Clinical Neurology and Neurosurgery 141 (2016) 43–47

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Gamma Knife Radiosurgery in the management of single and multiple brain metastases

D. Greto[a,*], S. Scoccianti[a], A. Compagnucci[b], C. Arilli[b], M. Casati[b], G. Francolini[a], S. Cecchini[a], M. Loi[a], I. Desideri[a], L. Bordi[c], P. Bono[c], P. Bonomo[a], I. Meattini[a], B. Detti[a], L. Livi[a]

[a] Radiotherapy Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy
[b] Medical Physics Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy
[c] Neurological Surgery Unit, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

ARTICLE INFO

Article history:
Received 8 October 2015
Accepted 14 December 2015
Available online 18 December 2015

Key words:
Radiosurgery
GammaKnife
Brain metastases

ABSTRACT

Objectives: To evaluate the efficacy and safety of Gamma Knife Radiosurgery (GKRS) in the treatment of single and multiple brain metastases.
Patients and methods: From October 2012 to June 2014 106 patients were treated with Radiosurgery (RS) for brain metastases at University of Florence. 77 out of 106 patients had a radiological follow up and their data were analyzed. The target was defined as the enhancing lesion. The prescription dose was defined depending on tumor volume and tumor location. Each patient performed an MRI one month after GKRS for the first three months and every 3 months thereafter. Overall survival was calculated from the day of RS until death. Local recurrence (LR) was defined as radiologic growth of the irradiated lesion, while distant brain recurrence (DBR) was the evidence of brain lesion outside the previous irradiated field. Both the LR and DBR were calculated from the RS till the day of radiological evidence of relapse. The correlations within patient and disease characteristics and the outcomes of survival and disease control were analyzed.
Results: Mean follow up was 7.2 ± 4.8 months (range: 2.4–22.8 months). At the time of analysis 21 patients (27.3%) were dead. The overall survival (OS) at 1 year was 74%. On univariate Cox Regression analysis female gender ($p = 0.043$, HR: 0.391, 95% CI: 0.157–0.972) and age >65 years ($p = 0.003$ HR: 4.623, 95% CI: 1.687–12.663) were predictive for survival. On multivariate analysis, age older than 65 years ($p = 0.005$HR: 4.254, 95% CI: 1.544–11.721) was confirmed as associated with worsened overall survival. 19 patients (24.7%) had recurrence in the radiosurgery field. The median time to local failure was 4.8 ± 2.0 months (range: 1.8–9.4 months) from GKRS. On Cox Regression univariate analysis, the only factor associated with higher risk of local failure was a number of treated lesions more than 4 ($p = 0.015$, HR: 3.813, 95% CI: 1.298–11.202), no significant parameters were found at the multivariate analysis. The median time to develop distant brain failure was 6 ± 4.32 months (range: 1.08–21.6 months). Median distant brain control was 74% at 1 year. None of the factors analyzed was statistically significant for the distant brain relapse. The radiosurgery treatment was well tolerated. One patient treated for seven metastases developed seizures 8 h after GKRS, he was treated with steroids and anticonvulsants. One patient had radiologic evidence of radionecrosis without any neurological symptoms.
Conclusions: In well-performing patients with stable systemic disease radiosurgery can be performed as an exclusive treatment for brain metastases. Younger patients could have a greater benefit from the RS, on the other hand our finding confirm no correlation between the survival outcome and the number of lesions treated.

1. Introduction

Most common intracranial neoplasms are represented by metastatic brain tumors (MBTs), with a reported incidence of 200,000 new cases each year in the USA [1].

* Corresponding author at: Largo Brambilla 3, 50141, Florence, Italy. Fax: +39 0557947330.
E-mail address: daniela.greto@gmail.com (D. Greto).

http://dx.doi.org/10.1016/j.clineuro.2015.12.009
0303-8467/

MBTs occur in 30% of patients with cancer [2] and, without an active treatment, median survival is 1–2 months [3].

Treatment of MBTs has conventionally been based on surgical resection (S) and Whole brain radiotherapy (WBRT) [4,5]; recently, Radiosurgery (RS) emerged as a promising treatment option [6].

The number, size, and the site of brain lesions influence clinician's choice to use S or stereotactic radiosurgey (RS) as a local treatment for MBTs, without any evidence of superiority of a local treatment over the other one in combination with WBRT [7].

Stereotactic radiosurgery (RS) can be used as a boost to WBRT, increasing LC (LC) [8,9], or even alone, in selected cases [5–12].

We retrospectively present our single institutional experience with Gamma Knife Radiosurgery (GKRS) in a population of patients with both single and multiple brain metastases.

2. Patient and methods

We retrospectively collected data of 106 patients treated with Gamma Knife Radiosurgery for brain metastases since october 2012 to june 2014 at University of Florence. 29 patients were lost during the follow up and were excluded from the current analysis.

An assessment of the primary tumor and a restaging radiological examination was performed before radiosurgery procedure with a CT and/or a PET scan depending on clinical choice. Only patients with controlled primary tumor and stable extracranial disease underwent radiosurgery for brain metastases. Control of the primary tumor and extracranial disease was defined as remission or stable disease, without any clinical, laboratory, or radiological findings suggestive of primary tumor or extracranial disease progression, at 2 months before GKRS. Before GKRS all patients performed an MRI with contrast at least 30 days before treatment.

Radiosurgery was performed with a Gamma Knife Perfexion (Elekta, Inc., Stockholm, Sweden).

A Leksell stereotactic headframe was applied under local anesthesia. T1 MP-RAGE sequences with double-dose gadolinium-based contrast acquired at 1 mm slices were used for the stereotactic MRI. At the Gamma Plan software the target was defined as the enhancing lesion. The tumor volume was obtained to decide the prescribed dose, these dose selection criteria were mainly based on RTOG 9508 criteria [9], if more than one lesion was treated the sum of the single lesion volume was also considered such as the volume of healthy brain that receive more than 10 Gy and the dose to 50% of the brain <5.0 Gy [13].

Doses lower than 15 Gy were chosen in case of critical anatomical site such as brainstem.

For all plans the number of isocenters used, PTV coverage and Gradient Index (GI) were reported.

After treatment steroids were administered at the discretion of treating physician. Each patient performed an MRI one month after GKRS for the first three months and every 3 months thereafter.

Principal patients and disease features are summarized on Table 1.

Overall survival was calculated from the day of RS until death. Patterns of intracranial failure were evaluated in all patients with follow up MRI. Local recurrence (LR) was defined as radiologic growth of the irradiated lesion, while distant brain recurrence (DBR) was the evidence of brain lesion outside the previous irradiated field. Both the LR and DBR were calculated from the radiosurgery till the day of radiological evidence of relapse. The correlations within patient and disease characteristics and the outcomes of survival and disease control were analyzed.

2.1. Statistical analysis

Survival analyses were carried out in relation to specific events: death, local and distant recurrence. Time to events was measured from the date of RS to the date of the specific event.

Table 1
Baseline population features.

	n (%)
Sex	
Female	39 (50.65)
Male	38 (49.35)
Age	
≤65	41 (53.24)
>65	36 (46.75)
Histology	
Breast	12 (15.58)
NSCLC	34 (44.16)
Melanoma	8 (10.38)
Kidney	9 (11.68)
Colon	6 (7.79)
Others	7 (9.09)
Previous treatments	
Surgery	3 (3.90)
WBRT	8 (10.40)
RS other site	4 (5.19)
Surgery + WBRT	2 (2.59)
None	60 (77.92)

NSCLC, non small cell lung cancer; WBRT, whole brain radiotherapy; RS, radiosurgery.

Overall survival (OS) was calculated from the day of RS until death or last follow-up. Patients who died before experiencing a disease occurrence were considered censored at their dates of death. Patterns of intracranial failure were evaluated in the all patients with follow up MRI. Local recurrence (LR) was defined as radiologic growth of the irradiated lesion, while distant brain recurrence (DBR) was the evidence of brain lesion outside the previous irradiated field. Both the LR and DBR were calculated from the radiosurgery till the day of radiological evidence of relapse.

The correlations between patient and disease characteristics and the outcomes of survival and disease control were analyzed.

Events rates were calculated according to the Kaplan–Meier method. Differences between groups of patients were evaluated using the log-rank test.

Univariate Cox proportional regression model was used to obtain the hazard ratios (HRs) for specific event. A multivariate Cox proportional regression model was used to identify independent factors for specific event.

All two-sided *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS statistic software (IBM SPSS Statistics 22 version).

3. Results

Since october 2012 to june 2014, 106 patients with brain metastasis were treated with GKRS. Of all the 106 patients only 77 had a radiological MRI follow up and were considered for the current analysis.

The mean population age was 63.3 years (range: 25–87), about half of patients were males (38 out of 77). All patients had a KPS ≥ 70. The Radiation Therapy Oncology Group RPA (Recursive Partitioning Analysis) was I in 29 patients (37.7%) and II in 48 of the treated patients.

All patients received chemotherapy before treatment or during the subsequent follow-up. The total number of analyzed metastasis was 186, mean target volume was 0.39 cc (range: 0.006–1.86 cc). The mean number of treated lesions in each patient was 2 (range: 1–11).

The most frequent primary tumor was Non Small Cell lung Cancer (NSCLC) (44.16%), 12 patients had a breast tumor, 17 patients had radioresistant histologies, in particular 8 melanoma (10.4%) and 9 kidney cancers (11.7%). Six patients (7.8%) had colorectal