Radiosurgery Using Tomotherapy for Patients with Brain Oligo-metastasis: A Retrospective Analysis on Feasibility and Tolerance

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Abstract. *Aim: Aim of the study was to evaluate feasibility and toxicities of exclusive radiosurgery using tomotherapy in patients with brain oligo-metastases. Patients and Methods: Between 2008 and 2013 68 patients underwent stereotactic radiosurgery (SRS). Mean patient age was 63 years. Brain was the only site involved in 32 patients, while 36 had extracranial disease. Pre-SRS MRI 56 patients had sovratentorial lesions, 10 subtentorial and 2 patients had both. Fifty-two patients had 1 brain lesion, 11 had 2, and 5 patients had three. All patients underwent SRS using Tomotherapy. The median delivered dose was 18 Gy. Results: After a mean follow-up of 13 months, 14 patients were alive, while 54 patients had died. Two patients had complete response, 32 had partial response, 21 stable disease and 13 disease progression. Overall response rate was 80.9%. One- and two-year overall survival were 41,2% and 24,7%, while local control 61.5% and 37.7%. Toxicity was acceptable. Conclusion: SRS using tomotherapy has been proven feasible as non-invasive exclusive treatment for oligometastatic patients with good prognostic score.*

Brain metastasis (MTS) is the most common intracranial tumor in adults. It is estimated that 20% to 40% of cancer patients will develop brain MTS during the natural course of their disease (1). The most common sites of primary site are the lung, breast, skin, kidney and colon (2). The most known parameter to predict prognosis is the recursive partitioning analysis (RPA); this classification includes the main and well-known prognostic factors for brain MTS: age, Karnofsky performance status and controlled primary tumors (3). Recently two different quantitative classifications were proposed: the first one is the Graded Prognostic Assessment (GPA) (4) which also includes the number of lesions, the second one was the Score Index for Radiosurgery (SIR), currently the most complete, also including the volume of the largest lesion (5).

At the time of diagnosis patients usually experience headache, neurological deficits and/or seizures commonly caused by peritumoral edema, while cognitive impairment is demonstrated in 65% of them (6).

Actually, the main treatment options to treat brain MTS are surgery, stereotactic radiosurgery (SRS) and/or whole-brain radiotherapy (WBRT). In recent years the advent of frameless SRS offered a minimally-invasive option (as opposed to surgery) with significant results in terms of disease control. Still surgery is the "gold standard" treatment for single brain MTS larger than 3-4 cm with mass-effect (level 1). At the same time SRS+/-WBRT can be considered (level 1) (7) for single brain MTS (less than 3-4 cm) not resectable or incompletely resected. Results from retrospective studies suggest that surgery and SRS are comparable in the treatment of solitary brain MTS (8, 9) in terms of local control and survival, even if some authors show better local results using SRS (10). If multiple lesions are present in patients with good prognosis (>3 months) the role of surgery is restricted to obtaining biopsy samples or relieving mass-effect of large symptomatic MTS. When SRS is performed, certain studies (11, 12) suggest that a low disease volume would be the best selection criterion while the number of metastatic lesions did not reach significance. Patients with multiple brain MTS and poor prognosis should be considered for palliative care with or without WBRT (7).

To date, the role of WBRT after surgery or SRS is controversial. Whereas survival remains the most important

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end-point, local control, neurological quality of life, and costs are other significant end-points usually taken into account in more recent studies (8). Actually the risk of long-term neurotoxicity (particularly in terms of cognitive decline in long-term survivors) represents the main concern about adjuvant WBRT. Results from EORTC phase III trials show that adjuvant WBRT reduces intracranial relapses and neurological deaths but no improved overall survival was demonstrated; moreover WBRT was not able to prolong functional independence (13, 14)

Patients and Methods

Between January 2008 and August 2013 68 consecutive patients (37 males, 31 females) underwent SRS. Totally 89 brain solid tumor MTS were treated. Small-cell lung cancer brain MTS was an exclusion criterion from our analysis, even if some authors suggest that SRS is a potentially effective and minimally-invasive treatment option also for this type of MTS either given alone or after WBRT failure (15). At the time of diagnosis all patients had ECOG status 0-1, mean age was 63 years (range=35-85, median=64). All patients had biopsy-proven metastatic solid cancer; in 43/68 (63%) patients primary was lung cancer, in 12/68 patients (18%) breast, in 9/68 patients (13%) renal clear cell cancer and finally in 4/68 (6%) patients other neoplasms were involved (melanoma, colorectal cancer). All patients have already been submitted to multiple systemic therapy before being submitted to SRS. All patients were completely re-staged with total body CT scans, bone scans and brain MRI before being submitted to SRS due to avoidance of massive extra-cranial progression disease (PD) or multiple brain MTS. In 32/68 patients (47%) brain was the only site involved by MTS, while in the other 36/68 other sites of tumor spreading were present (bone, lung, liver, lymphnodes). Brain staging showed sovra-tentorial lesions in 56 patients (82%), infra-tentorial in 10 (15%) and both in 2 patients (3%). Moreover, 52 patients (76%) had only one brain lesion, 11 (16%) and 5 patients (8%) had two and three MTS respectively. Patients were then classified according to different prognostic index: Graded Prognostic Assessment (GPA) (3) and Recursive Partitioning Analysis (RPA) (4). Table I summarizes main patients' features.

Table I. *Patients' characteristics*.

Gender	M	37	54%
	F	31	46%
Age	Range	35-85	
	Mean	63	
	Median	64	
Primary Tumor	Lung	43	63%
	Kidney	9	13%
	Breast	12	18%
	Other	4	6%
RPA	1	13	19%
	2	51	75%
	3	4	6%
GPA	1	6	9%
	2	19	28%
	3	41	60%
	4	2	3%
Number of lesions	1	52	76%
	2	11	16%
	3	5	7%
Lesions Site	Sovratentorial	56	82%
	Subtentorial	10	15%
	Both	2	3%

GPA, Graded prognostic assessment; RPA, recursive partitioning analysis.

RT Simulation and planning treatment delivery. All patients were submitted to dedicated simulation kilo-Volt (kV) computed tomography (CT). Before starting with CT scan, written informed consent was obtained from every patient. All patients lied down the CT couch in supine position with arms beside the body; a head-neck rigid frameless thermoplastic mask was made for every patient to maximally reduce set up displacements. kV images (with or without contrast enhancement depending on lesion size) with 1.0 mm slice thickness were obtained with our CT simulator (Aquilon 16 Large Bore Toshiba, 120 kV, 80 mA) after rigid immobilization was completed. Acquired planning CT images were then transferred to the contouring workstation via our Institution network and Pinnacle software was used for contouring target volume and critical structures including brain, brainstem, cord, cochlea (if needed), chiasm, eyes, crystallines and optic nerves. All CT images obtained were co-registered with 1.5T MRI brain scans (using axial T1 FSE and axial T1 Contrast enhanced slides) to improve delineation accuracy of the target volume and organs at risk. A CT-Gross Target Volume (GTV) and MRI-GTV was contoured and an expansion margin of 3 mm from MRI defined GTV was applied for obtaining planning target volume (PTV) also including imaging uncertainty (mega-Volt CT pixel size). Treatment plans were then validated by a physics and a senior radiation oncologists of our Unit. All patients underwent SRS with HI-ART Tomotherapy in single session so treatment plans were all performed using HT planning station. All plans were prescribed according to ICRU83 at the median of PTV (50%), limiting cold (V95 >98%) and hot spots (V_{107} <2%). The median dose prescribed was 18Gy (range=10-22).

Dosimetric index. Treatment plans quality were evaluated according to the methods proposed by Barra et al (16) with three different dosimetric index:

1 – Conformity Index initially proposed by Tanyi (17) is defined as follow:

$$CI = \frac{V_{tv} x V_{PTV}}{V^2_{PTV,95\%}}$$

V_{tv} is the treated volume defined as the volume included in the 95% isodose, V_{PTV} is the volume of PTV and $V_{PTV,95\%}$ is the Volume of PTV included in 95% isodose. A conformity index near 1 means a good target coverage and good healthy tissue sparing from high doses.

2 – Homogeneity Index is defined as the ratio of Maximum (D_{max}) and Prescription (D_p) dose in PTV.

$$HI = \frac{D_{max}}{D_p}$$

3 – Gradient Score Index, proposed by Wagner et al (18), reflect the ability of healthy tissue sparing. GSI is calculated from effective radii (expressed in cm) of 50% isodose and 95% isodose.

$GSI = 100 - \{100 \times [R_{50\%} - R_{95\%} - 0.3]\}$

Table II. *Dosimetric index comparison*.

PTV Vol [cc] (Mean)	Conformity Index (Mean)	Homogeneity Index (Mean)	Gradient Score (Mean)	Reference Index
6.2±5.7	1.36±0.17	1.04±0.02	50±20	Barra *et al*. (16)
14.9±12.4	1.26±0.10	1.18±0.09	43±14	Han *et al*. (20)

PTV, Planning Target Volume.

Table III. *Mean and median overall survival, local control, progression-free survival*.

	Mean (months/95 CI%)	Median (months/range)
Overall survival	17.4 (12.4-22.3)	8.3 (5.2-11.5)
Local control	19.9 (15.1-24.7)	15.0 (10.8-19.2)
Progression-free Survival	9.9 (7.4-12.4)	6.3 (4.3-8.2)

Treatment setup. Patient positioning were performed without invasive stereotactic frame. MVCT of the whole brain were performed before treatment delivery with the highest resolution allowed by the imaging system (Fine Course, 2 mm). Co-registrations of planned kVCT and MVCT focused on bone structures and target were used for minimizing the uncertainty in patient positioning.

Follow-up and outcomes. After treatment all patients were monitored for a follow-up (FUP) period in order to assess acute/late toxicity and clinical outcomes. Mean FUP was 13 months (range=4-65).

First clinical evaluation was planned after 40-60 days from SRS and it was performed with general and neurological examination, total-body CT scan and brain MRI. After first evaluation Brain Scans were repeated every 3 months. In agreement to CTCAE v4.0 acute toxicities were identified as events that appear within 90 days from the execution of radiotherapy, while other side effects compared after three months were described as late toxicity. According to Response Assessment in Neuro-Oncology (RANO) criteria treatment responses were divided in: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) (19).

Results

We retrospectively reviewed our cohort by performing descriptive and analytic statistical analysis (mean, median, range, standard deviation (SD), standard error (SE), proportion) to characterize patients, neoplasms and treatment features. Acute and late toxicities were also analyzed. Overall survival (OS), progression-free survival (PFS) and local control (LC) were estimated using Kaplan-Meier methods. Data on OS, PFS and LC were calculated starting from the day of radiation therapy session until the date of event or last follow-up available. CR, PR and SD were included in the overall response (ORR) rate. OS was defined as the time from the session of Radiotherapy and the death of the patient or the last follow up available. PFS was defined as the time from the session of Radiotherapy and the intracranial or extracranial progression of disease. Local control (LC) was defined as stabilization or reduction after radiotherapy treatment compared with the initial brain MRI. All statistical analyses are performed using biostatistical software SPSS 17.0 v.21 (IBM, Milan, Italy). Confidential intervals, Chi-Square and Wilcoxon tests are used to compare percentages, mean and median. OS, LC and PFS were subjected to univariate (Log-Rank test) and multivariate analysis (Cox-Regression) to find out clinical-, patient- or tumor-related prognostic factors. All factors analyzed having $p<0.05$ were defined as "statistically significant".

Treatment plan. All 68 treatment plans respected dosimetric treatment goals (V_{95} >98, V_{107} <2%). All treatments were delivered in a single tomotherapy session and the more frequent prescription dose to the lesion was 18 Gy (41%), then 20 Gy (38%) and 16 Gy (9%). Mean beam time was approximately 20 min, positioning and imaging of patients required not more than 10 min for a mean room time of 30 min for each patient. Dosimetric Index was in good agreement with values obtained in similar published studies with Helical Tomotherapy (20). Results are outlined in Table II.

Clinical outcomes. After a mean FUP of 13 months (range=4-65) 14 patients (21%) were still alive while the remaining 54 (79%) died. Fifty-two (96%) of them died due to disease progression, while the remaining 2 (4%) died of other causes. Mean and median OS, LC, PFS are outlined in Table III with the relative 95% confidence interval.

All patients received single-session RCS but different doses were planned due to lesion size or position and to respect main constraints of organs at risk. Mean dose delivered was 18 Gy (range=10-22): four patients (6%) were submitted to single session RCS with a delivered dose >20 Gy, 56/68 (82.3%) with 16-18 Gy and the remaining 8/68 (11.7%) with a dose equal or inferior than 15 Gy. After radiotherapy treatment patients were steadily followed-up with clinical evaluation, brain MRI and total body CT scan every 3-4 months. Restaging after SRS showed a CR in 2/68 patients (3%), PR in 32/68 patients (47.2%) and SD in 21/68 patients (30.9%); 13/68 patients (19.1%) unfortunately had intracranial-progression disease (PD). The ORR rate was 80.9% (55/68). OS at 1 and 2 years was, 41.2±6.1% and 24.7±5.8%, respectively, while 1- and 2-year progression-free survival and local control amounted to 52.3±6.4% and 12.7±5.1% and to 61.5±7.2% and 37.7±8.8% respectively

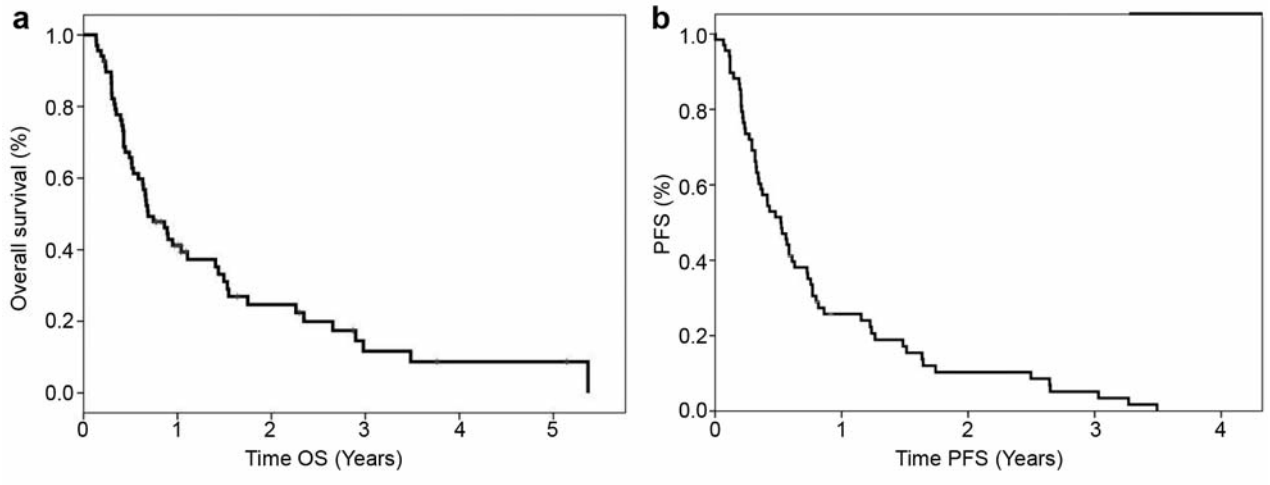

Figure 1. *a: Overall survival. b: Progression-free survival.*

(Figure 1a, 1b). Regarding local control 34/68 patients (50%) experienced intracranial disease progression during follow-up and mean and median time to cerebral failure were 9.6 and 5.5 months (range=1-41), respectively. Twenty out of 34 patients (58.8%) had "in-Field" relapse (defined as a radiological/clinical progression of the lesion already submitted to SRS) while 14/34 (41.2%) had "out-field" new lesions. Twenty four of 34 patients (70.5%) had clinical symptoms due to their cerebral relapse, but only 7/34 patients received another course of radiotherapy: 4/8 received whole brain irradiation (30 Gy in 10 Fractions) and the remaining 3/8 patients a second SRS (15-18Gy).

All clinical, pathological, patient and tumor-related factors were evaluated using univariate analysis, but only RPA class influenced both OS ($p<0.004$) and PFS ($p<0.02$), being a statistical significant prognostic factor. In addition to RPA class, PFS showed a significant dependence ($p<0.01$) from primary tumor location. *p*-Values of log-rank test are summarized in Table IV.

GPA class, age and primary tumor site showed a statistical trend in terms of OS such as GPA class and lesion position in terms of PFS. Local control was partially influenced by RPA class showing a statistical trend ($p<0.057$). In detail, RPA Class seems to have an important prognostic power both on OS and PFS, particularly patients classified as "RPA class 3" have a very poor prognosis rather than RPA class 1 or 2. On the other hand patients with primary lung cancer seem to have better prognosis than patients with MTS from breast, kidney or other primary cancer ($p<0.012$). OS and PFS in function of RPA class and Primary tumor site are shown in the Table V and Figure 2a, 2b, 2c. Factors that were found to be statistical significant at the univariate analysis were then analyzed with multivariate analysis using Cox-Regression but no significant factors were found. In addition no relevant correlation between calculated dosimetric index and OS, LC, PFS, acute toxicities and late toxicities have been found. Regarding toxicities 11/68 (16%) patients experienced acute side-effects while only 3/68 patients (1%) had late complications. Regarding acute side-effects 5/68 patients (7%) had G1 vascular damage, 3/68 patients (4,4%) G1-G2 dizziness, 2/68 patients (3%) G2 headache and just 1/6 patient (1,5%) G2 memory loss. Only 1 of them had clinical symptomatic consequences. About late toxicities only 3/68 patients (1%) experienced some symptoms with 2/68 patients having G2 headache and dizziness and 1/68 patient G1 vascular damage. No related treatment death were observed.

Table IV. *Log rank and univariate statistical analysis of patient factors.*

Variable	Overall survival	Local control	Progression-free survival
GPA	0.323	0.636	0.086
RPA	0.004	0.057	0.026
Age	0.172	0.811	0.217
Gender	0.130	0.216	0.264
Primary tumor site	0.198	0.363	0.012
Sovra/Subtentorial	0.506	0.786	0.106
Number of metastases	0.449	0.942	0.716
Total dose	0.704	0.909	0.880

GPA, Graded prognostic assessment; RPA, recursive partitioning analysis.

Discussion

SRS has now become the most widely used focal treatment modality for patients with brain metastases, since it is largely non-invasive and does not require general anesthesia (21). More recent data (22) suggest that the use of SRS can be

Table V. *RPA effect on overall and progression-free survival.*

RPA Class	Mean overall survival [days/CI95%]	Median overall survival [days/CI95%]	Mean progression-free survival [days/95%]	Median progression-free survival [days/95%]
1	614 (315-913)	559 (106-1012)	393 (226-560)	447 (40-854)
2	527 (351-704)	271 (178–364)	288 (200-376)	191 (116-265)
3	124 (86-162)	107 (56-158)	97 (66-127)	75 (39-111)

RPA, Recursive Partitioning Analysis.

extended even to patients with more than four MTS, as it has been demonstrated that OS and toxicities do not significantly differ between patients with two to four MTS and those with five to ten. Moreover, despite an increased need for salvage therapy, the average cost is lower for patients treated with SRS alone then for those treated with SRS+WBRT (23). In our cohort doses given in a single fraction depended on diameter of the lesion with higher doses for the smallest ones (<20 mm of maximum diameter) according to RTOG 90-05 recommendation. Almost 3 randomized trials comparing SRS alone with SRS and WBRT (SRS+WBRT) showed that adding WBRT to SRS in patients who have up to 4 newly-diagnosed brain MTS does not improve OS. While the addition of WBRT reduces intracranial failure rates, patients treated with SRS+WBRT are at greater risk of developing learning and memory impairment than patients who were submitted to RCS alone (24-26). At 3 months, patients who underwent WBRT were more likely to experience cognitive decline compared to those who only received radiosurgery (26). Based on these results, it could be useful to introduce in our clinical practice a cognitive assessment, like the Montreal Cognitive Assessment (validated for use in Parkinson's disease) in order to examine the radiation-induced injury on cognitive function (27). Most common side-effects of WBRT are fatigue, somnolence and headache, hair loss in terms of acute sub-acute toxicity and neurocognitive decline and leukoencefalopathy in terms of late toxicities. The last ones remain the most distressing effects, and different strategies have been tested to avoid it. One possibility is the use of Memantine as done in RTOG0614 study driven by Brown *et al*. where its use allowed a significant longer time to cognitive decline in the memantine arm. Another approach that seems to have promising results is the hippocampal-sparing WBRT, as demonstrated in several studies (28). Recently Lin *et al*. (29) demonstrated in a prospective phase II study that no statistically significant differences are present between various neurocognitive function scores obtained from patients interview at baseline and at post-radiotherapy intervals. In our study 34/68 patients (50%) experienced intracranial disease progression during follow-up and mean and median time to cerebral failure were 9.6 and 5.5 months (range=1-41), respectively. After relapse WBRT was used as salvage therapy in 4 patients after a median time of 6 months, while 3 patients underwent a second stereotactic radiosurgery treatment (15-18 Gy). The use of stereotactic retreatment is actually used more and more often in patients with oligometastatic disease with extracranial stable disease after systemic treatment. Shultz *et al*. (30) showed that multiple courses of SRS, deferring WBRT, could be a safe and effective approach. In their study they evaluated 652 MTS in 95 patients treated with 2 or more courses of SRS with just 8% of patients developing clinically significant toxicity. In our study OS seems to be strictly related to RPA class, with a significant better prognosis for RPA class 1 with 1-year OS of 61.5±13.5%, 21.6±5.8% and 0.0% respectively for patients in RPA 1, 2 or 3 as similarly reported in literature (16). Sahgal *et al*. (31) reported in a recent review that age is a significant parameter for distant brain failure, with a longer intracranial recurrence-free time survival for younger patients who can benefit of SRS alone. Moreover, according to these authors patients with a single metastasis had significantly better survival and lower risk of distant brain failure than patients who had 2 to 4 MTS. In our study age and number of MTS were not found to have a significant statistical impact on OS, PFS and LC but age showed a trend ($p<0.17$) in terms of OS with younger patients having a better prognosis. Among toxicities, radiation-related white matter changes (WMC) was detected with MRI in 2/68 patients (3%) and radionecrosis in other 2 patients (3%); our findings seems to be in agreement with main international literature. Particularly Stokes *et al*. (32) found that, after one year, 71.5% of patients whose treatment included WBRT developed WMC (42.9% grade 2; 28.6% grade 3) but only 1 patient (3%) receiving SRS alone had this kind of toxicity. Pure radionecrosis was then histologically confirmed in 2 patients showing that an aggressive surgical attitude may be advisable in symptomatic patients with suspected cerebral radionecrosis, to have histologic confirmation, to obtain a long-lasting relief from mass effect and brain edema and to improve the overall quality of life, sparing a prolonged corticosteroid therapy (33). Finally, to date the role of systemic therapy is a point of controversy, whilst the central nervous system is considered a sanctuary site for drugs

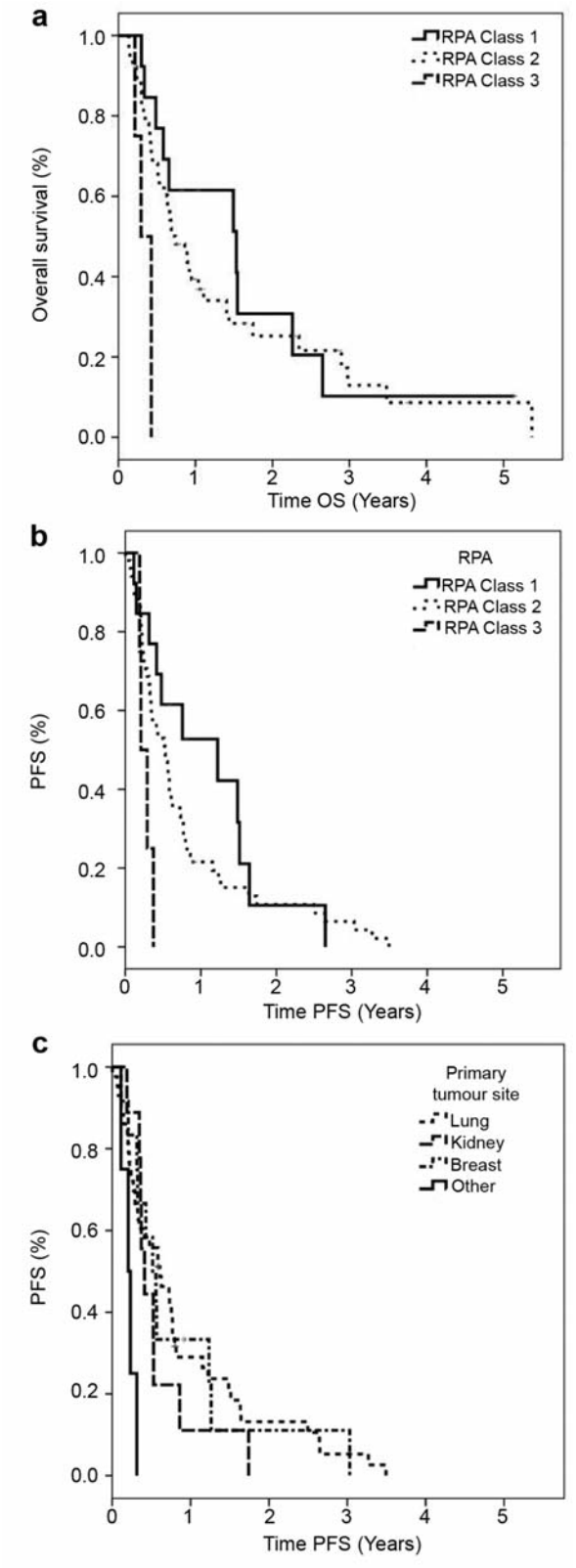

Figure 2. *a: Overall survival in function of RPA. b: Progression-free survival in function of RPA. c: Progression-free survival in function of primary tumor site.*

penetration. Medical or Radiation Oncologists can choose whether employing a chemotherapeutic agent such as temozolamide, topotecan, irinotecan that are considered drugs with a good central nervous penetration depending on primary tumor histology (34). The RTOG 0320 study demonstrated that patients who underwent WBRT+SRS alone showed a better OS, time to central nervous system progression, performance status and a lower toxicity profile, while the association with temozolomide or erlotinib was found to have a detrimental effect (35). Emerging therapies seem to be promising in primary and secondary prevention; Steeg *et al.* (36) suggested that certain drugs (*e.g.* temozolomide, pazopanib, vorinostat) can help prevent CNS dissemination in breast cancer.

Conclusion

Single-session SRS with frameless immobilization head-neck mask using tomotherapy has proven feasible and very well-tolerated as exclusive treatment for patients with brain oligo-MTS and good prognostic score, providing encouraging results in terms of clinical outcomes. RPA class and primary tumor histology seems to be the most important prognostic factors in terms of OS and PFS while younger age seems to have some relevance for local control.

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