BRAIN METASTASES IN MALIGNANT MELANOMA - TREATMENT OPTIONS AND RECOMMENDATIONS

Malignant melanoma has a high propensity to metastasize to the brain, so nearly 37% of patients eventually develop clinically diagnosed brain metastasis, but in autopsy series up to 75% of the patients who died of melanoma progression have brain metastasis. Headache and seizures are the most common symptoms, but also cognitive and language dysfunction or focal motor dysfunction can be described. Brain metastases from malignant melanoma are often richly vascularized, tend to haemorrhage and present variable degrees of melanin production. There are many prognostic classifications, the median overall survival ranging between 2 to 13 months. The systemic treatments are represented by chemotherapy with Dacarbazine or Nitrosourea drugs with limited efficacy and new molecules like B-RAF inhibitors and Monoclonal Antibody that modulate the immune response, molecules that can produce better response and outcomes. Local treatments are surgery, whole brain or focal stereotactic radiotherapy. The metastasis resection or radiosurgery are considered equally effective in achieving local tumor control (60-90%) and also in overall patient survival, the treatment choice depending on prognostic factors and brain tumor complications. The whole brain radiotherapy after either surgery or radiosurgery significantly reduced the probability of relapse at initial and new cerebral sites, but without significant benefice in terms of functional independence and median survival.

Keywords:
Malignant melanoma, brain, radiotherapy

Abstract

Malignant melanoma has a high propensity to metastasize to the brain, so nearly 37% of patients eventually develop clinically diagnosed brain metastasis, but in autopsy series up to 75% of the patients who died of melanoma progression have brain metastasis. Headache and seizures are the most common symptoms, but also cognitive and language dysfunction or focal motor dysfunction can be described. Brain metastases from malignant melanoma are often richly vascularized, tend to haemorrhage and present variable degrees of melanin production. There are many prognostic classifications, the median overall survival ranging between 2 to 13 months. The systemic treatments are represented by chemotherapy with Dacarbazine or Nitrosourea drugs with limited efficacy and new molecules like B-RAF inhibitors and Monoclonal Antibody that modulate the immune response, molecules that can produce better response and outcomes. Local treatments are surgery, whole brain or focal stereotactic radiotherapy. The metastasis resection or radiosurgery are considered equally effective in achieving local tumor control (60-90%) and also in overall patient survival, the treatment choice depending on prognostic factors and brain tumor complications. The whole brain radiotherapy after either surgery or radiosurgery significantly reduced the probability of relapse at initial and new cerebral sites, but without significant benefice in terms of functional independence and median survival.

Cite this article

Brain metastases in malignant melanoma - treatment options and recommendations

Metastazele cerebrale în melanomul malign - opţiuni terapeutice şi recomandări

Cuvinte-cheie:
Melanom malign, creier, radioterapie

Rezumat

Melanomul malign are o tendinţă mare de metastazare la nivel cerebral, la 37% dintre pacienți putându-se diagnostica metastaze cerebrale, înși în seriile de autopsie 75% dintre pacienți decedați prin evoluția bolii au metastaze la nivel cerebral. Cefalееa și crizele comitale sunt principalele manifestări clinice, dar se pot descrie de asemenea și tulburări cognitive și de vorbire, precum și deficite motorii. Metastazele cerebrale sunt bogat vascularizate, au tendinţa de sângerare intratumorală și prezintă niveluri diferite de melanină. Există mai multe scoruri de clasificare prognostică, supraviețuirea medie situându-se între 2 și 13 luni. Tratamentele sistemice sunt reprezentate de Dacarbazină sau derivați de Nitrozo-uree, medicamente cu eficacitate limitată și de noile molecule precum inhibitorii de B-RAF sau anticorpii monoclonali care modulează răspunsul imun, molecule care determină răspunsuri mai bune și evoluții favorabile. Tratamentele locale sunt chirurgia, radioterapia pan-encefalică sau cea stereotactică. Reacția chirurgicală sau radiochirurgia sunt considerate egale eficace atât în ceea ce privește controlul local (60-90%), cât și supraviețuirea, alegerea tratamentului depinzând de factorii de prognostic și de complicațiile locale ale metastazei. Iradierea întregului encefal, fie după chirurgie, fie după radiochirurgie, reduce semnificativ rata recidivelor cerebrale atât la locul inițial, cât și în alte teritorii cerebrale, însă fără a aduce un beneficiu semnificativ de independență funcțională sau supraviețuire.
Malignant melanoma has a high propensity to metastasize to the brain, so nearly 37% of patients eventually clinically diagnosed brain metastasis, but in autopsy series up to 75% of the patients who died of melanoma progression had brain metastasis. Brain metastasis typically occur relatively late in the course of melanoma - a median interval of 2.2 to 3.8 years after the diagnosis of the primary tumor. Risk factors associated with brain metastasis include male gender, mucosal or head and neck primaries, thick or ulcerated neoplasms, acral lentiginous or nodal lesions, and stage IV disease.

**Clinical presentation**

Headache (42% of patients) and seizures (about one third of the patients) are the most common symptoms, but the also cognitive and language dysfunction or focal motor dysfunction can be present.

**Pathological and radiological features**

Melanoma hystopathological diagnosis is based on the presence of epithelioid cells with abundant pink cytoplasm, large nuclei and giant cherry-red nucleoli. The usual immunohistochemistry (IHC) melanocytic markers include S-100, HMB-45, Melan-A, and MITF. S-100 is a low-molecular weight calcium binding protein that stains all melanomas with very high sensitivity but low specificity in CNS metastases due to their widespread expression in neurons, astrocytes, Schwann cells and gliomas. The HMB-45 (Human Melanoma Black 45) is a melanocyte-specific monoclonal antibody directed against a membrane glycol-protein, the Melan-A (Melanoma Antigen) also known as MART-1 (Melanoma Antigen Recognized by T cells), which is a protein antigen found on the surface of melanocytes. The MITF (Microphthalmia-associated transcription factor) is a transcription factor involved in melanocyte development. All of these markers have lower sensitivities for metastatic lesions, therefore a combination of markers seems to be necessary for a correct diagnosis.

From radiological point of view intracerebral metastatic melanoma has a distinctive presentation because of its often extensive vascularity, tendency to haemorrhage and variable degrees of melanin production.

a) Melanoma metastases are hypervascular, therefore all lesions show contrast enhancement in Computed Tomography (CT) and Magnetic Resonance Images (MRIs). In Dynamic contrast-enhanced MRI, they show an elevated relative cerebral blood volume (rCBV), the ratio between the blood volume in the pathological area (tumor) and the normal adjacent cerebral parenchyma. The mean rCBV of melanoma metastases (5.35±2.32, range 3.14-9.23) is significantly greater than those of high-grade glioma (2.61±1.17, range 1.3–5.0) and of lung carcinoma metastases (2.94±0.86, range 1.43-4.04).

b) Intratumoural haemorrhage is a much more common feature of melanoma metastases in comparison to other brain metastases. On noncontrast CT, 75% of melanoma brain metastases appear hyperdense (increased attenuation), a sign of recent haemorrhage.

c) Depending on the brown melanin pigment concentration, the melanoma metastases can be classified into “melanotic” (containing greater than 10% melanotic cells) or “amelanotic” (containing less than 10% melanotic cells), with implication in radiological appearance. Melanotic metastases are hyperintense on T1-weighted images and hypointense on T2-weighted images, and the amelanotic metastases are hypointense or isointense on T1-weighted images and hyperintense or isointense on T2-weighted images.

**Prognostic factor and risk classification**

There are many classification systems (scores) of patients with brain metastases, the main prognostic factors being the age, the clinical performance (Karnofsky or ECOG/OMS scale) and the status of extracranial disease (controlled or progressive cancer).

**Recursive partitioning analysis (RPA)**

The Recursive partitioning analysis (RPA), is derived from patients treated with Whole Brain Radiotherapy (WBRT) in several Radiation Therapy Oncology Group (RTOG) studies, based on Karnofsky performance status (KPS), age and status of extracranial disease.

Class 1: patients with KPS ≥70, ≤65 years with controlled primary and no extracranial metastases. Median overall survival is 7.1 months.

Class 2: patients with KPS ≥70 and all other than Class 1. Median overall survival is 4.2 months.

Class 3: patients with KPS <70. Median overall survival is 2.3 months.

**The Score Index for Radiosurgery in Brain Metastases (SIR)**

The Score Index for Radiosurgery in Brain Metastases (SIR) is a prognostic score obtained by retrospective...
Survival analysis of brain metastases patients treated with radiosurgery and it is based on the five major prognostic factors: age, KPS, extracranial disease status, number of brain lesions, and largest brain lesion volume.

**Graded Prognostic Assessment (GPA)**

The Disease-Specific Graded Prognostic Assessment (DS-GPA) was validated and refined based on a multi-institutional retrospective analysis of 4259 patients with brain metastases from breast, small-cell and non-small-cell lung carcinoma, gastrointestinal cancers, melanoma, and renal cell carcinoma. All those patients were treated with brain WBRT with or without boost to the metastases. The GPA index for melanoma is based only on Karnofsky Performance Scale (KPS) and the number of brain metastases present.

**Systemic treatments**

Systemic chemotherapy has shown little benefit in the treatment of stage IV melanoma, including those with brain metastasis and therefore the chemotherapy was usually reserved for salvage therapy.

Dacarbazine (DTIC), an alkylating agent, was the first drug approved for metastatic melanoma but no Central Nervous System (CNS) objective response and no clear survival advantage were observed. An explanation for this limited efficacy is the failure of systemic drugs to pass the blood-brain barrier.

Fotemustine (Muphoran), a nitrosourea (chloroethyl-nitrosourea) that penetrates the blood-brain barrier, compared with DTIC shows similar (low) objective response rates (5%), durations of response (5.8 months with fotemustine v 6.9 months with DTIC) and time to progression (1.8 v 1.9 months, respectively)\(^{(10)}\).

Temozolomide, an oral alkylating agent analog of DTIC, can cross the blood-brain barrier and concentrate in the central nervous system (approximately 28-30% of its plasmatic concentration)\(^{(14)}\). Clinical benefit of Temozolomide as a single agent remains modest but encouraging against melanoma brain with 7% objective response, 29% disease stabilization, and median survival of 2.2 months\(^{(14,15)}\).

Ipilimumab is a fully human IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 is an inhibitory immune checkpoint receptor, that plays a critical role in regulating the adaptive immune response by interrupting the costimulatory signal essential for T-cell activation. By negating the inhibitory action of CTLA-4, Ipilimumab augments T-cell responses to tumor antigens, resulting in immune-mediated antitumor activity\(^{(16)}\). In a prospective Phase II trial, patients with melanoma who had at least one brain metastasis were treated with Ipilimumab (10 mg/kg). The Overall Survival (OS) for patients with asymptomatic metastases (no corticosteroids needed) was 31% at 1 year and 26% at 2 years, whereas symptomatic patients (patients receiving corticosteroids) had OS rates of 19% at 1 year and 10% at 2 years. These results indicate that Ipilimumab is associated with prolonged survival in patients with melanoma that has metastasized to the brain, without excessive toxicities\(^{(17)}\).

Vemurafenib and Dabrafenib are BRAF kinase inhibitors, approved for the treatment of patients with melanoma carrying mutated BRAF (in 40-60% of melanomas)\(^{(18)}\). BRAF protein is a cytoplasmic protein kinase belonging to a RAF (Rapidly Accelerated Fibrosarcoma) kinase family, that plays a role in regulating the RAS-RAF-MEK-ERK signalling pathway, which affects cell division, differentiation,

<table>
<thead>
<tr>
<th>Points</th>
<th>KPS</th>
<th>No brain metastases</th>
<th>GPA Score</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 70</td>
<td>&gt; 3</td>
<td>0-1</td>
<td>3.4 months</td>
</tr>
<tr>
<td>1</td>
<td>70-80</td>
<td>2.3</td>
<td>1.5-2.5</td>
<td>4.7 months</td>
</tr>
<tr>
<td>2</td>
<td>90-100</td>
<td>1</td>
<td>3</td>
<td>8.8 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5-4</td>
<td>13.2 months(12)</td>
</tr>
</tbody>
</table>

**Treatment options. Systemic versus Local treatments**

Neither the RPA, nor SIR classification take into consideration the metastases histological type.

```
<table>
<thead>
<tr>
<th>Points</th>
<th>GPA Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.4 months</td>
</tr>
<tr>
<td>1</td>
<td>4.7 months</td>
</tr>
<tr>
<td>2</td>
<td>8.8 months</td>
</tr>
</tbody>
</table>
```

Oncology & Dermato-oncology

Brain metastases in malignant melanoma - treatment options an recommendations
and secretion\textsuperscript{19}. The mutated BRAF gene leads to constitutive activation of the RAF/MEK/ERK signaling pathway and consequently promote tumourigenesis. Vemurafenib produces a 50% response rate, with a response duration between 8 and 32 weeks. The median overall survival was 46 weeks for the patients with an objective response and 21 weeks among the nonresponding patients\textsuperscript{20}. The other BRAF-inhibitor, Dabrafenib demonstrated a better response rate (53% against 19%) and Progression Free Survival (5.1 months against 2.7 months) compared to DTIC\textsuperscript{21}.

**Local treatments** are represented by surgery, whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS).

**Surgical resection** remains an important option for the diagnosis (biopsy or surgical resection to differentiate metastasis from primary tumors or other brain lesions) and treatment of brain metastases. From therapeutic point of view, the resection of brain metastases may be preferred in some circumstances:

1. patients with good prognosis: KPS \( \geq 70\% \), controllable extracranial disease or having only bone metastases from breast cancer or lung cancer (very good prognostic patients).
2. patients with a brain lesion causing mass effect or peritumoural oedema. In this case, if there are multiple brain metastases, surgical resection is recommended for the dominant lesion (Debunking, cytoreduction surgery).
3. patients with a radio-resistant primary cancer (e.g., renal cancer or melanoma), which do not benefit of WBRT. In contrast, surgical resection is not generally recommended for relatively radiosensitive tumour types such as small cell lung cancer, germ cell tumours or leukaemia and lymphoma, metastases that are more likely to be treated with WBRT\textsuperscript{22}.

**Whole Brain Radiotherapy (WBRT)**, 30 Gy in 10 fractions (3 Gy per fraction) over two weeks using a simple technique with a pair of parallel opposed lateral 6 MV photon fields has been widely adopted as a standard treatment of multiples brain metastases. For good performance (\( \leq 4 \) brain metastases , no extracranial metastases and RPA class 1) higher dose like 40 Gy in 20 fractions or 45 Gy in 15 fractions were associated with improved overall survival compared with standard dose. The dose escalate increase the Overall Survival from 27\% to 50\% at 6 month and from 4\% to 20\% at 1 year and the Local Control at 12 months from 0\% to 13\%\textsuperscript{23}.

**Stereotactic radiosurgery (SRS)**

Stereotactic radiosurgery (SRS) refers to the precise and focused delivery of a single, high dose of radiation in a single session and has been used to treat various intracranial and skull base lesions. The dose is heterogeneous delivered, with a very high dose inside the tumor and a rapid dose decline (dose fall off) outside the tumor volume\textsuperscript{24}. For the treatment of brain metastases with SRS, a large single dose of typically 15-25 Gy is applied to the target volume(s).

**Tumor target and Organ at Risk volumes delineation** should be based on contrast enhanced MRI of the brain (axial, sagittal and coronal axes are used) coregistered with the radiation treatment planning computer tomography (CT). The Gross Target volume (GTV) should encompass the contrast-enhanced tissue in the planning CT and the MRI. The Clinical Target Volume (CTV), representing the tissue volume that contains the visible tumor plus all subclinical microscopic malignant disease, is obtained by adding a margin of 0-1 mm around the GTV. The Planning Target Volume (PTV) is a geometrical concept that considers the inherent uncertainties (geometrics errors) that can appear in treatment procedures. The PTV-to-CTV margin depends on the treatment technique, in SRS with invasive fixation it is general practice to use PTV=CTV whereas for non-invasive fixation, the PTV is CTV plus 1 to 2 mm margins. The principals Organs at risk that must be delineate are the brain parenchyma and the brainstem, the optic nerves and optic chiasm\textsuperscript{25}.

**Dose planning.** To assure the high conformity of the dose distribution with the target volume (PTV), the prescribed isodose should cover at least 95\% of the target volume and the conformity index (how well the volume of a radiosurgical dose distribution conforms to the size and shape of a target volume) should not be less than 0.5-0.6\textsuperscript{27}. The SRS total dose must take into account the normal tissue tolerance limits to avoid severe toxicity, like brain radio-necrosis. The maximum tolerated doses of single-fraction radiosurgery depends of tumor diameter and volume, 24 Gy for tumors of \( \leq 20 \) mm, 18 Gy for tumors of 21-30 mm, and 15 Gy for tumors of 31-40 mm in maximum diameter\textsuperscript{28}. The constraint doses for the principals Organs at Risk are:
The patient correct installation. The brain radiosurgery involves precise positioning of the patient and the target volume in 3-dimensional space and require the monitoring of patient position in order to track potential isocenter displacements and to realign the target during the treatment session. ExacTrac X-ray 6D (ET) system (BrainLab) has 2 in-room-mounted orthogonal x-ray tubes and 2 detectors that can monitor the patient’s anatomy in the treatment position and offers high detection and subdegree positioning accuracy for rotations. The kV images were acquired and an automatic image fusions with 6 degrees of freedom (6D) on digitally reconstructed radiographs (DRRs) is performed to setup refinement\(^{(30)}\). The X-ray verification data from patients showed a high installation accuracy, with a random error less than 0.3 mm in each direction and rotational deviations less than 0.2-0.3°\(^{(31)}\).

Stereotactic radiosurgery (SRS) results in terms of efficacy and toxicity

Efficacy. For all primitive tumor types the local control is achieved in 85–91% cases and the 1-year tumor control rates range between 69% and 81% with lower local control (60%) in tumors larger than 2 cm\(^{(32)}\). The reported survival of 7-14 months after SRS, equivalent to that reported after surgical resection, the 1-year and 2-year survival rates were 58% and 24%, and the 1-year and 2-year local control rates were 92% and 84%, respectively. Histopathological type, age, and sex were not shown to be a significant factor for the treatment efficiency. For melanoma patients the local tumor control rates were 72-84% and the median survival were 14.5 months for RPA Class I and 5 months for patients in RPA Class II or III. For RPA Class I and a solitary brain metastasis the median survival was 22 months\(^{(33)}\).

Toxicity. The most common complication of SRS is represented by brain radionecrosis, that may occur in up to 50% of treated lesions. Factors related to the development of radionecrosis include the dose (total dose and prescription isodose), the treated volume, and volume of the brain receiving a specific dose. The volume of brain receiving 10 and respectively 12 Gy (V10 and V12) seems to be the most independent predictors of both symptomatic and asymptomatic, the cut-off value proposed for single-fraction radiosurgery being V10 Gy <10.5 cc and V 12 Gy <7.9 cc.

One major problem for irradiated patients is differential diagnosis between tumor recurrence and radio-necrosis in case of appearance of T1 contrast enhancement MRI images in the irradiated area.

In favour of radio-necrosis are the following criteria:

1) central hypo-intensity (necrosis) with increased peripheral edema in the treated area.
2) a clear absence of perfusion (black hole) within the contrast-enhanced lesion at perfusion MRI.
3) regression or stability (for at least 4 months) of enhancing areas on serial follow-up MRI.

The tumor recurrence is argued by:

1) an intense perfusion within the contrast-enhanced lesion at perfusion MRI.
2) a progression of enhancing lesion on serial MR imaging during a minimum follow-up period of 4 months\(^{(34)}\).
Evidences and recommendations

Surgery versus Radiosurgery

Radiosurgery and surgery are local treatment options for limited number of brain metastases (usually one to three metastases). The advantages of SRS over neurosurgical resection are the non-invasive approach that make it possible even for patients with significant comorbidities and the facility to treat multiple lesions. Radiosurgery might be preferred in patients with lesions of <3-3.5 cm in diameter without mass effect (less than 1 cm midline shift), especially if located in eloquent brain regions or surgically inaccessible regions. SRS is effective in radiosensitive as well as radioresistant histologies due to the single high radiation dose. Surgery is required for histological confirmation of the malignancy and in cases of symptomatic metastases (intracranial hypertension, symptomatic haemorrhage), especially for the large lesions in the posterior fossa. No prospective phase III randomised trial exist to compare surgery with radiosurgery, but retrospective series suggest at least equal efficacy in achieving local tumor control (60–90%) and also in overall patient survival[33].

Radiosurgery versus Whole Brain Radiotherapy

In a German study (University of Cologne) 117 previously untreated patients with one to three brain metastases were treated from 1991 to 1998 by exclusive radiosurgery in one single median dose of 20 Gy (15-25 Gy), without adjuvant WBRT. The most frequent primary tumor type was non-small-cell lung cancer (30%), followed by malignant melanoma (27%). The outcomes of radiosurgery group were compared to a historical group of 138 patients with one to three lesions but treated by WBRT (30-36 Gy/3-Gy fractions). The median Overall Survival was significantly superior for radiosurgery group only for RPA 1 class (25 months versus 4.7 months) but not for RPA 2 (5.9 months vs 4.1 months) and RPA 3 (4.2 months vs 2.5 months) classes[36].

Radiosurgery versus Radiosurgery plus Whole Brain Radiotherapy

The Japanese JROSG 99-1 study was the first randomized Phase III trial comparing Stereotactic radiosurgery (SRT) alone versus SRS plus Whole Brain Radiotherapy (WBRT) on 132 patients with one to four newly diagnosed brain metastases, each less than 3 cm in maximum diameter. All patients were RPA classes I and II (KPS scores of ≥70). The radiation dose was prescribed to the tumor periphery, 22-25 Gy in one fraction for metastases up to 2 cm diameter and 18-20 Gy for...
those larger than 2 cm. For the combination arm the WBRT dose was 30 Gy in 10 fractions, and the SRS dose was reduced by 30%. Overall survival for all patients was not significantly improved by the addition of WBRT, but intracranial failure rates were considerably higher in those patients who did not receive WBRT (SRS alone). The median survival was 8 months for SRS alone against 7.5 months for SRS plus WBRT and the 1-year survival was 28.4% for SRS alone versus 38.5% for SRS plus WBRT (p = 0.42). The intracranial distant recurrence rates were at 1-year 63.7% for SRS alone versus 41.5% for SRS plus WBRT (p = 0.003\(^\text{[37]}\)).

In the United States the Radiation Therapy Oncology Group (RTOG) trial 95-08 randomized 333 patients with one to three newly diagnosed brain metastases to either WBRT or WBRT followed by SRS boost. All patients received WBRT in daily 2.5 Gy fractions to a total of 37.5 Gy over 3 weeks. For the radiosurgery group, the metastases up to 2.0 cm in broadest diameter are irradiated with a surface isodose prescription of 24 Gy, those larger than 2 cm but equal to or smaller than 3 cm with 18 Gy and those larger than 3 cm and less than or equal to 4 cm with 15 Gy, in one fraction. WBRT plus stereotactic radiosurgery provided survival benefit over to WBRT (median survival time 6.5 vs. 4.9 months) to patients with either single metastases, RPA class 1, or a favourable histological status\(^\text{[38]}\).

The neurocognitive function ant its impact on quality of life was studied in the EORTC 22952-26001 study, a Phase III trial on 353 patients with one to three brain metastases ≤3.5 cm (≤2.5 cm each for multiple metastases), stable extracranial disease, and WHO Performance Status (PS) scores of 0–2. They are treated with SRS alone (100 patients), surgery alone (79 patients) or local treatments with WBRT (99 with SRS plus WBRT and 81 with surgery plus WBRT). SRS median tumor surface dose was 20 Gy (range 14–25 Gy) and the WBRT prescription dose was 30 Gy in 10 fractions.

The primary end point was time to deterioration of performance scale to a level of ≤3 (i.e., capable of only limited self-care, or confined to a bed or chair for more than 50% of waking hours), and secondary end points included intracranial relapse, progression-free and overall survival, and late toxicities (quality of life data planned to be reported separately). Like in Japanese study the median overall survival was not significantly different between the two groups (10.7 months for no WBRT vs 10.9 months for WBRT, p = 0.89), but the overall intracranial progression at 2 years was significantly higher for patients without WBRT (78 vs. 48%; p < 0.001) and represent a major component of cause of death (44 vs 28%; p < 0.002). The authors conclusion is that WBRT after either surgery or SRS significantly reduced the probability of relapse at initial and new cerebral sites, but without significant benefice in terms of functional independence and median survival. No differences in toxicity rates were seen\(^\text{[39]}\).

**Recommendations**

**General recommendations**

American Society for Radiation Oncology (ASTRO) evidence-based recommendations:

1. The addition of fractionated whole brain radiotherapy (WBRT) after surgical resection of brain metastases does not improve overall survival or duration of functional independence, but improves treated brain metastasis control and overall brain control.
2. In patients with good prognosis and single brain metastasis (<3 cm), either surgery or radiosurgery may be considered.
3. Selected patients with brain metastasis(es) may be treated with radiosurgery alone.
4. Radiotherapy boost added to WBRT in patients with multiple brain metastases and good prognosis improves control over treated brain metastases as compared with WBRT alone\(^\text{[20, 27, 28]}\).
5. Two randomized trials showed that omission of WBRT after radiosurgery is associated with better neurocognitive outcomes and with better health related quality of life.
6. The randomized trial RTOG 9508 found an improvement in KPS and decreased steroid use at 6 months with the use of radiosurgery boost added to WBRT
7. WBRT alone may be considered, as there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases\(^\text{[40]}\).

**Radiosurgery recommendations**

Patients. Only patients with RPA classes I and II benefits (KPS ≥ 70 that mind Cares for self; unable to carry on normal activity or to do active work) with an life expectancy more than 3 months can be candidate for radiosurgery.

Brain metastases. Standard indication of radiosurgery remains for the patients with one to three brain metastases up to 3 cm maximal diameter. Multiple (>4) lesions can eventually being treated with fractionated radiosurgery, depending on metastases cumulative volume.

Dose and Volume: 24 Gy for < 2 cm, 18 Gy for 21-30 mm and 15 Gy for 31-40 mm, PTV=GTV + 1-2 mm.

Medication: Corticosteroids (to prevent perifocal edema) and anxiolytics 1 hour before the procedure.

Follow-up: Brain IRM 6 to 8 weeks after the radiosurgery and then every 3 months.

Adjuvant WBRT: increases local control but does not prolong survival when compared with radiosurgery and salvage treatment. A cause of neurocognitive risk it seems reasonable to withhold WBRT for as long as possible.
Conclusions

The chemotherapy regimens are still not sufficiently reliable as treatment options for brain metastases and local treatments are necessary. For single or few brain metastases the stereotactic radiosurgery provides highly effective and predictable local tumour control, equivalents to surgery , even for conventionally radioresistant metastases from melanoma or renal cancer. After a minimum doses of 18 Gy the reported local tumor control are 73–90% for melanoma brain metastases. Moreover the avoidance of WBRT can have a positive impact on the patient’s cognitive status and health related quality of life.