



Outcome and prognostic factors for older patients undergoing radiosurgery for brain metastases

Isacco Desideri^{a,*}, Carlotta Becherini^a, Luca Visani^a, Giulia Stocchi^a, Erika Scoccimarro^a, Matteo Mariotti^a, Viola Salvestrini^a, Silvia Scoccianti^a, Daniela Greto^a, Pierluigi Bonomo^a, Guido Pecchioli^b, Lorenzo Bordi^b, Alessandro Della Puppa^b, Giulio Francolini^a, Icro Meattini^a, Lorenzo Livi^a

^a Azienda Ospedaliero Universitaria Careggi, University of Florence, Radiation Oncology Unit, Florence, Italy

^b Azienda Ospedaliero Universitaria Careggi, University of Florence, Neurosurgery Unit, Florence, Italy

ARTICLE INFO

Article history:

Received 8 December 2019

Received in revised form 16 December 2019

Accepted 24 March 2020

Available online 4 April 2020

ABSTRACT

Purpose: Older patients with brain metastases (BM) are often excluded from clinical trials. The aim of our study was to investigate the outcomes following Gamma Knife radiosurgery (GKRS) in young old (65–74 years) and very old (≥ 75 years) patients with BM.

Methods: Between October 2012 and October 2018, we treated 89 patients aged ≥ 65 years with GKRS. Patients were divided in two groups: young old (YO) and very old (VO) patients. At baseline G8, Graded Prognostic Assessment (DS-GPA) and Basic Score for Brain Metastases (BSBM) were assessed for all patients. Survival analysis was estimated using the Kaplan-Meier (KM) method. Cox regression model was used to investigate the influence of significant factors on KM.

Results: Median age at the time of GKRS was 72.2 years (range 65–87). A mean of 2.52 lesions were treated per patient (range 1–14). Median overall survival (OS) for YO and VO patients was 14.2 and 15.7 months, respectively. At univariate analysis, there were no significant differences in OS between the two age groups. A high BSBM ($p \leq .0001$) and a high DS-GPA score ($p = .0069$) were associated with longer survival. A low DS-GPA score was the most powerful independent factor for predicting short survival (HR 1.76, 95% CI 1.25–2.46, $p = .001$) at multivariate analysis.

Conclusion: GKRS is a safe approach to treat BM in elderly patients. DS-GPA score represents an important prognostic factor for survival in elderly patients undergoing GKRS.

© 2020 Elsevier Ltd. All rights reserved.

1. Introduction

Brain metastases (BM) frequently occur in oncologic patients, and certain cancers such as lung cancer, breast cancer, melanoma, and renal cell carcinoma are associated with a higher risk. It is estimated that about 30% of patients with cancer overall will develop BM [1]. Additionally, improved cancer detection methods using more sensitive imaging modalities have increased the incidence rates of patients with BM [2,3]. Nowadays, multidisciplinary approaches are tailored for individual patients with BM. Currently available therapeutic options include surgical resection, whole-brain radiation therapy (WBRT) and stereotactic radiosurgery [4], that emerged in the last years as a valid treatment choice [5–8]. Older patients are often excluded from clinical studies exploring this setting since they are more likely to present

with multiple comorbidities, restricted physiologic reserve, and poor tolerance to certain therapies compared to younger patients. Several prognostic indices have been proposed in the past years taking into account patients' performance status (PS), primary tumour and extracranial disease control, and the total number of brain metastases [9–13]. Age has been historically considered a prognostic factor by a vast majority of these indices: RPA (recursive partitioning analysis classification based on the Radiation Therapy Oncology Group database) [9], SIR (score index for radiosurgery) [10], DS-GPA (Graded Prognostic Assessment) [11]. On the other hand, Basic Score for Brain Metastases (BSBM) and Diagnosis Specific-Graded Prognostic Assessment (DS-GPA) do not consider age as a reliable prognostic factor for BM patients [12,13].

The aim of this study was to evaluate the outcomes of either young old (65–74 years) and very old (≥ 75 years) patients who underwent Gamma Knife radiosurgery (GKRS) to determine the relevant survival factors in this population. Moreover, we aimed to assess the reliability of currently available prognostic indices in an older population undergoing GKRS and evaluate the utility of Geriatric 8 (G8) screening tool [14] in this subset of patients.

* Corresponding author at: Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero - Universitaria Careggi, University of Florence, Largo G. A. Brambilla 3, 50134 Florence, Italy.

E-mail address: isacco.desideri@unifi.it (I. Desideri).

2. Patients and Methods

2.1. Ethical Approval

This study was approved by our local ethical committee (Area Vasta Toscana Centro).

2.1.1. Patients' Characteristics

Between October 2012 and October 2018, we retrospectively analysed data from 89 patients aged 65 years and older treated with GKRS for BM at Radiation Oncology Department, University of Florence, Italy. Selected patients were divided in two groups: young old (65–74 years) and very old (≥ 75 years). At baseline G8, DS-GPA and BSBM were assessed for every patient.

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

An assessment of the primary tumour as well as a restaging radiological examination were performed before GKRS procedure with a computed tomography (CT) and/or a positron emission tomography (PET) scan, depending on clinical choice. GKRS for BM was preferentially administered to patients with a controlled primary tumour and a stable extracranial disease, defined as remission or stability, without any clinical, laboratory or radiological finding suggestive for progression at 2 months before GKRS. However, in some cases, for those patients with a good performance status, we considered radiosurgery as a valid treatment option even in the presence of a non-controlled primary tumour. Before GKRS, all patients performed a magnetic resonance imaging (MRI) with intravenous gadolinium-based contrast not later than 30 days before treatment.

2.1.2. Radiosurgical Treatment

A Leksell stereotactic headframe was applied under local anaesthesia. T1 MP-RAGE sequences with double-dose gadolinium-based contrast acquired at 1 mm slice thickness were used for the stereotactic MRI, performed in the same day of treatment. At the Gamma Plan software, the target was defined as the enhancing lesion. Tumour volume was taken into account to decide the prescribed dose, and dose selection criteria were mainly based on RTOG 9508 [15]: if more than one lesion was treated, the total volume was also considered as well as the volume of healthy brain receiving more than 10 Gy and the dose to 50% of the brain < 5.0 Gy [16].

2.1.3. Tumour Control and Follow Up

Time to events was measured from the date of GKRS to the date of death, local and distant recurrence. Overall survival (OS) was calculated from the day of radiosurgery to death or last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their dates of death. Local recurrence (LR) was defined as a radiologic growth of the irradiated lesion, while distant brain recurrence (DBR) was defined as the evidence of new brain lesions outside the previous irradiated field. Both the LR and DBR were calculated from the GKRS until the day of radiological evidence of relapse.

During follow up, MRI was performed every 3 months or at neurological symptoms onset and included continuous thin-cut T1-enhanced images as it was performed for GKRS. Leksell GammaPlan® software's co-registration method was utilized in order to compare follow up MRIs with planning MRI.

2.2. Statistical Analysis

The correlations between disease and patients' characteristics with survival and local control outcomes were analysed. Events rates were calculated according to the Kaplan–Meier method. The differences between groups were evaluated using the log-rank test. Univariate Cox proportional regression model was used to obtain the hazard ratios (HRs) for specific events. A multivariate Cox proportional regression

model was used to identify independent factors for specific events. All two-sided *p*-values lower than 0.05 were considered statistically significant. The statistical analysis was performed through the use of GraphPad PRISM statistical software v. 6.02 (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

3. Results

3.1. Patients' Data

From October 2012 to October 2018, 89 older patients underwent GKRS for a total number of 105 treatments and overall 264 treated lesions (average of 2.52 BM per patient, range of 1–14). The majority of patients were male ($n = 58$; 65.2%). Median age at the time of GKRS was 72.2 years (range 65–87 years). In particular, the 73.3% of patients were young old (YO) and the 26.7% very old (VO). Non-small cell lung cancer (NSCLC) was the most frequent primary tumour (63.8%), followed by renal carcinoma (10.5%). Overall mean follow-up was 9 months (range 3–63 months). Main patients' baseline characteristics are summarized in Table 1. In 53 cases only one lesion was treated, while in 16 cases more than 5 lesions were treated (Table 2). Eighteen patients had received a previous treatment for BM: 9 neurosurgical excision, 8 WBRT, 1 neurosurgery plus WBRT. At baseline, G8 score was ≥ 14 in the 66% of cases, DS-GPA was comprised between 1.5 and 2 for the 45% of patients and the mean BSBM was 2. In all cases radiosurgery was performed in single fraction. A mean overall dose of 22.1 Gy (range,

Table 1
Population's main characteristics.

Variables	Patients (%)	Treatments (%)
Gender		
M	58 (65.2%)	74 (70.5%)
F	31 (34.8%)	31 (29.5%)
Age		
YO	65 (73.0%)	77 (73.3%)
VO	24 (26.7%)	28 (26.7%)
Primary tumour		
NSCLC	56 (62.9%)	67 (63.8%)
RCC	10 (11.2%)	11 (10.5%)
Colorectal	6 (6.7%)	7 (6.7%)
Breast	5 (5.6%)	7 (6.7%)
Melanoma	7 (7.9%)	7 (6.7%)
Others	5 (5.6%)	6 (5.6%)
Previous Treatment		
No	71 (79.8%)	
Yes	18 (20.2%)	
Stable Primary Tumour		
No	23 (25.8%)	25 (23.8%)
Yes	66 (74.2%)	80 (76.2%)
Stable Extracranial Disease		
No	43 (48.3%)	58 (55.2%)
Yes	46 (51.7%)	47 (44.8%)
DS-GPA		
0–1	22 (24.7%)	24 (22.9%)
1.5–2	40 (45.0%)	42 (40%)
2.5–4	27 (30.3%)	39 (37.1%)
BSBM		
1	18 (20.2%)	20 (19%)
2	42 (47.2%)	50 (47.7%)
3	29 (32.6%)	35 (33.3%)
G8		
≥ 14	59 (66.3%)	69 (65.7%)
≤ 13	30 (33.7%)	36 (34.3%)
Corticosteroid Use		
No/Unknown	25 (28.1%)	39 (37.2%)
Before GK	40 (45.0%)	41 (39%)
After GK	24 (27.0%)	25 (23.8%)
Total	89	105

YO: Young Old, VO: Very Old, NSCLC: Non Small Cell Lung Cancer, RCC: Renal Cell Cancer, DS-GPA: diagnosis-specific graded prognostic assessment, BSBM: Basic Score for Brain Metastases, G8: Geriatric 8 assessment tool, GK: GammaKnife.

Table 2
GK treatments characteristics.

Number of GKRS treatments	Patients (%)
1	73 (82.0%)
2	14 (15.7%)
3	2 (2.3%)
Total	89
Number of irradiated lesions	Treatments (%)
1	53 (50.5%)
2	16 (15.2%)
3	10 (9.5%)
4	3 (2.9%)
5	7 (6.7%)
>5	16 (15.2%)
Total	105

GKRS: GammaKnife RadioSurgery.

18–24 Gy) was delivered with an average isodose of 58.4% (range 45–90%).

3.2. Survival Analysis

Median OS for YO and VO patients was 14.2 and 15.7 months, respectively (Fig. 1). At the time of analysis, 73 patients out of 89 had died: 67 due to extracranial disease progression, 2 to intracranial progression, 2 for myocardial infarction, 1 for stroke, 1 for gastric bleeding. Median progression free survival (PFS) for YO and VO was 8.3 and 7.8 months, respectively (Fig. 2). The mean local recurrence free survival (LRFS) was 7.3 months for young old patients and 18.7 for old patients (there were only 3 events in this group). The distant relapse free survival (DRFS) resulted in 7.7 months for YO patients and 6.4 months for VO patients. At univariate analysis, there were no statistical difference in OS and PFS between the two age groups. Local disease progression occurred for 16 treated lesions on 264 (6.0%), distant intracranial relapse was documented for 38 patients (42.7%). A high BSBM (score ≥ 3 ; $p \leq .0001$) and a high DS-GPA (score ≥ 2.5 ; $p = .0069$) were significantly associated with a longer survival (Figs. 3 and 4 and Table 3). At multivariate analysis, a low DS-GPA score was the most powerful independent factor predicting short survival (HR 1.756, 95% CI 1.252–2.456, $p = .001$). Moreover, on multivariate analysis, a controlled primary tumour ($p < .001$, HR 0.328, 95% CI 0.180–0.596) was a significantly favorable prognostic factor (Table 3). G8 score was not a valid prognostic tool for this population, since there were no differences in OS between patients with $G8 \geq 14$ and $G8 \leq 13$ (Fig. 5).

4. Discussion

The increase in life expectancy among industrialized countries makes the study on the impact that newly advanced technologies, such as radiosurgery, may have on older populations extremely crucial.

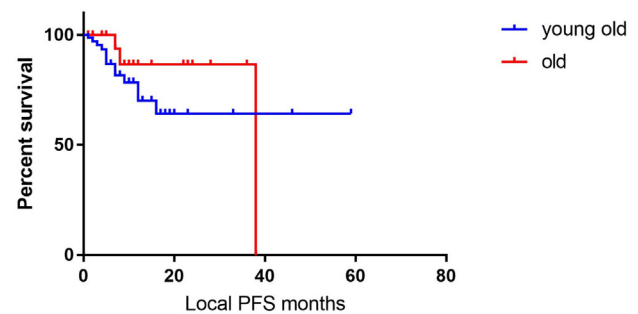


Fig. 2. Kaplan-Meier showing PFS for YO and VO patients.

As a matter of fact, older patients are rarely represented in clinical studies, thus leaving to the Oncologist the hard decision of which is the most appropriate treatment strategy for the above-mentioned group of population. This decision is even more complex in older patients with brain metastases. For many years, WBRT (Whole Brain RadioTherapy) has represented the main non-surgical therapeutic approach to this clinical condition, regardless of the patient's age. In recent years, we have been paying our attention on WBRT long-term effects; the survival of oncological patients affected by solid tumour in advanced metastatic stage has hugely improved lately thanks to the progress in systemic therapy indeed. The main purpose of our investigation was to analyse the upfront radiosurgery impact on older population (aged ≥ 65 , according to the WHO definition). We also aimed at examining the role of the most commonly adopted scores in the neuro-oncological setting (BSBM, DS-GPA), as well as the potential role of a geriatric evaluation carried out through G8 scale. Selected older patients were also divided into two groups ("young old" and "very old") in order to highlight differences in terms of survival. There were no statistically significant differences between the two age groups, as the results showed. A high score index for BSBM and a high DS-GPA were associated with longer survival, instead. DS-GPA score's great impact was confirmed also at multivariate analysis, as well as the prognostic effectiveness of a controlled primary tumour. Geriatric score G8 didn't prove as a valuable prognostic factor in our population. We are not actually surprised at this event: since that patients are strictly selected by a multidisciplinary team in order to undergo GKRS, they are inevitably exposed to a selective bias which leads to the selection of people with a proper performance status. The total number of treated metastases cannot be considered as a prognostic factor and its role has already been extensively discussed in literature [8]. Published studies on the role of radiosurgery in older adults have been extremely limited so far and only in a small part of them the role of prognostic scores was considered. Minniti et al. [17] have reported their experience with 102 patients aged ≥ 70 and all treated with radiosurgery between 2007 and 2011 for 1–4 metastases. At a median follow-up of 11 months, median OS was 13.2 months and median time to distant intracranial recurrence was 10 months. By the end of the study, most patients had died from extracranial progression of

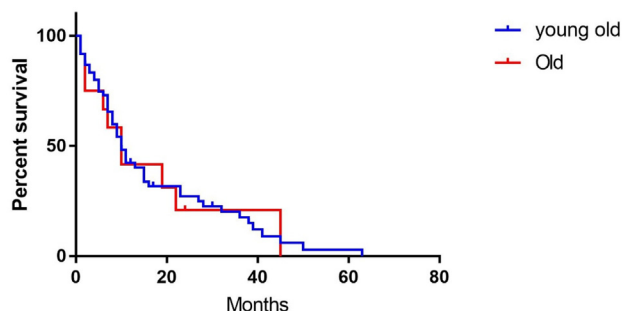


Fig. 1. Kaplan-Meier showing OS for YO and VO patients.

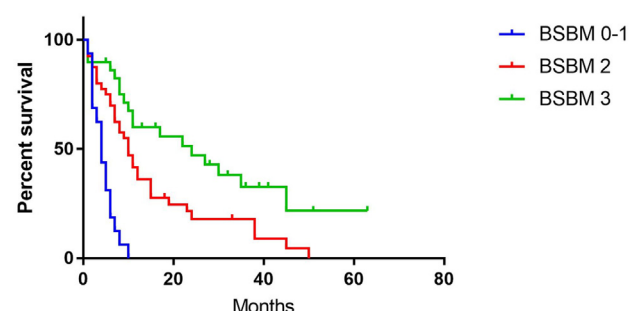


Fig. 3. Kaplan-Meier showing the association of BSBM score with OS.

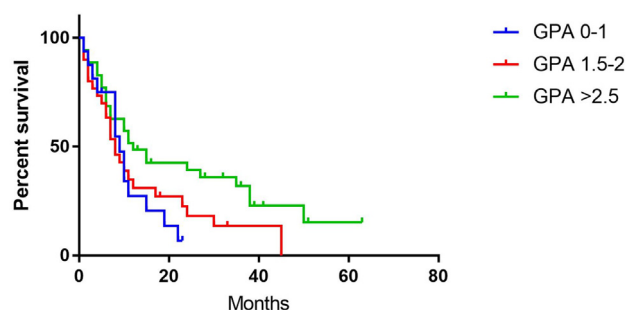


Fig. 4. Kaplan-Meier showing the association of DS-GPA score with OS.

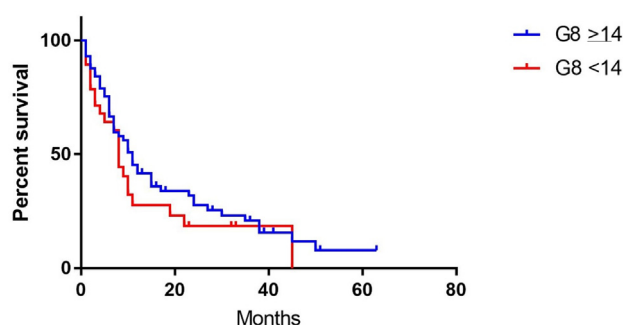


Fig. 5. Kaplan-Meier showing the association of G8 score with OS.

disease and only 9 locoregional recurrences were described. Yomo [18] has reported his experience with a consecutive series of 106 over-eighty patients exposed to radiosurgery. The 55% of the population had a single metastasis and the whole population had a median number of metastases of 2 (range 1–16). Median OS was 7.1 months, with a one-year neurological death rate of 12%. The authors concluded that a good performance status (KPS ≥ 70), a controlled primary tumour and the female sex were all independent favorable survival factors. Roh et al. [19], similarly to our experience, tried to identify survival and prognostic factors in a population aged ≥ 65 and treated with GKRS. One-hundred fifteen patients, with a median age of 72 years, were treated for 1–15 metastases (30 patients had only a single lesion). At a median follow-up of 5 months, median OS was 5.3 months. At multivariate analysis, female sex and a controlled primary tumour were statistically significant survival factors. Therefore, the authors concluded that female patients aged ≥ 65 with a controlled primary tumour were the ideal candidates for radiosurgery. Our experience significantly differs from what is reported in literature. First, our patients were all evaluated in a multidisciplinary setting by a team composed by a radiation oncologist and a neurosurgeon with a relevant expertise in radiosurgical treatments. All our patients were evaluated and stratified by means of prognostic tools, whose effectiveness in older adults was examined, differently from Minniti and his colleagues' experience. Yomo's work dwells only upon a specific geriatric population, the over-eighty's, without further stratification. Currently, Roh's experience is the closest to ours, considering both the exam population and the radiotherapy device used, and therefore his work can be easily compared with our study. Our records showed a clearly better result in terms of survival (14 months vs 4 months). The reason for such an important difference is hard to explain; in any case, it is appropriate to notice that the impact of EGFR-gene mutation on patients affected by NSCLC has not been examined, in contrast with the experience of our Korean colleagues. Surprisingly, OS in Korean patients with EGFR-mutation is close to the OS in our patients (19 months vs 14 months). Besides, in Roh's work no prognostic score was adopted in order to identify which patients could benefit the most from radiosurgery. The use of the main scores in geriatric population has been examined only in a single published work so far, according to our knowledge. Park et al. [20] have reported their experience with a series of 145 patients (all aged ≥ 70) treated with radiosurgery between 2004 and 2011. DS-GPA score proved as an important prognostic factor in this population, similarly to the results reported in our work.

Table 3

Significant independent prognostic factors for improved OS.

Parameters	p-value
BSBM score ≥ 3	<0.0001
GPA score ≥ 2.5	0.0069
Controlled primary tumour	<0.001

DS-GPA: diagnosis-specific graded prognostic assessment, BSBM: Basic Score for Brain Metastases.

5. Conclusion

GKRS is a reasonable approach to treat patients aged 65 years and older with BM, showing both survival benefit and toxicity profile similar to those observed in younger adults. Prognostic Indices excluding age as a detrimental factor are useful in selecting older patients for GKRS. DS-GPA score at the time of GKRS represents a powerful prognostic factor for survival in older patients undergoing radiosurgery.

Prior Presentation

This paper has been presented as oral communication at SIOG 2018 conference held in Amsterdam, Netherlands November 16–18, 2018.

Disclosures

The authors declare no conflict of interest.

Authors Contributions

All the authors contributed equally to this work.

References

- [1] Frisk G, Svensson T, Backlund LM, Lidbrink E, Blomqvist P, Smedby KE. Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden. *Br J Cancer* 2012;106:1850–3.
- [2] Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res* 2012 Nov;32(11):4655–62.
- [3] Ostrom QT, Wright CH, Barnholtz-Sloan JS. Brain metastases: epidemiology. *Handb Clin Neurol* 2018;149:27–42.
- [4] Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist* 2007 Jul;12(7):884–98.
- [5] Soliman H, Das S, Larson DA, Sahgal A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. *Oncotarget* 2016 Mar 15;7(11):12318–30.
- [6] Müller-Riemenschneider F, Bockelbrink A, Ernst I, Schwarzbach C, Vauth C, von der Schulenburg JM, et al. Stereotactic radiosurgery for the treatment of brain metastases. *Radiother Oncol* 2009;91:67–74.
- [7] Greto D, Scoccianti S, Compagnucci A, Arilli C, Casati M, Francolini G, et al. Gamma knife radiosurgery in the management of single and multiple brain metastases. *Clin Neurol Neurosurg* 2016 Feb;141:43–7.
- [8] Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387–95.
- [9] Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997 Mar 1;37(4):745–51.
- [10] Weltman E, Salvajoli JV, Brandt RA, de Moraes Hanriot R, Prisco FE, Cruz JC, et al. Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys* 2000 Mar 15;46(5):1155–61.
- [11] Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012 Feb 1;30(4):419–25.
- [12] Lorenzoni J, Devriendt D, Massager N, David P, Ruiz S, Vanderlinden B, et al. Radiosurgery for treatment of brain metastases: estimation of patient eligibility

- using three stratification systems. *Int J Radiat Oncol Biol Phys* 2004 Sep 1;60(1): 218–24.
- [13] Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys* 2010 Jul 1;77(3):655–61.
 - [14] Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 2012 Aug;23(8):2166–72.
 - [15] Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004 May 22;363(9422):1665–72.
 - [16] Yang CC, Ting J, Wu X, Markoe A. Dose volume histogram analysis of the gamma-knife radiosurgery treating twenty-five metastatic intracranial tumors. *Stereotact Funct Neurosurg* 1998 Oct;70(Suppl. 1):41–9.
 - [17] Minniti G, Esposito V, Clarke E, Scaringi C, Bozzao A, Lanzetta G, et al. Stereotactic radiosurgery in elderly patients with brain metastases. *J Neurooncol* 2013 Feb;111(3): 319–25.
 - [18] Yomo S, Hayashi M. Is upfront stereotactic radiosurgery a rational treatment option for very elderly patients with brain metastases? A retrospective analysis of 106 consecutive patients age 80 years and older. *BMC Cancer* 2016 Dec 15;16(1):948.
 - [19] Roh TH, Choi MS, You N, Jeong D, Jang AH, Seo MR, et al. Identifying candidates for gamma knife radiosurgery among elderly patients with brain metastases. *J Neurooncol* 2018 May;137(3):559–65.
 - [20] Park JY, Moon KS, Lee KH, Lim SH, Jang WY, Lee H, et al. Gamma knife radiosurgery for elderly patients with brain metastases: evaluation of scoring systems that predict survival. *BMC Cancer* 2015 Feb 14;15:54.