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Stereotactic radiotherapy for lung oligometastases

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ABSTRACT

30–60% of cancer patients develop lung metastases, mostly from primary tumors in the colon-rectum, lung, head and neck area, breast and kidney. Nowadays, stereotactic radiotherapy (SRT) is considered the ideal modality for treating pulmonary metastases.

When lung metastases are suspected, complete disease staging includes a total body computed tomography (CT) and/or positron emission tomography-computed tomography (PET-CT) scan. PET-CT has higher specificity and sensitivity than a CT scan when investigating mediastinal lymph nodes, diagnosing a solitary lung lesion and detecting distant metastases. For treatment planning, a multi-detector planning CT scan of the entire chest is usually performed, with or without intravenous contrast media or esophageal lumen opacification, especially when central lesions have to be irradiated. Respiratory management is recommended in lung SRT, taking the breath cycle into account in planning and delivery. For contouring, co-registration and/or matching planning CT and diagnostic images (as provided by contrast enhanced CT or PET-CT) are useful, particularly for central tumors. Doses and fractionation schedules are heterogeneous, ranging from 33 to 60 Gy in 3–6 fractions. Independently of fractionation schedule, a BED_{10} > 100 Gy is recommended for high local control rates. Single fraction SRT (ranges 15–30 Gy) is occasionally administered, particularly for small lesions. SRT provides tumor control rates of up to 91% at 3 years, with limited toxicities.

The present overview focuses on technical and clinical aspects related to treatment planning, dose constraints, outcome and toxicity of SRT for lung metastases.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; lung metastases; organ motion; hypofractionation; BED; local control; toxicity

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Introduction

The lung, a very common seeding site for many primary tumors (30–60% of cancer patients) [1], is probably where local treatments have been most extensively investigated. Surgery is standard, according to findings of large retrospective studies and a few prospective trials. In 1997, the "International

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Registry on Lung Metastases" reported the results of 5206 lung metastases treated with surgery [2]. The primary tumor was epithelial in 43% of patients, sarcoma in 42%, germ cell in 7%, and melanoma in 6%. Actuarial overall survival, after complete resection, was 26% at 10 years and 22% at 15 years, with a median survival time of 35 months [2].

Due to its ablative effect, stereotactic radiotherapy (SRT) has recently emerged as a potential alternative to surgery in patients with lung oligometastases [3]. In 702 patients with pulmonary metastases who were treated with SRT, the primary tumor was in the colon-rectum in 25.7%, the lung in 16.6%, the head and neck area in 11.4%, the breast in 9.2%, the kidney in 8.1%, the skin in 6.5% and other areas in 22.1% [4].

Nowadays, SRT is considered the ideal modality for treating pulmonary metastases as it provided high tumor control rates [4–7]. The SABR COMET study, a randomized phase 2 multicentric trial, first showed that SRT improved overall survival (OS) compared with palliative standard of care [8–10]. SRT could work in concert with systemic therapy and is probably not as costly as surgery in terms of toxicity and invasiveness [11].

As appropriate patient selection is a major issue, today's challenge is to determine conditions when SRT improves progression-free survival (PFS) and OS, thus impacting upon prognosis [12, 13]. Factors include performance status, disease-free interval of over 12 months, volume and number (usually under 5) of metastatic lesions in the lung, no metastases elsewhere and primary tumor histology.

The present overview focuses on technical and clinical aspects related to treatment planning, dose constraints, outcome and toxicity of SRT for lung metastases.

Staging and selection of oligometastatic patient

When lung metastases are suspected on chest X-ray evidence during an oncological follow-up, complete disease staging includes a total body computed tomography (CT) and/or positron emission tomography-computed tomography (PET-CT) scan, which, however, are nowadays the imaging modalities commonly used for the follow-up. In defining oligometastatic patients PET-CT has higher specificity and sensitivity than a CT scan [14–15] when investigating mediastinal lymph nodes, diagnosing a solitary lung lesion and detecting distant metastases [16, 17].

Lung metastases are often diagnosed clinically, without pathological confirmation. Patients with oligo- metastatic or -progressive disease (i.e., disease progression at a limited number of anatomic sites, with continued response or stable disease at other sites of disease), who are the best candidates for lung SRT, need to satisfy the following criteria:

- disease free interval of over 12 months;
- fewer than 5 small metastatic lesions;
- primary tumor control;
- favorable histology;
- good patient performance status;
- no counter-indications to high-dose RT (BED_{10} > 100 Gy) [16].

Although SRT was reported to achieve high local control rates [5–7], OS was poor in many series, demonstrating that eradication of widespread microscopic disease is crucial for disease control. Consequently, ablative SRT should be integrated with systemic treatments, particularly immunological therapies. In this setting, circulating biomarkers are potentially useful as the presence of specific microRNA (miRNA) in the peripheral blood of oligometastatic patients seemed to be linked to different tumor phenotypes, with diverse biologically aggressive patterns and metastatic potentialities [18].

Treatment planning

A multi-detector planning CT scan of the entire chest (2–3 mm thick slice) is usually performed with the patient in the treatment position. Each patient is immobilized in a comfortable, reproducible position, supine with arms raised above the head, in order to prevent arm interference with the beams. Some centers use intravenous contrast media or esophageal lumen opacification, especially when central lesions have to be irradiated. Immobilization systems include, for example, a stereotactic body frame, vacuum cushions, thermoplastic masks or abdominal compressors.

Respiratory management is recommended in lung SRT, taking the breath cycle into account in planning and delivery, in order to lower treatment-related toxicity. In fact, the amplitude of lung movements during respiration, which is the greatest in the cranio-caudal direction, can exceed 2 cm in some cases

[19]. Strategies include 4D-CT, which assess tumor motion during the breathing cycle, and procedures for breathing control (such as abdominal compression, Deep Inspiration Breath Hold (DIBH), optical surface imaging systems, and Active Breathing Control (ABC) device). They require active patients' collaboration with some discomfort and longer treatment delivery time [20, 21]. Another strategy for organ motion control is tumor tracking, which is specific for treatment delivery phase. Main tumor localization techniques are fluoroscopic tumor imaging, implanted marker imaging and tumor position reconstruction by means of an external surrogate of a respiratory movement signal [22–24].

Moreover, also modern Image-Guided Radiation Therapy (IGRT) with cone beam computed tomography (CBCT) is crucial for SRT accuracy: it can visualize the target immediately before (or even during) the SRT session, allow the volumetric registration with planning CT with on-line correction of set-up errors and organ motion. Respiratory-correlated 4D-CT methods should be integrated, when available, because they provide complementary information on the interfraction trajectory of the tumor [22, 25, 26].

Contouring

The target is outlined on sequential axial CT images that are reconstructed in 3D, using the lung window (1600–400 Hounsfield units). Co-registration and/or matching planning CT and diagnostic images (as provided by contrast enhanced CT or PET-CT) are useful, particularly for central tumors [27]. Identifying the biological tumor volume on PET-CT images by means of diverse, non-validated segmentation methods (SUV Max uptake or thresholding) should be performed only in the clinical trial setting.

Organs at risk (OARs) are healthy lung tissue (i.e. lungs minus the gross tumor volume-GTV or internal target volume — ITV), spinal cord, esophagus, heart, trachea and bronchi, the great vessels and ribs. Parallel organs need to be contoured in full and their constraints are expressed as dose-volume. A planning organ at risk volume (PRV) is required for serial organs with the reference standard being maximum dose to the point [28, 29]. Auto-contouring software is useful because so many OARs need to be contoured.

Doses, fractionation and constraints

Doses and fractionation schedules for treating lung metastases are heterogeneous, ranging from 33 to 60 Gy in 3–6 fractions [28–34], with dose prescription at the isocenter or at an isodose [35]. Single fraction SRT ranges from 15 to 30 Gy [8, 36–39], especially for small lesions. Although fractionated schedules seemed to provide better local control of larger lesions than single-dose SRT (maybe because of reoxygenation and redistribution processes), Siva et al. found no significant difference in outcomes [40]. Definitive results in terms of safety are still awaited from the ongoing TransTasman Radiation Oncology Group (TROG) randomized phase II study comparing single fraction *vs* fractionated treatment for lung metastases [41].

In a cohort of over 3700 patients, an alfa/beta ratio > 10 Gy for lung metastases was defined [42] and, despite differences in schedules, BED_{10} > 100 Gy is always crucial for obtaining high local control rates [43–45]. In most series, the BED value was calculated at the periphery, as the dose prescription was usually at the 70 or 80% isodose. This prescription ensured delivery of "ablative doses" at the periphery, higher doses at the isocenter and a steep dose fall-off outside the target volume.

Currently, even though there is no consensus on normal tissue dose constraints, greater uniformity has emerged and American Association of Physicists in Medicine Task Group 101 (AAPMTG101) [19] or Navarria et al. [46] are suggested for clinical practice (Tab. 1).

Table 1. Suggested dose constraints for lung metastases

Total healthy lung — PTV	V5	< 30%
	V10	< 20%
	V20	< 10%
	Mean dose	< 4 Gy
Total lungs	V5	< 30%
	V10	< 20%
	V20	< 10%
	Mean dose	< 4 Gy
Spine	D1%	< 20 Gy
Heart	D1%	< 30 Gy
Esophagus	D1%	< 30 Gy

PTV — planning target volume

The lesion site, which is associated with risk of toxicity, influences decision-making on fractionation schedule and dose constraints. Peripheral lesions (with or without chest wall contact) are associated with greater risk of rib fractures than central tumors which are more often linked to mediastinal toxicity, e.g. esophageal stenosis. Dose constraints for the trachea and bronchi, the great vessels, esophagus and chest wall were defined on the basis of toxicity data from several studies [47–50]. To prevent stenosis in the trachea, main, lobular and segmentary bronchi, maximum doses, as expressed in EQ2, are, respectively, 93 Gy, 103 Gy, 124 Gy and 121 Gy. In the aorta and great vessels, a maximum dose of 52.5 Gy in 5 fractions was associated with grade 2–5 toxicity in 1.2% of patients, while a maximum dose of 45 Gy in 3 fractions was linked to toxicity in 2.3%. Even though doses to the upper part of the heart and great vessels (especially the superior vena cava) were associated with non-cancer related death in a population treated with SRT for stage I non-small-cell lung cancer (NSCLC), these data need further validation [51]. The use of "risk-adapted" protocol and specific constraints ensured that treatment of central or peripheral tumors was without excessive toxicity [52–55].

In 5-fraction schedules D_{1cc} of 32.9 Gy and 50.7 Gy, and maximum doses of 43.4 Gy and 61.4 Gy were associated with 50% probability of developing, respectively, grade 2 and 3 esophagitis. It must be noted that chemotherapy may increase esophageal toxicity.

There is no consensus on chest wall constraints as there is no uniform definition of chest wall anatomy. Radiation-induced injury ranges from chest pain to painful or painless rib fractures, with the latter leading to under-estimates of their real incidence. In 4-fraction schedules, D_{70cc} of 16.2 Gy and 65.1 Gy and D_{2cc} of 43 Gy and 87.9 Gy were associated with, respectively, grade ≥ 2 toxicity rates of 10% and 50% [56].

According to Andolino et al. [57] the maximum dose to the chest wall and ribs should be under 50 Gy, and under 5 cc of the chest wall should receive doses ≥ 40 Gy.

Moreover, lung dosimetric constraints for SRT in case of multiple lung lesions were recently suggested [58].

Outcomes and follow up protocol

Table 2 summarizes the results of SRT as reported by selected studies. The main clinical presentation was a single metastasis but synchronous lung metastases were 1–2 or 1–3 in number in most trials, with some patients having 1-5 lesions [41]. Fractionated SRT was delivered in most studies [5, 6], with a few reports using single fractions [6, 7, 37, 39]. For single or few lung metastases (< 3–5, according to different selection criteria), probability of 1-year local control was between 70–95% [4–7, 28–34, 39]. In Siva's review, 2-year local control and PFS were 91% and 54.5%, respectively [40].

Local control varied with risk factors, i.e., doses, primary histology, metastatic tumor volume, preceding chemotherapy and extra-thoracic disease [5, 16, 59–61]. An analysis of patient registry data showed that local control rates were linked to BED_{10} > 100 Gy and tumor volume < 11 cm^3 [45]. Osti et al. [59] associated lesion volume < 10 cm^3 and primary tumor histology with local control rates, showing that NSCLC, colon-rectal and breast cancers had better outcomes than melanoma, sarcoma and kidney disease.

Different prognostic factors, including the primary tumor, influenced OS [6, 16, 30, 39, 62, 63]. Median survival times were 30, 26 and 22 months for lung metastases from colon-rectal, breast and lung tumors, respectively [64]. Since patient selection is crucial for SRT, Tanadini-Lang et al. conducted a multi-centre, retrospective study in an attempt to integrate patient and disease factors so as to develop a nomogram that would predict OS [65]. Significant prognostic factors were Karnofsky performance index, primary tumor and its control, the maximum diameter of the largest treated metastasis and the number of metastases (not limited to pulmonary metastases) (1 *vs* > 1). All these were included in the nomogram to predict 2-year OS in four different risk groups. The benefit of SRT was probably higher in good-prognosis patients. The nomogram could also be used to select a high-risk population that might benefit from adding systemic therapy to SRT.

Follow-up is generally conducted using total body or chest only CT scans (according to the primary tumor). SRT-related toxicity is reported in about 25% of patients. On CT images, consolidation, with or without air bronchogram, or fibrosis

Table 2. Selected studies investigating the role of SRT in lung metastases

Study (year) [ref.]	Pts (n)	Dose and fractionation	Median follow-up (months)	Local control	Overall survival	Toxicity
Wulf et al. (2005) [36]	27	30 Gy/3 36 Gy/3	13-17	2-yr: 71%	1-yr: 48% 2-yr: 21%	Grade 3:1 (3.7%) Grade 5: 1 (3.7%)
Okunieff et al. (2006) [33]	50	50 Gy/10 48 Gy/6 57 Gy/3	18.7	3-yr: 91%	2-yr: 50%	Grade 2: 6.1% Grade 3: 2%
Hof et al. (2007) [39]	61	12–30 Gy/1	14	3-yr: 63.1%	3-yr: 47.8%	No Grade 4 G3: 3 (5%)
Norihisa et al. (2008) [34]	34	48 Gy/4 60 Gy/5	27	2 yr: 90%	2-yr: 84%	Grade 2: 4 (12%) Grade 3: 1 (3%)
Brown et al. (2008) [28]	35	60 Gy/4	18	77% (crude)	2 yr: 72.5%	Grade 3–4: 1 (2.8%)
Rusthoven et al. (2009) [5]	38	60 Gy/ 3	15.4	2-yr: 96%	2-yr 39%	No grade 4 Grade 3: 3 (8%)
Ricardi et al. (2012) [6]	61	45 Gy/3 26 Gy/1	20.4	2-yr: 89%	2-yr: 66.5%	Grade 3: 1 (1.6%)
Inoue et al. (2013) [16]	87	48 Gy/4 60 Gy/10 52 Gy/10 50 Gy/5	37	3-yr: 80%	3-yr: 32%	Grade 4: 1% Grade 3: 6%
Osti et al. (2013) [59]	66	23 Gy/1 30 Gy/1	15	2-yr: 89.1%	2-yr: 31.2%	Grade 3: 2 (3%)
Filippi et al. (2014) [7]	67	26 Gy/1	24	2-yr: 88.1%	2-yr: 70.5%	Grade 2–3 late radiological: 8 (12%)
Navarria et al. (2014) [46]	78	48 Gy/4 60 Gy/3 60 Gy/8	20	3-yr: 89%	3-yr: 73%	No Grade 2 or more
Ricco et al. (2017) [44]	447	48-54 Gy/3-5	NR	3-yr: 58.9%	3-yr: 33.3%	NR
Casamassima et al. (2017) [60]	279	Median Dose: 33 Gy/1–3	19	Median: 18	Median: 56	No Grade 3

Pts — patients; NR — not reported

are frequently observed [65]. Even though the differential diagnosis between local relapse or post-radiation therapy alterations may be difficult, a biopsy will distinguish between the two [66]. Use of a PET-CT scan is still under debate. Some authors reported inflammation at 48 months after the end of SRT in 50% of patients [67], thus impacting on PET-CT ability to distinguish between tumors and radiation-induced injury.

Treatment toxicity

Using risk-adapted schedules and validated OAR constraints, the toxicity profile of SRT for lung metastases is generally favorable as SRT is well-tolerated [6, 7, 43, 67]. The cumulative rates of toxicity ≥ G3 range from 2% to 10% [16, 40]. Grade 3 radiation pneumonitis (RP), which is one of the major dose-limiting toxicities, is quite infrequent and has been reported in about 5% of patients [6, 16, 62, 67]. RP is usually asymptomatic with only radiological findings after SRT. Grade ≥ 2 RP has been correlated with some dosimetric factors such as mean lung dose (MLD) > 6 Gy and the lung volume receiving at least 20 Gy (V20) > 10%. Regarding heart toxicity, to date there is no clear correlation between cardiac complications and lung SRT, whereas in literature several studies have been pub-

lished on patients affected by lymphoma or breast cancer treated with conventional fractionation on large volumes with conformal techniques. Based on the few available data, the following heart dose constraints for 4-fractions SRT have been proposed: Dmax < 45 Gy, V40 ≤ 1 cm^3, and V20 ≤ 5 cm^3 [54]. In SRT for centrally located tumors, the esophagus is another organ at risk with reported late side effects ranging from stricture to perforation [68]. It has been suggested to keep maximum dose under 30 Gy depending on the SRT fractionation schedule. Other critical structures in SRT of central lesions are the trachea and the proximal bronchial tree. The most commonly reported serious adverse events included hemoptysis, stenosis, occlusion or fistula formation. Other side effects, such as radiation dermatitis, rib fractures and brachial plexopathy, were rarely reported [54, 69, 70].

Together with lesion site (central *vs* peripheral), other factors that might affect toxicity are lesion dimension (> 5 cm) and systemic therapy (e.g. gemcitabine) [7, 16, 40, 71–72].

Conflicts of interest

The authors have no conflict of interest to declare.

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