Stereotactic Radiotherapy for Pulmonary Oligometastases

A Systematic Review

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Introduction: Hypofractionated stereotactic body radiotherapy (SBRT) is an emerging noninvasive technique for the treatment of oligometastatic cancer. The use of small numbers of large doses, should in theory, achieve high rates of local control. The aim of this literature review is to critically assess the use of SBRT for the treatment of pulmonary metastases as judged by its effect on local control, survival, and toxicity.

Methods: A systematic literature search was performed. Both single fraction stereotactic radiosurgery (SRS) and hypofractionated radiotherapy (SBRT) were considered individually. Thirteen institutions reported results regarding SBRT and seven institutions regarding SRS (a total of 29 publications). Outcomes, techniques, radiobiology, and the scientific rigor of the reported studies were analyzed.

Results: A wide range of techniques, doses, and dose fractionation schedules were found. Three hundred thirty-four patients with 564 targets were reported in the SBRT series. The 2-year weighted local control was 77.9%. The corresponding 2-year weighted overall survival was 53.7%, with a 4% rate of grade 3 or higher radiation toxicities. One hundred fifty-four patients with 174 targets were treated in the SRS series. The 2-year weighted local control was 78.6%. The corresponding weighted 2-year overall survival was 50.3%, with 2.6% rate of grade 3 or higher toxicities.

Conclusion: There was insufficient evidence to recommend a consensus view for optimal tumor parameters, dose fractionation, and technical delivery of treatment. This indicates the need for further prospective studies. However, high local control rates that could potentially lead to a survival benefit justifies the consideration of stereotactic radiotherapy for patients with limited pulmonary oligometastases.

Key Words: Stereotactic, Radiotherapy, Radiosurgery, Metastases, Lung.

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The management of patients with distant metastasis from solid tumors is usually conducted with palliative intent, with rare exceptions. Treatment predominantly involves the use of systemic chemotherapy, with targeted radiotherapy or other local measures typically reserved for symptom relief.[1] Chemotherapy is delivered without expectation of long-term survival. Observing the natural history of breast cancer, Hellman and Weichselbaum[2] hypothesized the existence of a state intermediate between widespread metastatic disease and locally confined disease and coined the term "oligometastasis." In this setting, the role of potentially ablative local targeted therapies has been investigated either with curative intent in the assumption that oligometastases are the only remaining burden of disease or in the hope that reduction of tumor burden will increase the effectiveness of subsequent chemotherapy (Norton-Smith hypothesis[3]). Metastasectomy has been shown to increase median survival in patients with single brain metastases from 15 to 40 weeks ($p = 0.01$).[4] Systematic reviews of the resection of hepatic metastases show a median 5-year survival of 25 to 30%.[5,6] Similarly, a systematic review of adrenalectomy for metastases showed a median 5-year survival of 25%.[7] Surgical resection of pulmonary metastases is also becoming increasingly prevalent.

Pulmonary parenchymal tissue represents a common site for metastatic seeding. Sarcoma and epithelial malignancies (in particular colorectal cancers) have a particular tendency toward metastasis to the lung. In the International Registry of Lung Metastases, 5206 cases of lung metastasectomy were recorded. Resected tumors were epithelial in 43%, sarcomatoid in 42%, germ cell in 7%, and malignant melanoma in 6%, respectively. An overall 5-year overall survival rate of 36% was reported in completely resected cases,[8] with a 15-year survival of 22%. The median survival was 35 months. These results are remarkably good, given the typically poor survival for patients with metastatic solid tumors.

More recently, less invasive techniques have been used to treat oligometastatic lung disease. These include radiofrequency ablation and stereotactic radiotherapy and are especially attractive approaches in patients who refuse or are unsuitable for surgery. "Radiosurgery" was a term first coined by Swedish neurosurgeon Lars Leksell in the 1950 to describe single-dose ablative radiotherapy delivered to brain lesions through stereotaxy.[9] The term stereotaxis applies to the realization of tumor position via the use of coordinates derived from external surrogate markers or fiducials. These fiducials allow the determina-

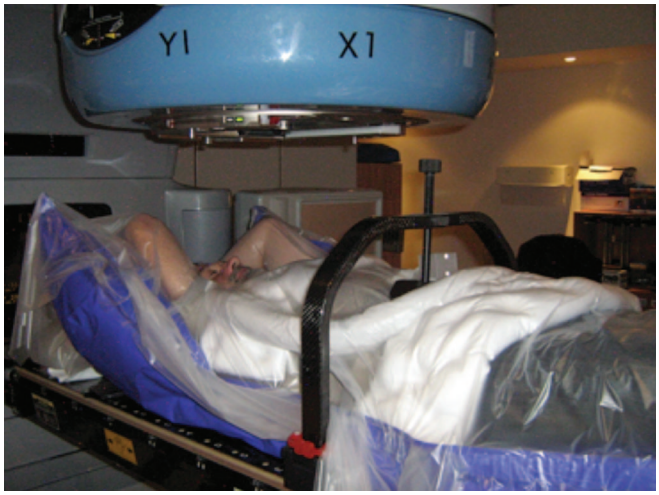

FIGURE 1. Stereotactic body frame and vacuum immobilization, with abdominal compression, Peter MacCallum Centre.

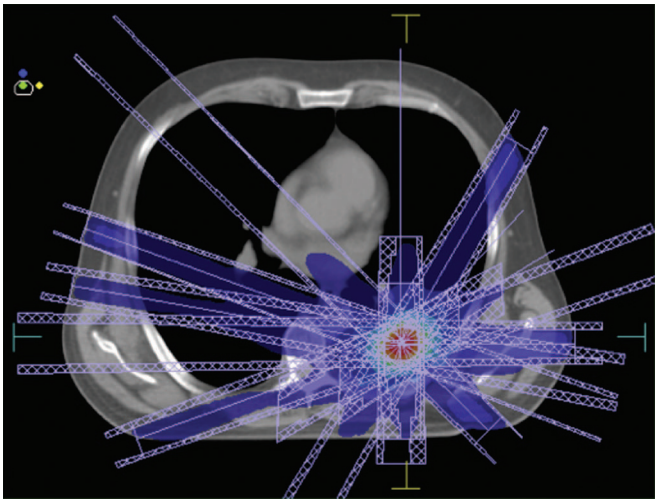

FIGURE 2. Axial computed tomography dose color wash and beam arrangement, Peter MacCallum Cancer Centre.

tion of tumor coordinates in the sagittal, coronal, and axial planes. This principle has been extrapolated to the stereotactic delivery of hypofractionated treatments for pulmonary metastases. Lax et al.[10] developed the first stereotactic body frame to enclose the body from head to midfemoral region with vacuum stabilization to provide high surface contact (Figure 1). Both single fraction radiosurgery and hypofractionated pulmonary radiotherapy have been reported using stereotactic techniques.

THE BASIC PRINCIPLES OF STEREOTACTIC TREATMENT

Stereotactic techniques are usually combined with hypofractionation, defined as the delivery of a small number of large doses of radiation. This is a major departure from the typical fractionation of standard radiotherapy delivered with curative intent to epithelial tumors, which generally involves the use of 30 or more small doses, (1.8–2 Gy per fraction) delivered 5 days per week. Recent work with hypofractionation for pulmonary malignancies has resulted in the use of fractions up to 30 Gy delivered in an accelerated fashion over 1 to 3 weeks.[11–13] The very large hypofractionated doses used in stereotactic body radiotherapy (SBRT) can be given safely because (a) the treated volumes are small with tight margins and (b) the technique employs a large number of beams (eight or more), which individually contribute a small dose along their path but together result in a much larger dose where they intersect and are summed at the locus of the cancer (Figures 2 and 3).

The linear quadratic (LQ) equation[14] is often used to estimate cell survival to radiation. The LQ equation is used to calculate biologic equivalent doses (BEDs) between the various fractionation schemes reported below, because this allows a direct comparison of effective doses for early effects to tumor and normal tissues. However, at very large doses per fraction, radiotherapy becomes tissue ablative, and the LQ equation may underestimate the effect,[15] therefore the absolute values of the BED calculations should be interpreted with caution.

The term "radiosurgery" to describe single fraction ablative radiotherapy is misleading, as it does not involve surgery at all. It could be argued that it is an anachronism that should be consigned to history, and that radioablation is a more appropriate term. Similarly, the definition of stereotaxis has been somewhat loosely applied throughout the literature. The need for stereotactic methods for precise tumor localization has been largely replaced by image-guided radiotherapy, although the term "stereotactic" is still often used. Image-guided radiotherapy involves the use of some method of radiologic localization of the tumor in the treatment room immediately before or during treatment delivery. This may be with volumetric soft tissue imaging devices attached to the treatment machine (for example cone beam computed tomography [CT]), or with implanted radiopaque fiducials that are detectable by orthogonal kilovoltage x-rays. In this review of the literature, we will consider all

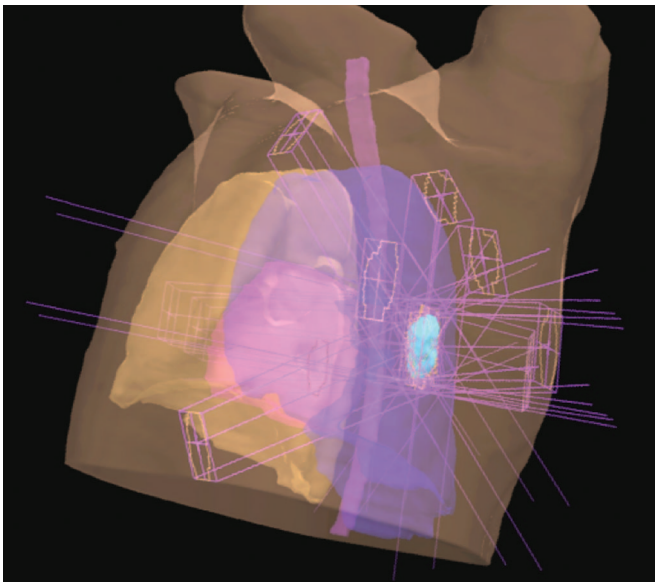

FIGURE 3. Three-dimensional reconstruction of noncoplanar beam arrangement around target (cyan), Peter MacCallum Cancer Centre.

TABLE 1. Reference(s), Patient/Target Population, and Tumor Characteristics

Author(s)	Patients/ Targets	Target Size, Median (Range)	Eligible Locations	Number of Synchronous Metastases	Primary/Histology (%)	Phase I Data?	Motion Management
Nakagawa et al.[16]	14/21	Median 40 ml (5–126 ml)	Central/peripheral	1	36% liver, 21% lung, 14% colon, 14% thymoma, 7% esophagus, 7% myeloma	No	Megavoltage CT pretreatment planning CT and treatment with shallow breathing
Hara et al.[17]	11/15	<40 mm, median 4 ml (1–16 ml)	Central/peripheral	Not specified	36% lung, 27% liver, 18% H & N, 9% cervix, 9% breast, 9% bladder	Yes	End expiratory and max inspiratory phases for planning CT, pretreatment CT, respiratory-gated treatment and custom bed for immobilization
Wulf et al.[18]	25/25	<25 ml	Central/peripheral	1 to 2	45% lung, 10% breast, 8% colon, 8% kidney, 8% sarcoma, 6% HCC, 12% others	No	4D planning CT, pretreatment CT and stereotactic body frame
Le et al.[11]	12/12	Mean 26 ml, median 27 ml	Central/peripheral	1 to 2	63% AdenoCa, 22% SCC, 6% NSCLC, 6% sarcoma, 3% HCC	Yes	4D planning x-rays, orthogonal x-rays ± respiratory tracking via CyberKnife, vacuum immobilization
Fritz et al.[19]	25/31	CTV, median 6 ml (2.8–55.8 ml)	Peripheral only	1 to 2	32% lung, 29% rectal, 19% breast, 10% H & N, 10% other	No	Three phase CT planning three phase pretreatment CT Stereotactic body frame
Hof et al.[20]	61/71	Median 10 ml (1–53 ml)	Central/peripheral	1 to 2	51% lung, 13% colorectal, 6% breast, 30% other	Yes	Fluoroscopy, dynamic 4D planning CT, stereotactic body frame + abdominal compression

CT, computed tomography; NSCLC, non-small cell lung cancer.

definitions of stereotactic radiotherapy and radiosurgery published to date. A large proportion of published reports regarding stereotactic hypofractionated radiotherapy address treatment of both primary non-small cell lung cancer (NSCLC) and metastatic pulmonary lesions. This review will focus only on the reported outcomes of those patients treated for metastatic disease.

MATERIALS AND METHODS

A literature search was performed using Medline for the period from 1990 to April 2009. The search was limited to articles in English print and employed the following terms; "stereotactic AND radiotherapy OR Radiosurgery NOT cerebral NOT brain" was combined with "lung OR pulmonary OR thoracic" and "metastases OR metastatic OR oligometastases." This yielded 115 publications. Where multiple publications existed for a single institution, outcome data from only the most recent or most relevant articles were included. However, previously published information regarding treatment techniques could be considered if this gave useful additional information. Several groups published articles that reported data on the treatment of both pulmonary metastases and primary lung cancers in the same article. In such cases, only data relevant to metastases were considered. In total, 13 institutions reported on stereotactic fractionated radiotherapy, and seven institutions reported on single fraction stereotactic radiosurgery. Relevant information concerning tumor characteristics, treatment techniques, duration of follow-up, treatment-related toxicities, and radiobiological information is shown in Table 1. Two-year overall survival and local control data, when not reported, were extrapolated from reported time points assuming a constant hazard. Weighted mean 2-year local control rate, BED, and 2-year overall survival have been calculated using the average of each of the categories with respect to the contribution of the number of patients within each dataset.

SINGLE FRACTION RADIOABLATION

In total, there were six institutions reporting single fraction stereotactic "radiosurgery" for thoracic metastases. These institutions are tabulated in chronological order of publication, from 2000 to 2007 (Table 1). This experience encompasses 148 patients with 175 targets, which highlights the paucity of data available for this technique. Only Fritz's and Hof's groups analyzed their data prospectively, collectively treating 86 patients. Hara et al., Le et al., and Hof et al. have all performed phase I dose escalation studies. There are no reported randomized phase III studies of single fraction stereotactic radioablation.

Five of the six groups treated both central and peripheral tumors. Three of these six groups prescribed a lower dose to centrally located tumors. The justification for treating central tumors with more caution can be extrapolated from the stereotactic experience in NSCLC. Timmerman et al.[21] reported a 2-year freedom from severe toxicity for peripheral tumors of

TABLE 2. Lengths of Follow-Up, Outcomes, Toxicities Dose, Organ Constraints, Toxicities, and BED

Group	F/U Period (mo) Median (Range)	Outcomes	Single Fraction Dose	Constraints for Critical Organs	Toxicity	BED at Isocenter	BED at Periphery
Nakagawa	Median 10 (2–82)	95% crude LC, median survival 9.4 mo estimated 2-yr o/s 35%, estimated 2-yr LC 91%	Median 20 Gy (range, 15–25 Gy) prescribed to covering isodose	Not specified	No grade 3+ or above	Not reported	60 Gy median
Hara	Median 13 (3–24)	62% 1-yr LC at <30 Gy, 86% 1-yr LC at 30 Gy, 79% total crude LC, estimated 2-yr LC 48%	<30 Gy ($n = 8$) 30 Gy ($n = 7$) prescribed to isocenter	Not specified	9% grade 3 and 18% grade 2 radiation pneumonitis	Not reported	87.5 Gy median
Wulf	Median 14 (2–37)	100% crude LC and 33% actuarial 2-yr o/s	26 Gy, prescribed to covering isodose	Mediastinal organs	No grade 3 or above	138 Gy	93.6 Gy
Le	Median 18 (9–32) (pooled with NSCLC)	67% crude LC at 15–20 Gy, 56% crude LC at 25 Gy, 1-yr o/s 56%, estimated 2-yr o/s 32%, estimated 2-yr LC 56.3%	15 Gy–20 Gy ($n = 3$), 25 Gy ($n = 9$), prescribed to covering isodose	Mediastinal organs and lungs	19% pneumothorax with fiducial insertion (pooled with NSCLC)	73% patients received >100 Gy	62% patients received >50 Gy
Fritz	Median 22 mo (6.8–83 mo)	87% crude LC, 73% 2-yr o/s	30 Gy prescribed to isocenter	Mediastinal organs	73% radiological pneumonitis	120 Gy	100 Gy
Hof	Median 14 (1.5–82)	65.1% 2-yr o/s, 47.8% 3-yr o/s, 73.7% 2-yr LC, 63.1% 3-yr LC	24 Gy ($n = 28$), 26 Gy ($n = 20$), other doses ($n = 23$) all prescribed to isocenter	Mediastinal organs and lungs	5% grade 3 pneumonitis	Variable	Not reported

BED, biological equivalent doses; NSCLC, non-small cell lung cancer.

83%, compared with only 54% for central tumors ($p = 0.004$). Although there were no grade 5 toxicities reported in the oligometastatic patients of Le et al.,[11] there were three in the corresponding NSCLC cohort, all to central targets. Two of these deaths occurred after initiation of adjuvant gemcitabine chemotherapy. Larger tumor size was also predictive of severe toxicity.

There was considerable variation in target size treated throughout the groups. In the largest reported study of 61 patients, the median volume was small at only 10 cm^3. Four of the six institutions allowed up to two synchronous metastases to be treated. All of the institutions used some method of motion management at planning and/or treatment. Four of the six institutions reported the use of an immobilization device. Three of six used a stereotactic body frame. Le et al. reported results with the use of a CyberKnife (Accuray, Sunnyvale, CA) while all other groups used a gantry operated linear accelerator.

The median follow-up reported among the groups ranged from 9 to 22 months. There were few toxicities reported (Table 2). There were five grade 3 toxicities reported and no grade 4 or 5 toxicities reported among the institutions. Crude local control varied markedly among the groups. The BED in 2 Gy fractions using an α/β ratio of 10 were reported in four of the seven groups. The BED could be calculated in a further two studies. The mean weighted 2-year local control rate was 78.6% (range, 48–91%). The weighted 2-year overall survival was 50.3% (range, 33–73%). Of those reported, the mean weighted BED at the periphery was 87.1 Gy.

HYPOFRACTIONATED RADIOTHERAPY

There are 13 institutions that have reported experience with stereotactic fractionated body radiotherapy, tabulated in chronological order of publication (Table 3). This corresponds to a considerably larger reported experience than single fraction radioablation for pulmonary oligometastases, with a total of 334 patients and 564 targets. In total, five institutions prospectively enrolled data, with the most robust data being published by Rusthoven et al.[38] with a multi-institutional phase II trial. Three of 13 institutions completed a phase I dose escalation study before selecting a fractionation schedule. Again, there are no phase III randomized trials of fractionated stereotactic radiotherapy. Target sizes varied considerably between institutions. Two of 13 institutions excluded central targets, whereas one group treated central targets with an altered fractionation. The majority of institutions limited treatment for three or less synchronous pulmonary metastases. One group treated between one and five synchronous targets, inclusion criteria that test the concept of the oligometastatic state, whereas two groups did not specify any limitations.

Eight of 13 institutions reported the use of a stereotactic body frame or immobilizing cradle (Table 4). Six of these groups and one other group used abdominal compression to reduce tumor excursion during the respiratory cycle. All institutions reported techniques used to manage tumor motion at simulation or at treatment delivery. The use of a body frame and soft-tissue pretreatment verification (through CT) has been shown to be a rigorous and reproducible method of reducing setup error.[25,39] Dose fractionation varied from 33 Gy/6 fractions up to 60 Gy/3 fractions, with treatment delivery time varying greatly between institutions. Beam arrangement ranged from 3 to 12 static noncoplanar and coplanar beams, although the use of photon arc therapy was reported in 5 of 13 groups. Brown

TABLE 3. Reference(s), Patient/Target Population, and Tumor Characteristics

Author(s)	Patients/ Targets	Target Size Median (Range)	Eligible Locations	Number of Synchronous Metastases	Phase I Data?	Primary/Histology (%)
Lax et al. and Blomgren et al.[22,23]	13/17	Volume 48 ml (3–198 ml)	Central/peripheral	Not specified	No	Not reported
Uematsu et al.[24]	29/43	≤4 cm	Central/peripheral	Not specified	No	35% colorectal, 26% lung, 17% breast, 7% kidney, 7% sarcoma, 7% others
Nagata et al.[25]	9/9	Not reported	Central/peripheral	1 to 2	No	44% colon, 22% H & N, 11% lung, 11% liver, 11% sarcoma
Onimaru et al.[26]	20/32	<6.0 cm median 2.5 cm (0.6–6.0 cm)	Central/peripheral	1 only	Yes, at affiliated hospital	45% renal, 22% lung, 6% bladder, 6% breast, 6% H & N, 3% liver, 3% rectal, 3% melanoma, 3% thymic, 3% thyroid
Wulf et al.[18,27,28]	25/51	17 ml (1–155 ml)	Peripheral only	1 to 2	No	45% NSCLC, 10% breast, 8% colon, 8% kidney, 8% sarcoma, 6% liver, 4% thyroid, 8% others
Song et al.[29]	13/20	Range, 1–5.5 cm	Central/peripheral	1 to 2	No	15% sarcoma, 15% H & N, 15% kidney, 8% breast, 8% lung, 8% esophagus, 8% uterine, 8% ovarian, 8% colon, 8% testes
Min Yoon et al.[30]	53/80	PTV = 43.9 ml (4.3–213 ml)	Central/peripheral	1 to 3	Yes	28% lung, 22% liver, 19% colorectal, 11% H & N, 8% esophagus, 4% uterine, 2% gastric, 2% anal, 2% breast, 2% sarcoma
Aoki et al.[31]	8 targets	<50 mm mean = 11.8 ml (3–44 ml)	Central/peripheral	1 to 3	No	62% lung, 13% liver, 13% esophagus, 13% H & N
Milano et al. and Okunieff et al.[32–34]	50/125	2.1 cm median (0.3–7.7 cm) volume median 4.7 (0.1–125 ml)	Central/peripheral	1 to 5	No	29% CRC, 20% breast, 16% lung, 35% other
Norihisa et al.[35]	34/43	40% <15 mm, 51% 15–30 mm, 9% 30–40 mm	Central/peripheral	1 to 2	No	65% AdenoCa, 15% SCC, 9% RCC, 6% adenoid cystic, 3% pleomorphic carcinoma, 3% osteosarcoma
Brown et al.[36]	35/69	<5.0 cm range, 0.7–152 ml	Central/peripheral	1 to 3	No	22% lung, 18% kidney, 15% sarcoma, 10% H & N, 6% urothelial, 6% testicular, 4% colorectal, 10% others
Salazar et al.[37]	7 targets	124 ml (pooled with NSCLC)	Central/peripheral	1 to 2	No	28% lung, 28% CRC, 14% breast, 14% H & N, 14% tongue
Rusthoven et al.[38]	38/63 lesions	Targets <5 cm, median 4.2 ml (0.2–52.3 ml)	Peripheral only	1 to 3	Yes	24% colorectal, 18% sarcoma, 18% kidney, 13% lung, 8% melanoma, 8% H & N, 5% breast, 5% other

NSCLC, non-small cell lung cancer; PTV, planning target volume; CRC, colorectal carcinoma; SCC, squamous cell carcinoma; RCC, renal cell carcinoma.

reported results with the use of a CyberKnife, whereas all other groups used a gantry operated linear accelerator.

The median follow-up period reported among the 13 institutions ranged between 8.2 and 44 months (median of 18.2 months follow-up). Local control varied widely from 67% crude to 96% at 2 years (Table 5). Weighted 2-year local control was 77.9%. Overall survival varied widely among institutions, reflecting variation patient characteristics rather than in treatment techniques. Weighted 2-year overall survival was 53.7% (range, 33–89%). Three institutions reported local control and overall survival results pooled with a similarly treated NSCLC cohort; these are noted below. Among the institutions reported, toxicity was very low. This is likely to reflect the retrospective nature of the majority of reports and incomplete toxicity recording. The weighted rate of grade 3 or greater toxicity was 2.6%. There was a grade 5 esophageal necrosis reported in one patient treated to

TABLE 4. Radiotherapy Treatment Delivery; Immobilization, Margin Determination, Motion Management, Fractionation, Treatment Delivery Time and, Beam Arrangement

Study Group	Motion Management	Fractionation	Treatment Delivery Time	Beam Arrangement
Lax, Blomgren	Standard planning CT, stereotactic body frame	21–66 Gy in 1–3 fx prescribed to 66% isodose	Not specified	4–8 coplanar beams 6 or 21 MV
Uematsu	Planning and pretreatment slow-CT + x-ray, abdominal compression	33/6/1 to 76/8/6 prescribed to the 80% isodose	Variable	Not specified
Nagata	Planning CT + x-ray, pretreatment orthogonal x-rays, stereotactic body frame ± abdominal compression	48 Gy in 4 fx, prescribed to isocenter	Over 5–13 d (median 12)	6–10 noncoplanar static or up to 7 arcs of 6 MV
Onimaru	Planning CT in three phases; kilovoltage imaging pretreatment	48 Gy/8 fx, $n = 22$ for central targets or >3.0 cm, 60 Gy/8 fx, $n = 10$ for peripheral targets prescribed to isocenter	8 fx delivered over 2 wk	4–12 static beams or 3–4 arcs
Wulf	Planning 4DCT, pretreatment CT, Stereotactic body frame	3 × 10 Gy $n = 12$, 3 × 12–12.5 Gy $n = 14$, prescribed to covering isodose	48–72 h fraction interval	5–9 static/arc fields
Song	Custom frame and stereotaxis with 6–7 infrared markers, pretreatment CT + orthogonal x-ray	median dose 35 Gy (27–45 Gy) maximum daily dose 15 Gy	3 consecutive days	4–8 coplanar beams or arcs
Yoon	Planning fluoroscopy + CT, pretreatment CT, stereotactic body frame ± abdominal compression	30 Gy/3 fx, 19.8% patients 40 Gy/4 fx, 44% patients 48 Gy/4 fx, 36.7% patients (sample pooled with NSCLC), 90% isodose covering PTV margin	Consecutive days	3–8 coplanar and noncoplanar beams (median 5)
Aoki	Planning fluoroscopy + CT simulation, thermo shell and headrest	54 Gy/9 fx prescribed to isocenter	15 d median (11–22 d)	4–6 10 MV noncoplanar beams
Milano, Okunieff	Respiratory gating with orthogonal kilovoltage x-rays. Vacuum immobilization	50 Gy/10 fx ($n = 31$), 48 Gy/6 fx to 57 Gy/3 fx ($n = 18$), 80% isodose covering PTV	<2 wk, preference for daily treatment	Not specified
Norihisa	Planning CT simulation, x-ray fluoroscopy, stereotactic body frame ± abdominal compression	48 Gy/4 fx ($n = 17$), 60 Gy/5 fx ($n = 16$) prescribed to isocenter	4–18 d, median 12	5–7 noncoplanar 6MV
Brown	X-ray and optical tracking of fiducials, stereotactic body frame or vacuum pillow ± abdominal compression	5 Gy-60 Gy delivered in 1–4 fx prescribed to 60–85% isodose line	Not specified	Up to 150 beamlets, typically 64 beamlets
Salazar	Planning fluoroscopy CT, stereotactic body frame ± abdominal compression	Median dose 40 Gy/4 fx	Once weekly, 4 wk	Median of 5 fields
Rusthoven	"Slow" planning CT, pretreatment CT, or external fiducials, vacuum bag or cradle immobilization, ± abdominal compression	60 Gy/3 fx, prescribed to covering isodose	Not specified	Dynamic arcs or multiple noncoplanar beams

CT, computed tomography; NSCLC, non-small cell lung cancer; 4DCT, 4-dimensional CT.

48 Gy/4 fx to a central target. The BED in 2 Gy fractions using an α/β ratio of 10 were reported 10 of 13 groups, and a BED in 2 Gy fractions using an α/β ratio of 20 was reported in one group.

DISCUSSION

The wide variety of treatment techniques and dose fractionation schemes reported in the literature indicates that there is, as yet, no consensus as to a standard approach for the stereotactic radiotherapy of pulmonary metastases. The existing literature indicates that high levels of local control are achievable, but in the absence of randomized trials, the effect on survival is unknown. In the stereotactic NSCLC experience, Onishi et al.[40] retrospectively analyzed 245 patients and found that a prescription of BED >100 Gy at the isocenter predicted for local control (8.1% local failures versus 26.4% in targets receiving BED <100 Gy [$p < 0.01$]). Wulf et al.[18] concluded that the tumor control probability of 50% occurred at a BED of 94 Gy at the isocenter, and 50 Gy at the PTV margin, with a steep increase at higher doses. He concluded that some fractionation schemes (such as 54 Gy in three fractions[41] used for NSCLC in RTOG-0236) have a BED >150 Gy at the isocenter and are biologically in the plateau beyond the 90% tumor control probability and supralethal. Among the institutions reviewed using single fraction radioablation, Fritz et al.[19] and Wulf et al. prescribed doses closest to approximating these figures. Together, a total of 56 targets were treated with a reported 2-year local control of 93%.

TABLE 5. Treatment Results: Follow Up, Outcomes, Toxicity, and BED

Study Group	F/U Period Median (Range)	Outcomes	Toxicity	BED at Isocenter	BED at Margin
Lax, Blomgren	Median 8.2 mo (3.5–25)	94% crude control. Crude o/s 46%, mean survival 11.3 mo, estimated 2-yr LC = 83%	Not reported	Median 183 Gy	Median 112.5 Gy
Uematsu	Median 11 mo (3–31)	97% LC at 11 mo (data pooled with NSCLC cohort). Estimated 2-yr LC = 93.6%	Not reported	Range, 144–188 Gy	Not reported
Nagata	Median 19 mo (pooled with NSCLC)	67% crude local control	Pooled with NSCLC: only mild grade 1. No grade 3 or 4	105.6 Gy	Not reported
Onimaru	Median 18 mo (2–44)	48% 2-yr o/s, 69.6% 3-yr pooled LC for 48 Gy (n = 39), 100% 3-yr pooled LC for 60 Gy (n = 19)	One grade 5 esophageal necrosis in one patient, one other grade 2 chest pain, nil else	48 Gy/8 = 76.8 Gy early 60 Gy/8 = 105 Gy early	Not reported
Wulf	3 × 10 Gy median 17 mo	71% 2-yr LC at 3 × 10 Gy	Overall pneumonitis 3%	3 × 10 Gy: BED = 117.2 Gy	3 × 10 Gy: BED = 60 Gy
	3 × 12.5 Gy median 13 mo	92% 2-yr LC at 3 × 12.5 Gy o/s for both groups; 1 yr = 85%, 2 yr = 33%		3 × 12–12.5 Gy: BED = 168.6	3 × 12–12.5 Gy: BED = 84.4 Gy
Song	Median 14 mo (9–49), mean F/U 22.6 mo	90% crude local control, estimated 2 yr LC 87%	29% grade 1–2 toxicities (4 of 14 patients), 8% hilar fibrosis + collapse (1 of 14 patients), nil grade 3 or 4	Not reported	Not reported
Yoon	Median 14 mo (4–46)	70% LC at 30 Gy/3 fx, 77% LC at 40 Gy/4 fx	No pulmonary toxicity >2 reported in all groups	Not reported	Overall mean = 58.6–118.8 Gy
	Median 10 mo for 48/4 group	100% LC at 48 Gy/4 all groups pooled 2-yr o/s = 51%		Not reported	Mean for 48 Gy/4 fx = 92.7–118.8 Gy
Aoki	Median 17.7 mo (9.4–39.5)	95% crude LC (pooled with NSCLC), o/s at 2 yr 89.5%, estimated 2-yr LC = 93%	Nil grade 3 or 4 toxicities	86.4 Gy	Not reported
Milano, Okunieff	Median 18.7 mo (3.7–60.9)	3-yr actuarial LC 91.0 ± 13.2%, crude LC = 94%, estimated 2-yr LC = 92%, 2-yr o/s 50%	3/49 (6%) grade 2, 1/49 (2%) grade 3 pericardial effusion	Not reported	Minimum 56 Gy at PTV margin
Norihisa	Median 27 mo (10–80)	2-yr LC 90%. 2-yr o/s 84%	1/34 grade 3 toxicity, 6% (2/34) musculoskeletal, grade 2 pneumonitis in 12% (4/34)	132 Gy	Not reported
Brown	Median 18 mo (2–41)	77% crude o/s. Estimated 2-yr o/s = 72.5%, LC not reported, 84% response rate	One patient with grade 4 pneumonitis	6–110 Gy using α/β ratio of 20	Variable
Salazar	Median 44 mo (2–84)	86% crude LC, median o/s = 19 mo, 3-yr o/s 29%	Pooled toxicity with NSCLC: 19% overall, 7% grade 2, no grade 3 or 4	119.6 Gy	Not reported
Rusthoven	Median 15.4 mo (6–48)	2-yr LC 96%, 2-yr o/s 39%	10.5% grade 2, 7.9% grade 3, zero grade 4	Not reported	180 Gy

BED, biological equivalent doses; NSCLC, non-small cell lung cancer.

The influence of tumor volume on local control remains unclear. There is no clear correlation between large tumors and propensity for treatment failure. However, there may be some relationship between fractionation of radiotherapy and increased probability of tumor control in larger tumors. On analysis of German radiosurgical and hypofractionated data, Hof et al.[20] postulated that "hypofractionated radiotherapy is superior to single dose therapy in larger tumor volumes, where the effects of reoxygenation and redistribution gain importance," with the proviso that "patient numbers are much too small to date to provide sufficient reliability on the issue."

It is difficult to compare overall survival data with the historical surgical series. Most patients that were reported in these publications were medically inoperable with multiple medical comorbidities and competing risks for survival. The four largest series of stereotactic fractionated radiotherapy (Min Yoon et al.,[30] Milano et al.,[32,34] Rusthoven et al.,[38] and Norihisa et al.[35]) prescribed BEDs >100 Gy at the isocenter and/or the periphery of the targets. A total of 311 targets among 175 patients were treated with an overall crude local control rate of 91%. The 2-year weighted overall survival was 54.5%. By comparison, the 2-year overall survival rate in the International Registry of Lung metastases for completely resected metastases was 70%.[35] These figures suggest that impressive longevity can occur in carefully selected patients with locally confined metastatic pulmonary disease.

Reported toxicities were minimal between the institutions. There was a 2.6% rate (4 of 154) of grade 3 or higher toxicities in the radioablative series, and a 4% rate (9 of 224) of grade 3 or higher toxicities in the radiotherapy series. There was a low rate of grade 1 and grade 2 toxicities reported, which may reflect incomplete reporting associated with the retrospective design of the majority of these studies. There was a patient death due to esophageal necrosis related directly to fractionated radiotherapy of a centrally located target. Timmerman et al.[21] have reported higher incidence of grades 3 to 5 toxicities when treating targets <2 cm distance from the mediastinal envelope and the lobar bronchi with a dose of 54 Gy in three fractions (heterogeneity corrected[41]). This concurs with the Stanford University CyberKnife[11] radioablative data reported here, where three of the eight patients suffering major toxicities had centrally located tumors. Chemotherapy may exacerbate toxicity; Le et al.[11] reported two deaths when gemcitabine chemotherapy was used shortly after stereotactic radiotherapy, suggesting a potential radiation recall reaction. Evidence suggests increasing tumor volume is associated with increased toxicity. McGarry et al.[42] reported increased incidence of grade 3 and above toxicities when treating target diameters of >5 cm in a phase I dose escalation study. In this review, most institutions have either excluded or reduced the dose to centrally located tumors, and excluded very large tumors. Unfortunately, there has been scant long-term toxicity data collected for stereotactic hypofractionated therapy in the lungs. Pulmonary fibrosis is a well-known late effect associated with larger doses per fraction. The lack of a reported link between the number of treated metastases and subsequent toxicity is counter intuitive and be reflective of the short reported follow-up. As stereotactic techniques and survival improve, we are likely to encounter increasing issues with late toxicities many months to years after initial therapy.

Difficulties in assessment of tumor response were not specifically addressed in the publications reviewed. Large doses per fraction used in SBRT may cause segmental atelectasis or focal fibrosis,[43] which can confound response assessment with conventional CT. There is scant data to address optimal tumor response assessment in stereotactic radiotherapy for oligometastatic disease. In the setting of SBRT for NSCLC, Timmerman et al.[21] reported that 17 of 70 patients had increased opacity on CT suspicious of recurrence. Despite this, only three of these 17 patients had biopsy confirmed recurrence. Similarly, Takeda et al.[44] reported 20 of 50 patients treated with pulmonary SBRT with radiologic findings suspicious for recurrence, subsequently confirmed in only three cases. The role of 18F-fluorodeoxyglucose positron emission tomography in response assessment is still unclear. Evidence is limited, but it may be that normal tissue inflammation may confound metabolic response assessment. Henderson et al.[45] reported that more than half of the 14 patients treated with pulmonary SBRT maintained a moderately elevated metabolic activity on 18F-fluorodeoxyglucose positron emission tomography scanning, despite no patient failing locally with a median follow-up of 42 months.

The importance of tumor localization and motion management in the delivery of hypofractionated radiotherapy is paramount. It appears that it is equally important to have onboard imaging capable of volumetric soft tissue definition, without the need for patient transfer to the treatment position. Recently, Guckenberger et al.[46] reported experience using pretreatment on-board CT with a stereotactic body frame. The discrepancy between actual versus planned tumor position was 7.7 ± 1.3 mm, with poor correlation between tumor position and bony landmarks. Pretreatment CT should ideally be complemented with four-dimensional CT scanning in the planning phase to determine maximal tumor excursion. By minimizing setup uncertainty, a highly conformal dose can be delivered.

No inferences can be made from this data about ideal beam arrangements, number of beams, or beam energies used.

Quality of life is an issue that issue that is yet to be addressed. As yet, there has been no data published in the hypofractionated treatment of lung oligometastases using internationally validated quality of life measurement tools. In its current form, stereotactic hypofractionated radiotherapy is still in its infancy as an experimental treatment for oligometastases of the lung. At this point, a recommendation cannot be made for a fractionation scheme, which suggests the need for further prospective investigations. The most promising results seem to be from prescribing a BED of >100 Gy at the isocenter and a BED approximating 100 Gy at the tumor periphery. Comparisons with surgical data are difficult in the absence of randomized phase II data comparing metastasectomy with stereotactic radiotherapy. Once, a more robust dataset is collated for any of the described techniques and fractionation schemes, perhaps stereotactic radiotherapy may be considered a noninvasive alternative to surgery for the treatment of oligometastatic pulmonary disease.

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