BJR

Received:
25 October 2014

Revised:
6 February 2015

Accepted:
12 February 2015

doi: 10.1259/bjr.20140712

Cite this article as:
Bhattacharya IS, Woolf DK, Hughes RJ, Shah N, Harrison M, Ostler PJ, et al. Stereotactic body radiotherapy (SBRT) in the management of extracranial oligometastatic (OM) disease. Br J Radiol 2015;88:20140712.

FULL PAPER

Stereotactic body radiotherapy (SBRT) in the management of extracranial oligometastatic (OM) disease

I S BHATTACHARYA, MRCP, D K WOOLF, FRCR, R J HUGHES, FRCR, N SHAH, FRCR, M HARRISON, FRCR, PhD, P J OSTLER, FRCR and P J HOSKIN, MD, FRCR

Cyberknife Unit, Mount Vernon Cancer Centre, Northwood, UK

Address correspondence to: Dr Indrani S Bhattacharya
E-mail: *indrani.bhattacharya@nhs.net*

Objective: A review of stereotactic body radiotherapy (SBRT) for oligometastases defined as three or fewer sites of isolated metastatic disease. The aim was to identify local control, overall survival (OS) and progression-free survival (PFS) of patients receiving SBRT for oligometastatic (OM) disease.
Methods: Data were analysed for SBRT delivered between 01 September 2010 and 31 March 2014. End points included local control, PFS, OS and toxicity.
Results: 76 patients received SBRT. The median age was 60 years (31–89 years). 44 were male. Median follow-up was 12.3 months (0.2–36.9 months). Major primary tumour sites included colorectal (38%), the breast (18%) and the prostate (12%). The treatment sites included lymph nodes (42%), the bone and spine (29%) and soft tissue (29%). 42% were previously treated with conventional radiotherapy. 45% were disease free after SBRT. 4% had local relapse, 45% had distant relapse, and 6% had local and distant relapse. Local control was 89%. The OS was 84.4% at 1 year and 63.2% at 2 years. PFS was 49.1% at 1 year and 26.2% at 2 years. Toxicities included duodenal ulcer and biliary stricture formation.
Conclusion: SBRT can achieve durable control of OM lesions and results in minimal radiation-induced morbidity.
Advances in knowledge: This cohort is one of the largest reported to date and contributes to the field of SBRT in oligometastases that is emerging as an important research area. It is the only study reported from the UK and uses a uniform technique throughout. The efficacy and low toxicity with durable control of local disease with this approach is shown, setting the foundations for future randomized studies.

Stereotactic body radiotherapy (SBRT) allows us to deliver ablative doses of radiation to extracranial sites, and this treatment modality can be considered in the setting of oligometastatic (OM) disease. Traditionally, systemic agents have been the mainstay of the management of metastatic disease, however, we have entered an era where in certain settings long-term local control or cure can be achieved. The idea of an OM state (defined as 1–3 isolated metastatic deposits) was first proposed in 1995 by Hellman and Weichselbaum[1] when they suggested that for many cancers, a few metastases exist at first, before the malignant cells acquire widespread metastatic potential. Following this, Niibe and Hayakawa[2] described the concept of oligorecurrence that whilst similar to oligometastases has control of the primary site of the malignancy allowing local therapies to achieve control of metastatic sites. Radical treatment of oligometastases and/or oligorecurrences may therefore achieve local control or cure in carefully selected cases. Local therapies including surgical resection, irradiation and radiofrequency ablation are radical treatment options to achieve this.[1,2] Local control rates of 80% have been achieved from several non-randomized studies of SBRT for oligometastases, and SBRT has been shown to be safe and effective.[3]

METHODS AND MATERIALS

Sequential patients selected for treatment of oligometastases with a maximum of three sites of disease were analysed. Patients were discussed within a specialist SBRT multidisciplinary meeting prior to acceptance onto this programme. All patients received positron emission tomography (PET) CT at 6 weeks prior to SBRT as screening for other sites of metastatic disease. Patient demographics, primary tumour site, site treated, radiotherapy (RT) details including technique and dose fractionation, relapse details and toxicity were recorded (as per common terminology criteria for adverse events v. 4)[4] and stored in an Infoflex database.

Radiotherapy technique

The CyberKnife® (Accuray Inc., Sunnyvale, CA) treatment system was used for all patients. This is an image-guided frameless system that directs a compact linear accelerator mounted on a robotic arm towards the tumour volume

with six degrees of freedom. Two orthogonal X-ray cameras are mounted on the ceiling, allowing for real-time tracking during the delivery of radiation.[5] Tracking was performed using spinal landmarks for treatments of the spine and lymph nodes in close proximity to the spine. Fiducial markers were used for tracking for all other treatment sites. Patients were immobilized using a vacuum bag prior to their CT planning scan, which acquired images using 1.0- to 1.5-mm thickness slices. During treatment, patient movement was monitored using the CyberKnife intra-fractional image guidance solution and relevant corrections applied.

Prescription dose

Treatment plans were generated on Multiplan (Accuray Inc.) using the Ray Tracing planning algorithm. Dose and fractionation were dependent on whether the patient had received previous external beam RT and normal tissue tolerances within the area to be treated. The dose was prescribed between the 70% and 80% isodose line, which encompassed 95% of the planning target volume (PTV). The prescribed doses ranged between 21 and 40 Gy in 3–10 fractions and were defined by the treating physician. The PTV was generated with a margin around the clinical target volume (CTV) ranging from 3 to 5 mm dependant on the method of tracking. Dose constraints of 21.9 Gy/3 fractions and 30 Gy/5 fractions were set as the maximum allowable dose to the spinal cord contour. Dose constraints to the spinal cord and other organs at risk (OARs) were based on data from the available literature.[6] An inverse optimization process takes into account normal tissue constraints, CTV and PTV coverage. In cases of reirradiation, the first course RT plans were reviewed, and the same OAR constraints (as the available literature) were applied when the dose–volume histograms were reviewed in the composite plan. Normal tissue recovery was taken into account in selected cases.

Treatment delivery

SBRT treatment was delivered on consecutive days. Endocrine therapy that was initiated prior to SBRT treatment was continued throughout treatment. No concomitant chemotherapy or biological agents were used. There was no routine prescription of pre-medications.

Follow-up

All patients were seen for toxicity assessment during their treatment and at 3 weeks following completion of treatment. Patients who were referred from other centres had their follow-up at their referring institution. Repeat diagnostic CT (and MRI or PET CT in selected cases) was obtained at approximately 3 monthly intervals following completion of treatment. Local failure was defined as an increase in size by >20% in one or more lesions as per the Response Evaluation Criteria in Solid Tumours v. 1.1.[7] Date of local and distant progression, toxicity and death were recorded.

Statistical analysis

Statistical analysis was performed with SPSS® statistical software (released 2012, IBM SPSS Statistics for Windows v. 21.0; IBM Corporation, Armonk, NY). Overall survival (OS), progression-free survival (PFS) and time to local relapse was assessed using the Kaplan–Meier method.[8] The database was locked on 1 June 2014. The primary end points included local control, OS and PFS. The secondary end point was toxicity.

RESULTS

76 patients received SBRT. Patient characteristics are described in Table 1. Major primary tumour sites included colorectal, 29 (38.2%); the breast, 14 (18.4%); and the prostate, 9 (11.8%). Treatment sites included lymph nodes [para-aortic (PA) and pelvic], 32 (42.1%); bone and spine, 22 (28.9%); and soft tissue (including liver, abdominal and pre-sacral lesions) 22, (28.9%).

34 (44.7%) patients remained disease free after SBRT at last follow-up. 3 (3.9%) had local relapse only, 34 (44.7%) had distant relapse only and 5 (6.6%) had both local and distant relapse. Actual local control rate was 89%. Eight patients had local progression (Table 2). Median time to local relapse was 9.9 months (1.8–10.8 months). Median time to distant relapse was 6.9 months (0.8–37.2 months). OS was 84.4% at 1 year and 63.2% at 2 years. PFS was 49.1% at 1 year and 26.2% at 2 years. The local relapse-free survival at 12 months was 87.1% and at 24 months was 71.9%. In those patients with breast and prostate cancer who received concomitant endocrine therapy, there were 0/13 relapses compared with 8/63 relapses in those who were treated with SBRT alone.

The range of prescription doses and equivalent dose in 2 Gy per fraction (EQD_2) is shown in Table 3. There was no significant difference in PFS or OS in patients who received 1- to 3-fraction SBRT *vs* more than 3-fraction SBRT. The median EQD_2 of the dose fractionations used was 41.6. There was no significant difference in PFS or OS in patients who received a dose schedule dichotomized by the median EQD_2.

There was no significant difference in PFS or OS in patients when comparing primary tumour sites or comparing the site treated. 32 patients (42.1%) had received previous RT within the SBRT field. Those patients who had received previous RT in the SBRT field had a significantly worse PFS. The PFS in those patients who had not received previous external beam RT was 61.5% at 1 year and 29.8% at 2 years. PFS in those patients who had received previous external beam RT was 34.4% at 1 year and 15.3% at 2 years. This was statistically significant ($p = 0.017$), however, there was no difference in OS.

Significant toxicities included one patient with grade 2 diarrhoea following pelvic node SBRT, two patients with duodenal ulcer formation (one following PA node SBRT and one following liver SBRT) and one patient with a benign biliary stricture and obstructive jaundice secondary to liver SBRT.

DISCUSSION

OM disease represents limited metastatic spread that is potentially curable with local therapy. These data show an excellent local control rate and are comparable to that of published data with local control rates of 80% and 2- to 5-year PFS of approximately 20%.[3] If we are able to achieve local

Table 1. Patient and tumour/treatment characteristics

Characteristics	*n* (%)
Gender	
Male	44 (57.9)
Female	32 (42.1)
Age (years), median (range)	60 (31–89)
Metachronous OM	76 (100)
Synchronous OM	0 (0)
Treatment of local recurrence	12 (15.8)
Regional lymphadenopathy	14 (18.4)
Distant metastases	50 (65.8)
Concomitant endocrine treatment	13 (17.1)
Treatment site	
Lymph node[a]	32 (42.1)
Bone	9 (11.8)
Spine	13 (17.1)
Head + neck	6 (7.9)
Liver	5 (6.6)
Pre-sacral	6 (7.9)
Abdominal	5 (6.6)
Primary tumour site	
Colorectal/anal	29 (38.2)
Breast	14 (18.4)
Prostate	9 (11.8)
Head + neck	6 (7.9)
Urology (non-prostate)	
Bladder	1 (1.3)
Ureter	2 (2.6)
Renal	5 (6.6)
Testicular	1 (1.3)
Other	
Upper GI	2 (2.6)
Gynae	3 (3.9)
Lung	2 (2.6)
Melanoma	2 (2.6)

GI, gastrointestinal; OM, oligometastases.
[a]3 were abdominal lymphadenopathy (primary tumour site included 1 testicular and 2 colorectal), 16 were aortic lymphadenopathy (primary tumour site included 9 colorectal, 1 renal, 1 gynaecological, 1 breast, 2 prostate, 1 gallbladder and 1 melanoma), 2 were neck lymphadenopathy (primary tumour site included breast and lung) and 11 were pelvic lymphadenopathy (primary tumour site included 8 colorectal, 1 gynaecological and 2 prostate).

control in patients with OM disease, this may translate into improved OS if no other sites of distant metastases manifest. In this study, patients underwent careful screening for other sites of metastatic disease prior to SBRT treatment; however, 51% patients still went on to develop distant metastatic disease. This highlights the current limitations of screening modalities such as PET CT and emphasises the need for new predictive markers in this setting.

The data reported here suggests that primary tumour histology has no significant difference in outcome in contrast to other published data that suggests that those patients with OM disease from a primary breast cancer have better outcomes. For example, one prospective study of SBRT in oligometastases performed a subgroup analysis of their primary breast cancer cohort.[3,9] The other primary tumour types consisted mainly of colorectal and lung cancers. They reported a PFS of 2 years of 36% for patients with breast cancer *vs* 13% for those with non-breast cancers. OS at 6 years was 47% *vs* 9%, and local control rate was 87% in breast cancers *vs* 74% in non-breast primaries. This may suggest that improved control of metastasis could result in better PFS. In contrast, another study reported that colorectal cancer lung metastases had a significantly worse local control rate than lung metastases from other origins.[3,10] This conflicts with the earlier study that found no significant difference in outcomes between colorectal and other non-breast histology.[9] Clearly, the current data is inconsistent, perhaps, reflecting different selection criteria and relatively small subgroup analyses in the available literature at present including this study.

The site of oligometastases has been shown to influence outcome with metastases confined to one organ, in particular bone or thoracic lymph-node metastases, having improved survival in comparison with lung or liver metastases.[3,11] Adrenal metastases had a worse OS and PFS than other sites.[3,12] This may be related to the haematological mechanism of spread for adrenal metastases. Separating tumour histology and the metastatic site can be difficult as certain tumours tend to metastasise to specific sites, for example, prostate cancer to bone (but not commonly to

Table 2. Failure of local control

Primary tumour site	Stereotactic body radiotherapy treatment site	Previous irradiation
Gynaecological-uterine carcinosarcoma	PA node	No
H + N	Neck node	Yes
Lung	Spine	Yes
H + N	Nasopharynx	Yes
Melanoma	Spine	Yes
H + N	Skull base	Yes
Gynaecological-cervix	Pre-sacral mass	Yes
Colorectal/anal	PA node	No

H + N, head and neck; PA, para-aortic.

Table 3. Summary of stereotactic body radiotherapy (SBRT) dose per fractionations used

SBRT treatment site	SBRT dose/fractionation (patient number)	EQD_2 ($\alpha/\beta = 10$) median (range), Gy	EQD_2 ($\alpha/\beta = 3$) median (range), Gy
Lymph node, $n = 32$	24–36 Gy/3–5 fractions (21)	42.8 (35.8–50.0)	78 (52.8–108.0)
	24–33 Gy/3–5 fractions (11)[a]	38.0 (31.3–42.8)	64.8 (40–108)
Bone + spine, $n = 22$	21–33 Gy/3–4 fractions (14)	41.6 (29.8–50.0)	78 (42–108)
	19.5–40 Gy/3–5 fractions (8)[a]	39.4 (26.8–60.0)	71.4 (37.1–92.4)
Liver, $n = 5$	45 Gy/3 fractions (5)	93.8	162
Head and neck, $n = 6$	21–30 Gy/3–6 fractions (6)[a]	38.8 (29.8–48.0)	51 (40.0–64.8)
Abdominal/pre-sacral, $n = 11$	30–45 Gy/3 fractions (4)	43.0 (35.8–93.8)	100.2 (78–162)
	24–35 Gy/3–10 fractions (7)[a]	39.4 (36.0–50.0)	52.8 (45.5–78.0)

EQD_2, equivalent dose in 2 Gy per fraction.
$EQD_2 = n \times d[(d + \alpha/\beta)/(2 + \alpha/\beta)]$. Where d is dose per fraction and n is number of fractions.
[a]Cases of reirradiation where doses were reduced or fractionated to comply with dose constraints based on the available literature.[6]

visceral organs) and non-small-cell lung cancers to the adrenal glands (while prostate, breast and colorectal cancers rarely metastasise to the adrenals).[3] The ability to delivery ablative doses of radiation to specific sites must also be considered. When irradiating pelvic bone metastases, there are fewer OARs, in comparison with spinal metastases where dose constraints to the spinal cord must be adhered to. Despite this, the data here showed no significant difference in outcome based on SBRT treatment site.

There is no overall agreement on doses needed for ablative RT in the setting of oligometastases. One study found that number of fractions (3 *vs* 5 fractions) as well as dose per fraction (>11 *vs* <11 Gy per fraction) and a biologically equivalent dose (>100 *vs* <100 Gy) to be significant predictors of local control.[3,13] The modelling studies arising from this series predicted that at least 48 Gy/3 fractions is required to achieve >90% 2-year control. In support of this view, a dose of ≥48 Gy/3 fractions was also associated with improved local control in 41 patients with colorectal cancer metastases.[3,14] In a large retrospective analysis of a series of 141 patients with lung or liver metastases, a dose of ≥54 Gy/3 fractions was associated with a higher local control rate *vs* a dose of 36–53.9 Gy (89% *vs* 59%, respectively).[3,15] Similarly in renal cancer metastases, single doses ≥24 Gy were superior to single doses lower than this or a hypofractionated schedule.[3,16] In contrast to these data, the study reported here found no significant differences in OS or PFS with doses above the median EQD_2 *vs* below the median EQD_2 or when comparing a 3-fraction treatment *vs* more than 3-fraction treatment. However, those patients who had previous RT within the SBRT treatment site had a significantly worse PFS. This may be related to the persistence of radioresistant cells following initial external beam RT but may also be related to differences in the microenvironment and tumour vasculature after previous RT.

Limitations of our findings include the retrospective nature of the data and range of dose fractionation schedules used with a relatively short follow up. Relatively small patient numbers prevent meaningful subgroup statistical analysis, however, the overall cohort is one of the largest in the literature at present, and the results support the concept of radical treatment for oligometastases.

Randomized controlled evidence is required to support the use of SBRT in oligometastases. Stereotactic ablative radiation therapy for comprehensive treatment of oligometastatic tumours (SABR-COMET) is a multicentre randomized Phase II trial currently assessing the impact of a comprehensive OM SBRT treatment programme on OS and quality of life in patients with up to five metastatic lesions compared with patients who receive standard of care treatment alone.[17] The primary end point is OS, and secondary end points include quality of life, toxicity, PFS, lesion control rate and number of cycles of further chemotherapy and systemic therapy. SABR-COMET aims to accrue a total of 99 patients within 4 years.

The Network Radiotherapy Group Oncology Group are currently conducting a Phase I study of SBRT for the treatment of breast, lung or prostate oligometastases (defined as ≤4 metastases). Metastases that are not resected must be amenable to SBRT, and local/regional disease should be treated as per standard of care with no evidence of progression. The primary objective is to determine the recommended SBRT dose for each of the metastatic locations being treated given the individual and overlapping fields when multiple metastases are treated with SBRT in a national clinical trials network setting.[18]

SBRT can achieve durable control of OM lesions and is well tolerated resulting in minimal radiation-induced morbidity. There is a worse outcome in those who have received previous RT. However, it is distant failure that predominates in defining the outcome of those with OM disease, and appropriate patient screening and development of predictive biomarkers is a priority to optimize the use of SBRT in this setting.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; **13**: 8–10.
2. Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol* 2010; **40**: 107–11. doi: 10.1093/jjco/hyp167
3. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013; **14**: e28–37. doi: 10.1016/S1470-2045(12)70510-7
4. US Department of Health and Human Services. *Common terminology criteria for adverse events (CTCAE) version 4.0*. Published 28 May 2009 (v4.03: 14 June 2010).
5. Lo SS, Fakiris AJ, Chang EL, Mayr NA, Wang JZ, Papiez L, et al. Stereotactic body radiation therapy: a novel treatment modality. *Nat Rev Clin Oncol* 2010; **7**: 44–54. doi: 10.1038/nrclinonc.2009.188
6. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010; **37**: 4078–101.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47. doi: 10.1016/j.ejca.2008.10.026
8. Sedgwick P, Joekes K. Kaplan-Meier survival curves: interpretation and communication of risk. *BMJ* 2013; **347**: f7118.
9. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012; **83**: 878–86. doi: 10.1016/j.ijrobp.2011.08.036
10. Takeda A, Kunieda E, Ohashi T, Aoki Y, Koike N, Takeda T. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. *Radiother Oncol* 2011; **101**: 255–9. doi: 10.1016/j.radonc.2011.05.033
11. Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Am J Clin Oncol* 2010; **33**: 157–63. doi: 10.1097/COC.0b013e3181979238
12. Milano MT, Katz AW, Muhs AG, Philip A, Buchholz DJ, Schell MC, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer* 2008; **112**: 650–8.
13. Stinauer MA, Kavanagh BD, Schefter TE, Gonzalez R, Flaig T, Lewis K, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. *Radiat Oncol* 2011; **6**: 34. doi: 10.1186/1748-717X-6-34
14. Bae SH, Kim MS, Cho CK, Kang JK, Kang HJ, Kim YH, et al. High dose stereotactic body radiotherapy using three fractions for colorectal oligometastases. *J Surg Oncol* 2012; **106**: 138–43. doi: 10.1002/jso.23058
15. McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravdahl D, Kavanagh B. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2009; **73**: 112–18. doi: 10.1016/j.ijrobp.2008.03.062
16. Zelefsky MJ, Greco C, Motzer R, Magsanoc JM, Pei X, Lovelock M, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1744–8. doi: 10.1016/j.ijrobp.2011.02.040
17. Palma DA, Haasbeek CJ, Rodrigues GB, Dahele M, Lock M, Yaremko B, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. *BMC Cancer* 2012; **12**: 305. doi: 10.1186/1471-2407-12-305
18. Radiation Therapy Oncology Group. NRG-alios protocol information. Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1311