months) and number of metastatic sites $\leq$5. The 2-year LC rate and OS were 89% and 73%, respectively, with median follow-up time of 18 months (range 6–45). In this analysis no factors statistically affected outcome of patients. This finding could be related to the characteristics of treated patients; most of them had unfavorable histology (mostly GI tumor and NSCLC), all with primary tumor controlled and disease-free interval greater than 12 months.[10]

Table 3 – Studies on hypofractionated SBRT for only lung metastases.

	Study year	No. of patients	No. of lung lesions	Primary site	Dose	LC	Toxicity
Norihisa et al.	2008	34	43	All (mostly from lung)	48 Gy/4 fr–60 Gy/5 fr within 4–18 days (median, 12 days)	2-year LC 90%	G2 12% G3 (pneumonitis) 3%
Rusthoven et al.	2009	38	63	All (mostly from colorectal)	48–60 Gy/3 fr	2-year LC 96%	G3 (pneumonitis) 2.6%
Oh et al.	2012	57	67	All (mostly from lung)	50–60 Gy/5–4 fr	3-year LC 94.5%	G2 (lung) 6% G5 in one pt Rib fractures 13%
Inoue et al.	2013	87	189	All (mostly from colorectal)	48 Gy/4 fr/4 days	2-year LC 80%	G3-4 10% (G4 in one pt)
Navarria et al.	2014	76	118	All (mostly from colorectal)	60 Gy/3 fr (peripheral)/3 days 48 Gy/4 fr (peripheral >2 cm) 4 days 60 Gy/8 fr (central)/10 days	2-year LC 89%	G1 80%

5. Prognostic factors

5.1. Histology

As previously described, many authors analyzed the prognostic impact of primary tumor's histology. In the Hof's series the local progression-free rate was lowest in metastases from colorectal cancer (0% at 36 months) compared with other histologies. Anyway, no statistically significant influence on local tumor control was found [20]. Also Oh's group confirmed this trend for metastatic tumors from the colorectum and the liver, with lower local control rates than those from other tumors (81.8%, 80.0%, and 100%, respectively, $p = 0.04$).[33] Inoue et al. evidenced a trend toward a worse local control for metastases from intestinal cancer with respect to breast cancer.[34] Milano and colleagues showed that patients with breast cancer have much better survival than other histologies. Progression-free survival at 2 years was 36% for patients with breast cancer compared with 13% for those with non-breast cancers, and overall survival at 6 years was 47% vs. 9%. The rate of local control is also higher.[26] Other experiences confirmed a worsening in local control in patients with high-risk histologies, as small cell lung cancer, sarcoma, renal cell carcinoma and melanoma.[23,30]

5.2. Disease-free interval

In Norihisa's and Inoue's series disease-free interval was associated to better OS rate. Norihisa's group showed significantly greater overall survival ($p = 0.02$) for patients with disease-free interval (DFI) >3 years than patients with DFI <1 year or between 1 and 3 years.[32] Inoue and colleagues separated the patients into two groups according to interval to recurrence of <12 or ≥12 months. The 3- and 5-year OS rates were 19% and 10%, respectively, for those with an interval to recurrence of <12 months, compared with 53% and 40%, respectively, for those with an interval to recurrence of ≥12 months ($p = 0.006$).[29]

5.3. Number of metastases

Different series confirmed the prognostic role of this feature. Salama's group showed the 2-year OS was 60.3% for patients with 1–3 metastases compared with 21.9% for patients with 4–5 metastases.[30] Wersall and colleagues reported the overall survival closely associated with the number of metastases. The patients with one to three metastases had median survival of 37 months, compared with 19 months in patients with more than three metastases.[24] In Hof's series the overall survival was significantly improved for patients with solitary metastases not developing further metastases during follow-up.[20] Ricardi et al. showed an evident trend toward improved PFS related to the number of metastatic lesions but this data were not correlated at multivariate analysis. Nevertheless, the selected group of patients ($n = 24$) with small (<3.3 cc) single metastasis had the more favorable outcome in terms of progression-free survival, with a PFS rate of 70% at 1 year and of 52.8% at 2 and 3 years.[21]

5.4. Size of metastases

The influence of tumor volume on local control is still an outstanding issue. However, most of the studies' data confirmed a close association between smaller lesions and improvement of local control rate. In several series smaller tumor volume was correlated to better disease control.[20,24,31] Similar data were described in univariate analysis by Osti et al. with a significant correlation between tumor small volume (<10 cc) and LC probability ($p < 024$).[23] Milano's and Kang's group showed tumor volume as independent prognostic factors of overall survival[26,28] but in these series the majority of the treated lesions were not pulmonary metastases (only 29% lung lesions, considering both studies). On the other hand, Oh and colleagues reported more favorable survival (64.0% vs. 38.9% at two years, $p = 0.032$) for patients with tumors smaller than 2.5 cm only at univariate analysis.[33] Moreover, tumor volume was significantly correlated to OS, CSS and PFS on multivariate analysis in Ricardi's series.[21]

5.5. Other prognostic features

Other characteristics of patients' population could influence survival and disease control rate. In Oh's univariate analysis patients with extrathoracic disease had lower survival (66.1% vs. 0% at two years, $p = 0.003$); multivariate analysis showed that the presence of extrathoracic disease was the only statistically significant factor ($p = 0.049$).[33] A similar result was reported by Inoue's group for ECOG performance scale (PS) that was significant by both uni- and multivariate analyses.[34]

6. Assessment of treatment response

Radiation-induced CT lung changes after SABR differ from those observed after conventionally fractionated radiotherapy. SABR employs complex beam arrangements to conform high-dose regions to the tumor and create steep dose gradients around the target volume, with a relatively large volume of lung receiving low/intermediate doses. Radiologic aspect after SBRT can be difficult to analyze and RECIST criteria could be inappropriate.[35] In some instances, CT changes after SABR can develop as mass-like patterns that mimic the appearance of recurrent disease. Benign CT lung changes follow common acute and late patterns, appearing predominantly as consolidation within the first 6 months after treatment, with a modified conventional pattern of fibrosis emerging 6 months to years after treatment. Current follow-up relies mainly on CT imaging, with positron emission tomography (PET) or biopsy when recurrence is strongly suspected. An enlarging CT opacity after SABR is the most frequently reported feature of recurrence. Although PET SUVmax may transiently rise immediately post-SABR and persist for over 12 months without recurrence, SUVmax ≥ 5 may serve as a useful cut-off for recurrence. The available evidence currently supports a definition of a recurrence as meeting either of two criteria: (1) increase in tumor size on CT imaging with SUVmax ≥ 5, or (2) pathology-proven disease.[36] Promising new techniques may involve more robust analysis of currently-obtained imaging, such as CT texture analysis, or introduction of novel

imaging modalities into routine clinical practice. Additional PET tracers such as 18-fluoroazomycin-arabinoside (FAZA) and 18F-fluoromisonidazole (F-MISO) are used for imaging hypoxia and perfusion imaging (CT or MRI-based) and have shown promise as prognostic or predictive biomarkers in oncology. All of these new imaging modalities could also be investigated for assessing response following SBRT.[37]

7. Combined SBRT and systemic therapy

The big question in this group patients is if, how and when to integrate SBRT with systemic therapy. The issue is ongoing and to date no clear evidences are available. Few studies were published on concomitant chemotherapy or biological therapy and fractionated or moderate hypofractionated radiotherapy.[38] Again, no selected studies about oligometastatic patients have been published. The only data employed concern patients with limited metastatic disease at diagnosis using a single drug or platinum-based chemotherapy given concurrently with radiotherapy.[39,40] Therefore, further evidences are needed.

8. Patients selection and future perspective

Many non-randomized studies have shown that SBRT for oligometastases is safe and effective with local control rate of about 80%. In most of the cases toxicity seems to be moderate and acceptable. The impact on survival outcomes is still unclear and prospective randomized trials are needed to confirm this issue. Recently, different cooperative groups are outlining prognostic model using age, tumor diameter, Performance Status and BED, to define the benefit of SBRT in terms of overall survival in patients with early-stage lung cancer.[41] Several prognostic factors regarding patients (age, KPS, comorbidity), disease status (histology, disease-free interval time, control of primary tumor, other metastatic sites) and characteristics of SBRT in relation to site and size of lung metastases, total dose delivered, fractionation and treatment time period have been investigated in oligometastatic patients and detailed in previous section. Based on published studies, the patient that might have major benefit from SBRT is patient with: breast histology, disease-free interval $\geq$12 months, control of the primary tumor, small lesions, limited number of lesions (up to three) and higher radiation dose delivered (BED > 100 Gy). Well-designed collaborative trials, including not only stratification of patients by histology but also considering disease-free interval, number and size of metastases, are necessary to draw final conclusions. To date, the discussion within a multidisciplinary team becomes crucial to perform a careful patients' selection in the setting of oligometastatic disease.

Conflict of interest

None declared.

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