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Original article

Comparison of survival and prognostic factors in patients treated with stereotactic body radiotherapy for oligometastases or oligoprogression

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ABSTRACT

Background and purpose: Clinical challenges arise in the oligoprogressive (OP) state with little evidence to support the use of ablative strategies. Our aim is to report on outcomes and prognostic variables following stereotactic body radiotherapy (SBRT) for OP and oligometastases (OM).

Material and methods: Overall (OS) and progression-free survivals (PFS) were calculated for 163 patients for 209 lesions (106 OM and 57 OP) treated with SBRT over 9 years. OS and PFS comparisons were calculated using the Kaplan–Meier actuarial survival and log rank methods. Uni, multi-variate analyses and cumulative incidences of local failure were performed using the Cox modelling and Gray's test respectively.

Results: The median OS and PFS was 37 and 15 months versus 21.7 and 6.4 months in the OM and OP groups respectively ($P = 0.02$ and $P = 0.01$). Performance status ($\geqslant 2$ HR 2.95) and number of metastases (1/2 vs $\geqslant 3$ HR 1.88) were independent prognosticators for survival. The 1/2-year PFS were 55%/25% versus 22%/6% in the OM and OP cohorts. Patterns of first relapse were four times higher outside the irradiated field and OP status ($p = 0.03$), $\geqslant 3$ metastasis ($p = 0.002$) and concurrent systemic therapy ($p = 0.001$) conferred a greater risk. Time to second-line treatment was 20 vs 11 months in the OM and OP groups ($P = 0.001$).

Conclusion: Survival and distant relapse following SBRT to OM/OP is determined by the extent of metastatic disease and performance status. Future research should address the benefit of integrating SBRT with systemic therapies to allow deferral or continuation of therapeutic agents.

Systemic therapies remain the mainstay of treatment for the majority of patients in the metastatic setting. The role of local therapies was suggested by Hellman and Weichselbaum who introduced the concept of *oligometastases* (OM), a hypothetical intermediate state between localised and widespread metastatic disease [1,2]. Their hypothesis suggested that treating low volume metastatic disease with ablative strategies could potentially cure or delay disease progression in certain subsets of patients. The precise definition of OM remains debated but usually refers to the presence of no more than 5 metastatic lesions [3]. Surgical series have supported this theory demonstrating superior survival outcomes following surgical resection of metastases compared to historical controls [4–9].

Stereotactic body radiotherapy (SBRT) and advances in image guidance have allowed for ablative doses to be delivered to target volumes whilst steep dose gradients allow relative sparing of normal tissues [10]. SBRT is now frequently used in the treatment of OM with many retrospective series supporting this as a safe and effective treatment modality [11–13]. Local 2 year control rates of 70–90% have been reported in the lung, liver and spine and the proportion of patients experiencing grade 3 acute or late adverse events is less than 10% [14–19].

In parallel, a greater understanding of tumour sequencing and driving mutations has led to an exponential rise in the use of targeted and immunotherapies. Clinical challenges arise when a few lesions progress on a background of widespread but stable metastatic disease, a so called *oligoprogressive* state [20]. It is sometimes unclear whether continuing, stopping or switching lines of systemic treatment is the best approach for the individual in the palliative setting. Ablative strategies, such as SBRT, are being

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increasingly given to these sites of *oligoprogression* (OP) with very little evidence to support a therapeutic benefit.

There have been a few small retrospective studies investigating the value of treating OP with SBRT for single tumour sites and suggested favourable survival outcomes [21–25]. This is a retrospective series to review and compare prognostic factors and outcomes between those patients in the OM or OP settings.

Methods

Patient selection

Patients with extracranial metastatic disease, including all primary tumours, histologies and sites, treated with SBRT were included in our analysis. OM patients were defined as those with 5 or fewer lesions all of which were treated radically with ablative measures (these could include a combination of SBRT, surgery or radio-frequency ablation). OP patients were defined as those where only the progressing lesions were treated with SBRT which could include any number of lesions. Performance status was evaluated by the criteria of the World Health Organisation (WHO). In the presence of multiple lesions the largest treated lesion was measured for GTV volume and dimension. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [26]. Concurrent systemic therapies were defined as either targeted, hormone, immuno or chemotherapies taken within a month before or after but not during SBRT. Synchronous local treatments were defined as those patients who received ablative therapies (including surgery, radiofrequency ablation (RFA) and/or SBRT) to separate oligometastatic lesions within two months of treatment. The multi-modality approach was chosen in those individuals where an ablative approach to all lesions could not be achieved safely by surgery, RFA or SBRT alone.

Stereotactic body radiotherapy techniques

Patient setup and immobilisation

All patients were treated according to departmental guidelines, the majority using LINAC-based SBRT and the remainder using Cyberknife when this unit was acquired in 2015. For LINAC-SBRT, patients were immobilised in an individualised vacuum cushion (Vacloc), respiratory motion was measured by a 4D CT scan and respiratory excursion minimised with abdominal compression. Internal target volumes (ITV) were created to account for observed motion and patients were treated in free breathing. Real-time tumour tracking was possible with the acquisition of a Cyberknife unit. Platinum fiducial markers were routinely used for liver SBRT patients to optimise image guidance when treated with LINAC-based SBRT and to permit tumour tracking when treating on the Cyberknife unit. LINAC-SBRT treatment planning was performed by Eclipse (Varian Medical Systems, Paolo Alto, CA) with intensity modulated radiotherapy (IMRT) using either multiple fixed coplanar beams shaped with multileaf collimators or more routinely, as of 2015, volumetric arc therapy (RapidArc).

Target volumes and dose

The gross tumour volume (GTV) was defined by diagnostic imaging and contoured on the 3 mm sliced CT simulation. For VMAT or IMRT treatment, an ITV accounting for tumour motion was defined by the 4D-CT. The planned target volume (PTV) for set-up uncertainty was defined by a symmetrical expansion of the ITV by 5 mm. The doses and fractionations varied with metastatic site and were as follows; lung 25–34 Gy × 1, 16 Gy × 3 or 8–10 Gy × 5 (BED_{10} 72–150 Gy), liver 6–10 Gy × 5 or 12 Gy × 4 (BED_{10} 48–106 Gy) bone 16–34 Gy × 1 or 6–7 Gy × 5(BED_{10} 42–150 Gy), adrenal 6–10 Gy × 5 (BED_{10} 48–100 Gy), lymph node 12 Gy × 6 or 6–10 Gy × 5 (BED_{10} 48–100 Gy). Departmental normal tissue constraints and dose prescription points were as per Radiation Therapy Oncology Group (RTOG)/NRG SBRT protocols as and published dose–volume constraint tables for hypofractionation [27]. As of 2015 all contours and treatment plans were reviewed at local Quality Assurance rounds.

Definitions and endpoints

Overall survival (OS) and Progression Free Survival (PFS), were defined per individual, from the date of first fraction of SBRT to death or disease relapse respectively. For those where an event was not reached the last date when the patient was confirmed still alive (in the case of OS) or had radiologically stable disease (in the case of PFS) was used for the survival time calculation. Disease relapse was defined as local or distant failure proven radiologically and/or pathologically. Local relapse (LR) was defined per lesion using RECIST 1.1 criteria (i.e. greater than 20% increase in dimensions pre- and post-treatment) and time to LR calculated from the date of first fraction of SBRT to the date of radiological imaging demonstrating LR [28]. For those patients without evidence of LR, the date of last radiologically stable disease was used. Time to second line treatment was defined per individual from the date of first fraction of SBRT to date of second line treatment (or follow up if not applicable). The metastatic disease-free interval was the time from initial diagnosis of the primary malignancy to the date when metastatic disease was first appreciated.

Statistical considerations

Paired *t* tests, rank sum and Fisher's tests were used for comparison of variables between the oligoprogressive and oligometastatic group with a p value of significance set at 5%. Overall and Progression Free Survival was calculated using the Kaplan–Meier actuarial survival methods, difference between survival was evaluated using log rank test. Only variables significantly associated with survival ($p < 0.05$ on log rank test) were considered for multivariate analysis and the final multivariate analysis used Cox modelling with stepwise selection of prognostic factors, keeping only variables predicting survival with a $p < 0.05$. Gray's test was used to compare cumulative incidences of local failure, distant relapse and death occurring at first event.

Results

A total of 163 patients with 209 lesions treated with SBRT between June 2007 and June 2016 were included; 106 patients in the OM and 57 in the OP groups (Table 1). The median follow-up was 34 months; OM median 38 months (0.3–90.9), OP median 24 months (1.6–69.7).

Similar characteristics were seen across both groups with regard to gender, performance status, primary histologies, GTV volumes, and biologically effective dose (BED). The OP group had a higher burden of disease with a greater proportion having more than 5 metastases (70% vs 0% $P < 0.001$), 3 or more organs involved (37% vs 4% $P < 0.0001$) and larger lesions, with those measuring greater than 50 mm (28% vs 13% $P = 0.03$). The OP group were younger (mean 59 vs 66 years $p = 0.0012$) with a greater proportion of those on concurrent systemic therapies (77% vs 9% $p < 0.0001$) receiving SBRT to liver lesions (35% vs 18% $p = 0.05$). The disease-free interval was significantly shorter in those with OP as opposed to OM disease (median 5.3 vs 21 months $p = 0.0013$).

The OM group demonstrated superior median survival rates than the OP group; 34 months (95%CI 23.3–58) compared to 22 months (95%CI 11.9–32.7, $p = 0.02$) respectively (Fig. 1 and Table 2).

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