Chapter 9
Secondary Malignant (Metastases)

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Brain metastasis is the most common indication for stereotactic radiosurgery (SRS). SRS is a safe and effective treatment modality for patients with good performance status and limited number of brain metastases. In addition, SRS serves as an adjuvant therapy for resected brain lesions. Accumulating studies also support the use of hypofractionated stereotactic radiotherapy (HSRT) delivering 27–35 Gy in 3–5 fractions for relatively large brain lesions and resection beds.

9.1 Pearls

- Brain metastases are the most common intracranial tumors in adults.
- Incidence of brain metastases has been increasing due to improvement in detection with MRI and improvement in extracranial disease control with systemic therapy.
- Up to 30% of patients with cancer develop brain metastases.
- Common primary malignancies metastasizing to the brain include lung cancer, breast cancer, melanoma, and renal cell cancer.
- Metastases are most commonly located at the grey-white matter junction.
- Distribution of metastases is approximately proportional to the blood flow to the different parts of the brain: cerebral hemispheres (80%), cerebellum (15%), and brainstem (5%).
- Patients commonly present with headaches, focal neurologic dysfunction, cognitive dysfunction, seizures, and/or stroke.

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- The imaging study of choice is a contrast-enhanced brain MRI. Brain metastases are suspected by the presence of multiple lesions, localization at the grey-white matter junction, circumscribed margins, and presence of vasogenic edema.

9.2 Prognosis Based on Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)

Non-small cell lung cancer (Lung-molGPA) [1].

	GPA scoring criteria		
Prognostic factor	0	0.5	1.0
Age (years)	≥70	<70	–
KPS	≤70	80	90–100
ECM	Present	–	Absent
No. of BM	>4	1–4	–
Gene status	*EGFR* neg/unk and *ALK* neg/unk	–	*EGFR* pos or *ALK* pos
Median survival (months) by GPA score	Adenocarcinoma: 0–1.0 = 6.9; 1.5–2.0 = 13.7; 2.5–3.0 = 26.5; 3.5–4.0 = 46.8 Non-adenocarcinoma: 0–1.0 = 5.3; 1.5–2.0 = 9.8; 2.5–3.0 = 12.8		

Abbreviations: *KPS* Karnofsky performance score, *ECM* extracranial metastases, *BM* brain metastases, *neg/unk* negative or unknown, *pos* positive

Melanoma (Melanoma-molGPA) [2].

	GPA scoring criteria		
Prognostic factor	0	0.5	1.0
Age (years)	≥70	<70	
KPS	≤70	80	90–100
ECM	Present	–	Absent
No. of BM	>4	2–4	1
BRAF gene status	Negative/unknown	Positive	
Median survival (months) by GPA score	0–1.0 = 4.9; 1.5–2.0 = 8.3; 2.5–3.0 = 15.8; 3.5–4 = 34.1		

Abbreviations: *KPS* Karnofsky performance score, *ECM* extracranial metastases, *BM* brain metastases

Breast cancer [3].

Prognostic factor	GPA scoring criteria				
	0	0.5	1.0	1.5	2.0
KPS	≤50	60	70–80	90–100	–
Subtype[a]	Basal	–	LumA	HER2	LumB
Age (years)	≥60	<60	–	–	–
Median survival (months) by GPA score	0–1.0 = 3.4; 1.5–2.0 = 7.7; 2.5–3.0 = 15.1; 4.5–4.0 = 25.3				

Abbreviations: *KPS* Karnofsky performance score
[a]Breast cancer subtype: Basal—triple negative; LumA—ER/PR positive, HER2 negative; HER2—ER/PR negative, HER2 positive; LumB—triple positive

Renal cell carcinoma [3].

Prognostic factor	GPA scoring criteria		
	0	1	2
KPS	<70	70–80	90–100
No. of BM	>3	2–3	1
Median survival (months) by GPA score	0–1 = 3.3; 2 = 7.3; 3 = 11.3; 4 = 14.8		

Abbreviations: *KPS* Karnofsky performance score, *BM* brain metastases

GI cancers [3].

Prognostic factor	GPA scoring criteria				
	0	1	2	3	4
KPS	≤60	70	80	90	100
Median survival (months) by GPA score	0–1 = 3.1; 2 = 4.4; 3 = 6.9; 4 = 13.5				

Abbreviations: *KPS* Karnofsky performance score

9.3 Tumor/Patient Selection

- SRS is generally recommended for patients with good performance status (KPS ≥70).
- Patients with brain metastases and a KPS <70 have poor overall prognosis, and should be considered for whole-brain radiotherapy (WBRT) versus best supportive care [4].
- Indications for SRS:
  - 1–4 brain metastases and surgery are not feasible secondary to location, comorbidities, or patient preference.
  - Status post-resection of a dominant or a few brain metastases (postoperative RT).

- SRS can also be considered for patients with good performance status and 4–10 brain metastases with low tumor burden (i.e., total volume of disease in the brain is low) [5].
- For patients with limited number of brain metastases, adding WBRT to SRS is generally not recommended. Although SRS + WBRT improves local and distant brain control, it leads to significant cognitive decline without improvement in overall survival [6, 7].
- Dose and fractionation are selected based on size and setting (refer to 9.5 and 9.9 for details):
  - For lesions ≤40 mm, a single-fraction SRS is given with doses of 15–24 Gy based on size.
  - For larger lesions or lesions near critical structures such as the brainstem and optic apparatus, a lower dose (12–14 Gy) can be used in a single-fraction SRS or Fractionated stereotactic radiotherapy (FSRT) with doses of 24–35 Gy in 3–5 fractions.
  - In the postoperative setting, SRS/HSRT to the surgical bed in 1–5 fractions is an alternative to WBRT.
- Re-irradiation with SRS is used in some institutions as salvage therapy for local failure after initial SRS. Several retrospective series report good local control rates but relatively high risk of radiation necrosis [8]. For select patients (surgically inaccessible local recurrence, small and limited number of lesions, etc.), repeat SRS may be an option, but the authors urge caution.

9.4 Treatment Planning Considerations

Simulation instructions	– Position: Supine – Immobilization: Customized head cast – 1 mm thick CT slices – Fuse MR brain (1 mm slices preferred) to help delineate target volume – Fuse pre- and postoperative MR for surgical bed treatment
Image guidance	Linac: Daily cone beam CT CyberKnife: Continuous skull tracking
Margins	– The authors use no CTV or PTV expansions for intact brain metastasis (Figs. 9.1 and 9.2) – Consider 1–2 mm expansion of postoperative bed CTV for resected brain metastasis (Fig. 9.3)
Tumor coverage considerations	– 100% of GTV (or CTV for postoperative cases) receives 100% of Rx (if GTV/CTV ≤20 mm) – ≥95% of GTV (or CTV for postoperative cases) receives 100% of Rx (if GTV/CTV >20 mm)

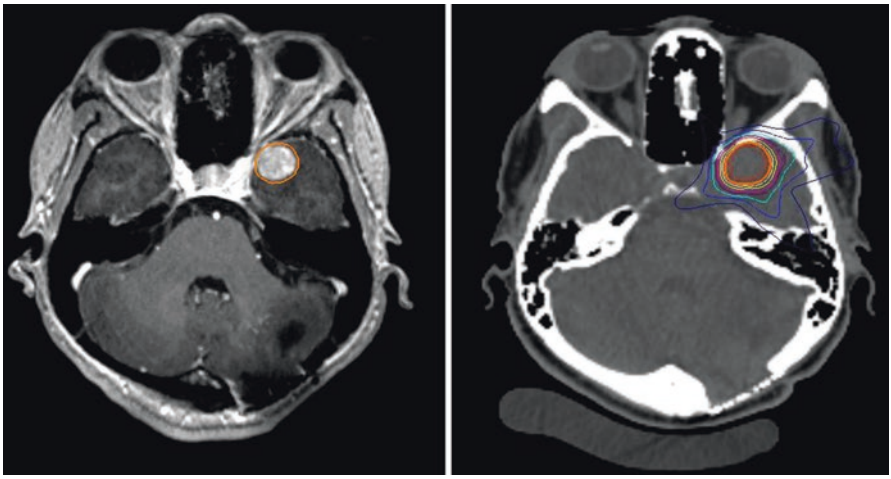

Fig. 9.1 Contouring of a left temporal lobe metastasis based on contrast-enhanced MR brain (left) and the treatment plan sparing optic structures (right)

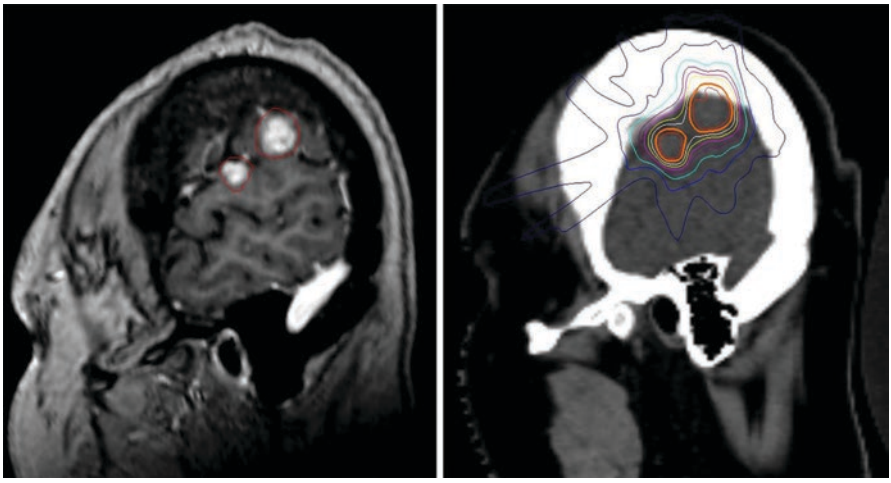

Fig. 9.2 Sagittal view of two adjacent left temporal brain metastases (left) and the treatment plan targeting both lesions (right)

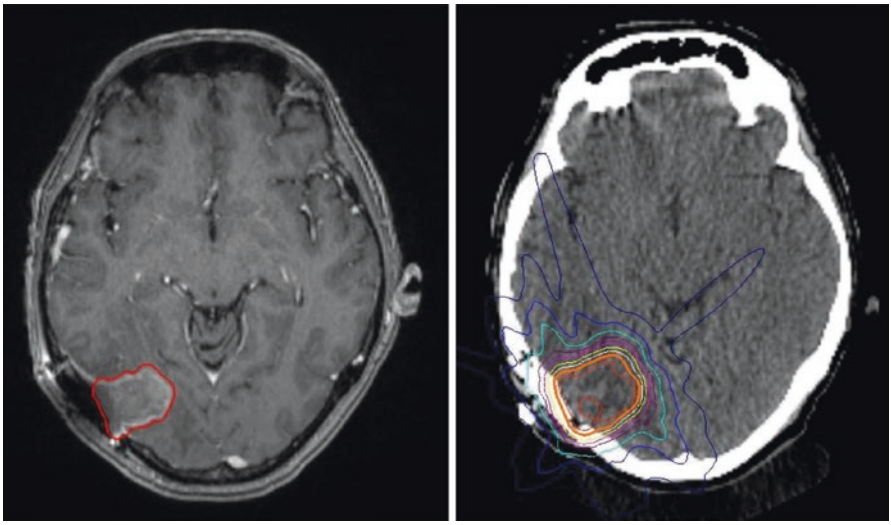

Fig. 9.3 Contouring of a right occipital surgical bed following a resection of a renal cell metastasis based on the postoperative contrast-enhanced MR brain (left) and the treatment plan (right)

9.5 Commonly Used Dose/Fractionation Schemes

Dose per fraction (Gy)	# of fractions	Total dose (Gy)	Notes
SRS for intact lesions			
RTOG 90–05 [9]			
20–24	1	20–24	≤20 mm
18	1	18	21–30 mm
15	1	15	31–40 mm
Hypofractionated stereotactic radiotherapy			
Manning 2000 [10]			
9	3	27	≤3 brain mets, median dose
Aoyama 2003 [11]			
8.75	4	35	≤4 brain mets, median dose
Ernst-Stecken 2006 [12]			
6	5	30	If combined with WBRT
7	5	35	All others
Murai 2014 [13]			
9–10	3	27–30	25–39 mm
6.2–7	5	31–35	≥40 mm
Postoperative SRS			
Minniti 2013 [14]			
9	3	27	>30 mm
N107C/CEC.3 [15]			

Dose per fraction (Gy)	# of fractions	Total dose (Gy)	Notes
20	1	20	<4.2 cc
18	1	18	≥4.2 and <8.0 cc
17	1	17	≥8.0 and <14.4 cc
15	1	15	≥14.4 and <20 cc
14	1	14	≥20 and <30 cc
12	1	12	≥30 cc and <5 cm
Mahajan 2016 [16]			
16	1	16	≤10 cc
14	1	14	10.1–15 cc
12	1	12	>15 cc

For intact lesions, the authors use 20 Gy × 1 = 20 Gy if ≤20 mm, 18 Gy × 1 = 18 Gy if 21–30 mm, and 6 Gy × 5 = 30 Gy if >30 mm. In general, postoperative CTV is >30 mm and 6 Gy × 5 = 30 Gy is used

9.6 Normal Tissue Tolerances

	TG101	QUANTEC	Our institutional practice
Brain parenchyma			
One fraction	NA	V12 <5–10 cc	V12 <10 cc
Toxicity	NA	<20% symptomatic necrosis	<20% symptomatic necrosis
Brainstem			
One fraction Three fractions Five fractions	Dmax ≤15 Gy, V10 <0.5 cc Dmax ≤23.1 Gy, V18 <0.5 cc Dmax ≤31 Gy, V23 <0.5 cc	Dmax <12.5 Gy	Same as TG101
Toxicity	≥grade 3 cranial neuropathy	<5% permanent cranial neuropathy or necrosis	≥grade 3 cranial neuropathy
Optic pathway			
One fraction Three fractions Five fractions	Dmax ≤10 Gy, V8 <0.2 cc Dmax ≤17.4, V15.3 <0.2 cc Dmax ≤25, V23 <0.2 cc	Dmax <12 Gy	Same as TG101
Toxicity	≥grade 3 neuritis	<10% optic neuropathy	≥grade 3 neuritis
Spinal cord			
One fraction Three fractions Five fractions	Dmax ≤14 Gy, V10 <0.35 cc, V7 <1.2 cc Dmax ≤21.9 Gy, V18 <0.35 cc, V12.3 <1.2 cc Dmax ≤30 Gy, V23 <0.35 cc, V14.5 <1.2 cc	Dmax = 13 Gy	Same as TG101

	TG101	QUANTEC	Our institutional practice
Toxicity	≥grade 3 myelitis	1% myelopathy	≥grade 3 myelitis
Cochlea			
One fraction Three fractions Five fractions	Dmax ≤9 Gy Dmax ≤17.1 Gy Dmax ≤25 Gy	Dose ≤14 Gy (prescription dose)	Same as TG101
Toxicity	≥grade 3 hearing loss	<25% sensory neural hearing loss	≥grade 3 hearing loss

9.7 Patient Management Considerations

- Premedication: If the patient is not already on steroids, premedicate with dexamethasone 4 mg PO prior to each fraction. Lorazepam 0.5–1 mg PO can be used prior to each fraction.
- Acute toxicities can include mild nausea, headaches, and in rare cases, new-onset seizures.
- The main dose-limiting late toxicity of SRS is radiation necrosis, which occurs in 5–10% of cases, 6 months to years after treatment.
  - Factors associated with increased risk of radiation necrosis include larger size of the brain metastasis and a history of prior radiation to the same region. Other tumor biology characteristics including renal cell or lung adenocarcinoma histology, HER2 amplification, and ALK/BRAF mutation may increase the risk of radiation necrosis [17].
  - Radiation necrosis is managed conservatively if asymptomatic or with moderate-dose steroids (e.g., dexamethasone 4 mg BID) if symptomatic. Surgical resection for palliation may be needed in severe cases.

9.8 Follow-Up

- According to NCCN guidelines [18]:
  - Brain MRI q2–3 months for the first year
  - Follow-up and imaging as clinically indicated after 1 year

9.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcomes
Dose escalation				
RTOG 90–05 [9] (phase I trial)	*N* = 156 Patients previously treated with WBRT	SRS dose escalation: ≤ 20 mm: 18 –> 21 –> 24 Gy 21–30 mm: 15 –> 18 –> 21 –> 24 Gy 31–40 mm: 12 –> 15 –> 18 Gy	3 years	– Maximum tolerated dose: ≤ 20 mm: 24 Gy 21–30 mm: 18 Gy 31–40 mm: 15 Gy – Total grade 3–5 toxicity: ≤ 20 mm: 18 Gy (8%), 21 Gy (11%), 24 Gy (10%) 21–30 mm: 15 Gy (13%), 18 Gy (20%), 21 Gy (38%), 24 Gy (58%) 31–40 mm: 12 Gy (10%), 15 Gy (14%), 18 Gy (50%)
WBRT ± SRS boost				
RTOG 95–08 [19] (randomized trial)	*N* = 333 KPS ≥70, 1–3 mets ≤40 mm	1. WBRT (37.5 Gy) 2. WBRT + SRS boost (15–24 Gy per RTOG 90–05)	Not reported	1. **WBRT** – 5.7-month median OS – 4.9-month median OS (single met) – 71% 1-year LC – 27% stable/improved KPS at 6 months 2. **WBRT + SRS** – 6.5-month median OS (p = NS) – 6.5 months (single met) (p = 0.039) – 82% 1-year LC (p = 0.013) – 43% stable/improved KPS at 6 months (p = 0.03)
SRS ± WBRT				
JROSG 99–1 [20] (randomized trial)	*N* = 132 KPS ≥70, 1–4 mets ≤30 mm	1. SRS (18–25 Gy) 2. SRS (30% reduction) + WBRT (30 Gy)	7.8 months (entire study) 49.2 months (survivors)	1. **SRS** – 8-month median OS – 73% 1-year LC – 76% 1-year brain tumor recurrence 2. **SRS + WBRT** – 7.5-month median OS (p = NS) – 89% 1-year LC (p = 0.002) – 47% 1-year brain tumor recurrence (p < 0.001)

Study	Patients	Treatment	Median f/u	Outcomes
Chang 2009 [6] (randomized trial)	*N* = 58 KPS ≥70, 1–3 mets	1. SRS (15–20 Gy) 2. SRS + WBRT (30 Gy)	9.5 months	1. **SRS** – 15.2-month median OS – 67% 1-year LC – 24% mean probability of neurocognitive decline at 4 months 2. **SRS + WBRT** – 5.7-month median OS ($p = 0.003$) – 100% 1-year LC ($p = 0.01$) – 52% mean probability of neurocognitive decline at 4 months
EORTC22952–26001 [21] (randomized trial)	*N* = 359 ECOG 0–2, 1–3 mets ≤35 mm	1. SRS (14–25 Gy) 2. SRS + WBRT (30 Gy)	1. **SRS:** 40 months 2. **SRS + WBRT:** 49 months	1. **SRS:** – 10.7-month median OS – 69% 2-year LC 2. **SRS + WBRT** – 10.9-month median OS (p = NS) – 81% 2-year LC ($p = 0.04$)
Brown 2016 [7] (randomized trial)	*N* = 213 ECOG 0–2, 1–3 mets < 30 mm	1. SRS (20–24 Gy) 2. SRS (18–22 Gy) + WBRT (30 Gy)	7.2 months	1. **SRS** – 10.4-month median OS – 73% 1-year LC – 64% cognitive deterioration at 3 months – 0.1 mean decline from baseline in overall quality-of-life score 2. **SRS + WBRT** – 7.4-month median OS (p = NS) – 90% 1-year LC ($p = 0.003$) – 92% cognitive deterioration at 3 months ($p < 0.001$) – 12 mean decline from baseline in overall quality-of-life score ($p = 0.001$)

Study	Patients	Treatment	Median f/u	Outcomes
Number of metastases				
Likhacheva 2013 [22] (retrospective study)	*N* = 251 brain mets (median 2, range 1–9)	– SRS alone (62% of patients, median dose: 20 Gy) – SRS + salvage SRS (22%), WBRT (13%), or surgery (3%)	9.4 months	– 11.1-month median OS – 94.6% 1-year LC – Factors associated with OS on multivariable analysis: Total tumor volume >2 cc, age ≥60, diagnosis-specific graded prognostic assessment, and extracranial disease – Number of brain mets not associated with OS
JLGK0901 [5] (prospective observational cohort study)	*N* = 1194 KPS ≥70, 1–10 brain mets < 3 cm each, <10 cc each, ≤15 cc total volume	SRS: <4 cc: 22 Gy 4–10 cc: 20 Gy	20.9 months (survivors)	1. **1 metastasis** – 13.9 median OS – 7% any grade toxicity 2. **2–4 metastases** – 10.8 median OS – 9% any grade toxicity 3. **5–10 metastases** – 10.8 median OS (p = NS vs. 2–4 metastases) – 9% any grade toxicity (p = NS vs. 2–4 metastases)
Hypofractionated stereotactic radiotherapy				
Manning 2000 [10] (phase II)	*N* = 32 ≤3 brain mets	HSRT with a linac Median 9 Gy × 3 = 27 Gy to the 80–90% isodose line	37 weeks (survivors)	– 11.8-month median OS – Acute toxicity: None – Late toxicity: Seizures (13%), radionecrosis (6%)
Ernst-Stecken 2006 [12] (phase II)	*N* = 51 KPS ≥60, ≤3 brain mets	HSRT with a linac 7 Gy × 5 = 35 Gy to the 90% isodose line 6 Gy × 5 = 30 Gy if additional WBRT	7 months	– 11-month median OS – 76% 1-year LC – Acute toxicity: None – Increasing rates of edema and necrosis if V4 ≥23 cc
Ammirati 2014 [23] (phase II)	*N* = 40 KPS ≥60, ≤3 brain mets	HSRT with a linac 6 Gy × 5 = 30 Gy Definitive or adjuvant following a surgical resection	16 months	– 16-month median OS – 11-month median PFS – 13% neurological death rate – Acute toxicity: None – Late toxicity: 8% radiation necrosis

Study	Patients	Treatment	Median f/u	Outcomes
Aoyama 2003 [11] (retrospective)	*N* = 87 ≤4 brain mets	HSRT with a linac Median 35 Gy/4 fx to the 80–90% isodose line	6.3 months (entire study) 7.6 months (survivors)	– 8.7-month median OS – 81% 1-year LC – Acute toxicity: 2% nausea, 1% hypomnesia, 1% seizure – Late toxicity: 1% nausea, 1% hemiparesis
Murai 2014 [13] (retrospective)	*N* = 54 brain mets ≥2.5 cm	HSRT with a linac Dose escalation: 3fx (2.5–3.9 cm): 18–22 Gy to 27–30 Gy 5 fx (≥ 4 cm): 21–25 Gy to 31–35 Gy	Not reported	– 6-month median OS – 78% 1-year LC – No ≥grade 3 toxicity at every level of dose
Postoperative SRS				
Mahajan 2016 [16] (randomized trial)	*N* = 131 1–3 mets, ≥1 met with complete resection, ≤4 cm resection cavity	1. SRS (12–16 Gy) 2. observation of the resection cavity	11.1 months	1. **SRS** – 17-month median OS – 72% 1-year LC 2. **Observation** – 18-month median OS (p = NS) – 43% 1-year LC (p = 0.015)
N107C/CEC.3 [15] (randomized trial)	*N* = 194 1–4 mets, s/p surgical resection of 1 met, <5 cm resection cavity	1. SRS (12–20 Gy) 2. WBRT (30 or 37.5 Gy) Unresected mets treated with SRS in both arms	11.1 months	1. **SRS** – 12.2-month median OS – 3.7-month cognitive deterioration-free survival – 60.5% 1-year surgical bed control – 36.6% 1-year overall brain control 2. **WBRT** – 11.6-month median OS (p = NS) – 3.0-month cognitive deterioration-free survival (p < 0.0001) – 80.6% 1-year surgical bed control (p = 0.00068) – 72.1% 1-year overall brain control (p < 0.0001)
Brennan 2014 [24] (phase II)	*N* = 49 1–2 brain mets s/p resection	SRS with a linac ≤ 2 cm: 22 Gy 2.1–3 cm: 18 Gy 3.1–4 cm: 15 Gy	12 months	– 78% 1-year LC – 56% 1-year distant brain control – Toxicity: 17.5% with radionecrosis

Study	Patients	Treatment	Median f/u	Outcomes
Jensen 2011 [25] (retrospective)	*N* = 106 s/p surgical resection, no prior WBRT	SRS with GammaKnife Median dose of 17 Gy to the 50% isodose line	Not reported	– 10.9-month median OS – 80.3% 1-year LC – 35.4% 1-year distant brain control – 37% received salvage WBRT at a median of 12.6 months
Choi 2012 [26] (retrospective)	*N* = 112 s/p surgical resection	SRS with CyberKnife Median dose of 20 Gy in 1–5 fx to a median 79% isodose line, 2 mm margin	11 months	– 17-month median OS – 90.5% 1-year LC – 46% 1-year distant brain control – 28% received salvage WBRT at a median on 7 months
Minniti 2013 [14] (retrospective)	*N* = 101 s/p surgical resection (resection cavity >3 cm)	SRS with a linac 9 Gy × 3 = 27 Gy to a median 83% isodose line, 2 mm margin	16 months	– 17-month median OS – 93% 1-year LC – 50% 1-year distant brain control – 24% received salvage WBRT

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