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Treating brain metastases from breast cancer - outcomes after Stereotactic radiosurgery.

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Abbreviations:
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Abstract:

Introduction:

Stereotactic radiosurgery (SRS) is an alternative to surgery or whole brain radiotherapy for control of single or multiple brain metastases in patients with breast cancer. To date, there is no clear consensus on factors that might predict overall survival (OS) following SRS.

Methods:

Retrospective analysis of consecutive patients with breast cancer and brain metastases, considered suitable for SRS by the regional neuro-oncology multi-disciplinary team (MDT). All patients were treated at a single NHS centre.

Results:

91 patients received SRS between 2013 and 2017, of whom 15 (16.5%) were alive at the time of analysis. Median OS post SRS was 15.7 months (IQR 7.7 – 23.8months) with no significant effect of age on survival (67 patients ≤65yr, 16.3 months; 26 patients >65yr, 11.4 months, p=0.129). Primary tumour receptor status was an important determinant of outcome: 31 Oestrogen receptor positive (ER+)/Human epidermal growth factor receptor 2 (HER2) negative patients had a median OS of 13.8 months, 14 ER+/HER2+ patients had a median OS of 21.4 months, 30 ER-/HER2+ patients had a median OS of 20.4 months and 16 patients with triple negative breast cancer (TNBC) had a median OS of 8.5 months. A larger total volume of tumour treated (>10cm^3), but not the number of individual metastases treated, was associated with worse survival (p=0.0002) in this series. Patients with stable extra-cranial disease at the time of SRS had improved OS compared to those with progressive extra-cranial disease (30 patients stable extra-cranial disease OS=20.1 months v 33 patients progressive extra-cranial disease OS=11.4 months; p=0.0011). 17 patients had no extra-cranial disease at the time of SRS with a median OS of 13.1 months.

Conclusions:

This single centre series of consecutive patients with brain metastases from breast cancer, treated with SRS, had a similar OS compared to previous studies of SRS. TNBC and

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ER+/HER2- histology, metastatic volumes >10cm^3 and progressive extra-cranial disease at time of SRS are associated with worse survival.

Keywords:

Stereotactic radiosurgery; Breast cancer; Brain metastases; Survival; Factors influencing survival; Intra-cranial disease

Introduction:

Breast cancer is commonly associated with the development of brain metastases (BM) with historical post-mortem studies suggesting BM may occur in up to 30% of patients [1, 2]. Survival is typically poor with one study reporting a median survival of 16 months after developing BM in patients treated with surgery and whole brain radiotherapy [3]. There are many factors that may influence both the incidence of BM and survival after developing BM including tumour receptor status. A series of 488 patients found those with human epidermal growth factor receptor 2 positive (HER2+) or triple negative (TNBC) breast cancer had an increased risk of developing BM. After diagnosis of BM, there was a significant difference in the median overall survival (OS) of patients according to receptor subtypes; 7.4 months for oestrogen receptor positive (ER+)/HER2- patients, 19.2 months for ER+/HER2+ patients, 7 months for ER-/HER2+ patients and 4.9 months for TNBC patients, with treatment including whole brain radiotherapy (WBRT), surgery or stereotactic radiosurgery (SRS) [4].

Traditionally, treatment for BM has been surgery or WBRT with both modalities associated with significant acute and chronic complications. In a meta-analysis of 742 patients treated for BM with surgery followed by WBRT, neurocognitive impairment was seen in 12-28% of patients [5]. More targeted treatment with SRS is associated with reduced levels of cognitive

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decline compared to WBRT (63.5% of patients v 91.7% of patients at 3 months respectively) and improved quality of life [6]. In a meta-analysis of 364 patients, SRS alone had a better pooled OS compared to WBRT but this was only statistically significant in patients less than 50 years old [7]. With improvements in systemic therapies for metastatic breast cancer, longer survival and reducing the risk of toxicity from treatment of BM is increasingly important [8].

Despite the apparent benefit of SRS there is a paucity of evidence examining patient criteria that might influence survival post treatment. The aim of this study was to assess the overall survival of breast cancer patients with BM treated with SRS at a single centre and to examine factors that might influence survival to help inform future research and clinical practice.

Methods:

Retrospective data was collected on consecutive breast cancer patients who received SRS for BM between November 2013 and August 2017 in a single tertiary NHS oncology centre in Bristol, UK. Data was censored on 1/5/19. Patient records were accessed to collect demographic and clinical information. All patients were recommended treatment following central discussion by the regional neuro-oncology MDT and review with a clinical oncologist.

For each patient, their date of diagnosis, receptor status and initial staging, split into local only, nodal or metastatic disease was collected. The date of BM diagnosis and extra-cranial disease status was accessed from The InSight PACS Medical Imaging system (Insignia medical systems, Basingstoke, UK). SRS treatment plans were reviewed for number and volume of

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metastases. The intra and extra-cranial disease status at time of death or last clinical review, as well as current patient status was obtained from patient records and imaging. Regional neuro-oncology MDT outcomes were reviewed to corroborate patient and treatment data. The number of lines and setting of systemic treatments given both before and after SRS treatment was collected where available.

Gamma knife radiosurgery was delivered using the Leksell Gamma Knife Icon with its inbuilt high-definition motion management system. Patients were immobilised with fixed frames. SRS treatment was planned from gadolinium contrasted T1 and T2 weighted MRI imaging, performed from the base ring to the vertex at 1-1.5mm slice thickness. Any discrepancy or distortion on the MRI images was checked via CT imaging for co-registration. The planned treatment volume was defined as the gross tumour volume on MRI imaging. Dose was prescribed according to tumour diameter: <2cm = 24 Gray (Gy), 2-3cm 22Gy, 3-4cm 20Gy. In single metastases where patients had not received whole brain therapy, doses were increased by 2Gy. 192 cobalt-60 sources delivered multiple narrow low energy beams of radiation. Patient motion was detected on any movement of >0.5mm and an automatic stop was inserted at 1.5mm and with consistent movements of >0.7mm a second stereotactic cone beam CT was used to reset the treatment plan [9].

Univariate statistical analysis was undertaken on survival data, using Mann-Whitney U tests to look for significance between groups using GraphPad Prism (v 8.0). Kaplan-Meier survival curves were generated to compare different groups; significance was checked with log-rank analysis of these curves. Results were deemed statistically significant if $p=<0.05$.

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Results:

91 patients with a median age of 57 years (range 23-78) received SRS, of whom 15 patients (16.5%) were alive at the date of analysis. Median OS for all patients was 15.7 months from time of SRS. The tumour receptor status was: ER+/HER2- 31 patients (33.3%), ER+/HER2+ 14 patients (15.1%), ER-/HER2+ 30 patients (32.2%), Triple negative 16 patients (17.2%), Unknown 2 patients (2.2%). 70/87 patients had extra-cranial disease at the time of SRS, in 7 of these patients the status of the extra-cranial disease was unknown, extra-cranial disease status was not known in 4 patients. Patients had a median of 2 brain metastases treated (Interquartile range (IQR) 1-4) and a median volume of 3.8cm^3 treated (IQR 1.0cm^3-8.2cm^3). Patient characteristics are summarised in Tables 1 and 2. Complete systemic treatment histories were available for 60/91 (65.9%) patients (Table 1). The majority of patients (62%) received at least one line of chemotherapy in the metastatic setting prior to SRS treatment. 38 patients received chemotherapy after SRS treatment, with most (76.3%) receiving one line, 18.4% of patients received two lines and 5.3% of patients received 3 lines.

Receptor profile:

There was a difference in the median time to the development of BM based on the primary tumour receptor profile: ER+/HER2- 79.3 months, ER+/HER2+ 68.6 months, ER-/HER2+ 39.3 months and TNBC 23.8 months. This reached statistical significance comparing TNBC and ER+/HER2- (p=0.036) and TNBC and ER+/HER2+ (p=0.045) (Table 3). The median OS following SRS was ER+/HER2- 13.8 months, ER+/HER2+ 21.4 months, ER-/HER2+ 20.4 months and TNBC 8.5 months. Patients with TNBC had a worse prognosis compared to all other subgroups (TNBC v ER+/HER2- p=0.025, TNBC v ER+/HER2+ p=0.0011, TNBC v

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ER-/HER2+ p=<0.001). ER+/HER2- pts had a poorer survival than ER+/HER2+ p=0.0499 and ER-/HER2+ p=<0.0242. (Table 3 and Figure 1).

Control of extra-cranial disease and age at the time of SRS:

At the time of SRS, 17 patients were known to have no extracranial disease (Median OS 13.1 months). When present, stable extracranial disease (stable disease or partial response on latest imaging) was associated with a significantly improved OS (33 pts stable extracranial disease OS=20.1 months, 30 patients progressive extracranial disease OS=11.4 months; p=0.0011) (Table 4 and Figure 2). 66 patients were under 65 with a median OS 16.3 months whereas 25 patients were over 65 with a median OS 11.4 months) (p=0.129) (Table 4).

Overall survival by number of lesions treated and volume of treatment:

During SRS, 39 patients had 1 lesion treated (OS 18.1 months), 33 patients 2-5 lesions treated (OS 10.1 months), 19 patients ≥6 lesions (OS 18.3 months) with no significant difference in OS between any category (Table 4). In contrast, the total volume of disease treated affected overall survival; tumours totalling <1cm^3 24 patients with median OS of 22.6 months, 1.1-5cm^3 29 patients OS of 16.3 months, 5.1-10cm^3 23 patients OS of 15.7 months and >10.1cm^3 15 patients OS of 9.2 months. A total volume >10cm^3 had a significant adverse effect on OS compared to all other categories (<1cm^3 p=<0.0001, 1.1-5cm^3 p= 0.0015 and 5.1-10cm^3 p=0.0023) (Table 4, Figure 3).

For 57/76 patients who had died at the time of analysis the disease status was known. 38.6% had progressive extra-cranial disease only, 26.3% had progressive intra-cranial disease only,

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26.3% had both progressive intra and extra-cranial disease and 8.8% died without known breast cancer progression.

Discussion:

This single centre retrospective series, reporting the outcome from treating brain metastases from breast cancer with SRS in a large tertiary referral centre in the UK found a median overall survival of 15.7 months which is consistent with other published retrospective studies [10-23].

Previous publications have considered multiple factors that might predict overall survival, including patient age at time of SRS, Karnofsky Performance Score, tumour receptor profile and the volume and number of brain metastases treated. The results of these studies are summarised in Table 5 [10-23]. Most have shown that TNBC has a lower OS compared to other receptor subtypes, however, the link between the total number and/or volume of brain metastases and overall survival following SRS is less clear. NHS England recommends that SRS should only be given with multidisciplinary team approval, a Karnofsky Performance Score >70, a maximum disease volume of $20cm^3$ and a predicted life expectancy of at least 6 months [24]. This is line with the American Society for Radiation Oncology guidelines which recommends use of SRS for single lesions <3cm in diameter in patients with a good prognosis [25].

Results from our series are consistent with a previous study of 2441 patients which suggested that ER+ patients develop BM later in their disease course with a median time to development of BM of 63.5 months compared to 30 months (HER2+) and 22 months (TNBC) [26]. Our

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study suggests not just ER+HER2- (79.3 months) but also ER+/HER2+ (68.6 months) develop BM later in their disease course. HER2+ patients will have received anti-HER2 therapies, often in both the (neo)adjuvant and metastatic setting which may have modified the time frame for development of BM. The longer time period to development of BM in ER+ breast cancers may be secondary to a more indolent disease course as well as the efficacy of anti-oestrogen therapies as shown in a meta-analysis of 62923 ER+ breast cancer patients where recurrent disease occurred at a steady rate between 5 and 20 years following 5 years of adjuvant endocrine therapy [27].

Compared to publications that have reported OS following the development of BM by receptor subtypes, where patients were mostly treated with WBRT, our study showed better OS across all receptor subtypes [10, 28, 29]. The improvement in OS is likely a result of careful patient selection, increased experience with SRS planning and implementation, improved systemic therapies and an increasing tendency to perform early scans allowing patients to be treated with smaller cerebral metastatic volume.

Patients with metastatic volumes totalling $<1cm^3$ had a median OS of 22.6 months, falling to 9.2 months for those with $>10.1cm^3$ treated. Although life expectancy for all groups was greater than six months as per NHS guidance, the reduced survival of patients with tumour volumes $>10cm^3$ may be due to higher rates of local recurrence seen after SRS alone (Meta-analysis of 364 patients treated for 1 to 4 brain metastases showed local recurrence rates of; 27% in patients treated with SRS alone v 12% in patients treated with both SRS and WBRT [8]) and perhaps in this subset of patients additional WBRT should be considered.

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Whilst the age of patients treated did not affect survival in our series, the presence and control of extra-cranial disease both at time of SRS and during follow up was important. Surprisingly, patients with disease limited to the brain did not have better survival than patients with controlled extra-cranial disease (13.1mths v 20.1mths). However, there was a higher percentage of TNBC patients (35.3%) in this cohort perhaps suggesting a propensity for TNBC to first metastasise to the brain compared to other receptor subtypes with further research needed to evaluate whether earlier systemic treatment could improve survival.. For patients with HER2+ breast cancer with intracranial disease as the only site of metastases the recently updated ESMO advanced breast cancer guidelines do not currently recommend the addition of chemotherapy to SRS [30]. Of the patients with extra-cranial disease at the time of SRS, those with controlled extra-cranial disease had significantly better OS than patients who had progressive disease both intra and extra-cranially. This supports ESMO and NICE guidelines which recommend systemic therapy should not be altered post-SRS in HER2+ patients with stable extra-cranial disease [30, 31]. Although patients with progressive systemic disease at the time of SRS had worse outcomes, the median OS for these patients is still 11.4 months and therefore this series suggests that in selected patients this should not be used in isolation as a reason to omit SRS. Patient numbers were too few to accurately assess the effect of chemotherapy after SRS.

Whilst results from this series must be interpreted with caution this study adds to the limited published literature on SRS for brain metastases secondary to breast cancer and highlights the improved OS in this patient cohort. The factors identified that predict survival can be used to help inform both patient selection and discussions between clinicians and patients about the potential benefits and risks of SRS. Future prospective, multi-centre studies with greater patient

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numbers, assessment of SRS technique, assessment of systemic anti-cancer therapy post-SRS and potential randomisation for patients with brain only disease between starting systemic therapy and SRS versus SRS alone should be designed to help in the development of more accurate guidelines for use of SRS in breast cancer.

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