

A Review of Stereotactic Radiosurgery Practice in the Management of Skull Base Meningiomas

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J Neurol Surg B 2014;75:152–158.

Abstract

Gross total resection of skull base meningiomas poses a surgical challenge due to their proximity to neurovascular structures. Once the gold standard therapy for skull base meningiomas, microsurgery has been gradually replaced by or used in combination with stereotactic radiosurgery (SRS). This review surveys the safety and efficacy of SRS in the treatment of cranial base meningiomas including 36 articles from 1991 to 2010. SRS produces excellent tumor control with low morbidity rates compared with surgery alone for asymptomatic small skull base meningiomas, patients with risk factors precluding conventional surgery, and as adjuvant therapy for recurrent or residual lesions.

Keywords

- ▶ meningiomas
- ▶ radiosurgery
- ▶ surgery
- ▶ skull base
- ▶ stereotactic

Introduction

Skull base meningiomas, including tumors arising from the dura of the clivus and petrous bone, sinus and tentorium, sphenoid bone, olfactory groove, and optic nerve sheath, represent 35 to 50% of all intracranial meningiomas.^{1–3} Tumors in these regions are often difficult to resect completely because of limited surgical access and intimate association with critical neurovascular structures.^{1,3–5} Microsurgery has traditionally been considered the treatment of choice for most skull base meningiomas, although rates of recurrence can be as high as 25% at 10 years after gross total resection.^{6,7} Recurrence may be significantly higher following subtotal resection (STR) or inadequate removal of the adjacent dura.^{5,6} Additionally, surgical resection carries a significant risk of damage to cranial nerves, especially in cases involving the

cavernous sinus, with rates of surgical morbidity approaching 30 to 40%.^{6,8}

Radiation-based therapies for skull base meningiomas offer several potential advantages over traditional surgical approaches. Subtotal resection followed by adjuvant radiation may reduce surgical morbidity, preserve neurologic function, and potentially provide better tumor control.¹ Stereotactic radiosurgery (SRS) as a stand-alone treatment can yield similar results to Simpson grade I resection for small and midsize meningiomas.⁹

For > 2 decades, gamma knife (GK) and linear accelerator (LINAC) have been used extensively in the radiosurgical treatment of skull base meningiomas. Meningiomas are particularly suitable tumors for treatment with SRS because they are often small at the time of diagnosis, well demarcated, accurately defined by computed tomography (CT) or

received

May 14, 2013

accepted after revision

July 1, 2013

published online

March 12, 2014

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0033-1354747>.
ISSN 2193-6331.

magnetic resonance imaging (MRI), rarely invade the brain, and derive their blood supply from the dura.^{1,10-12} SRS aims to achieve long-term tumor control with minimal morbidity and maximal functional outcomes.^{6,8,12,13} As an outpatient procedure, SRS may also be a cost-effective treatment option. We have surveyed the available published literature to outline the evidence, indications, and limitations of SRS practice in the treatment of skull base meningiomas.

Indications

The primary role of radiosurgery is to control small well-demarcated lesions while preserving the function of surrounding brain tissue and neighboring cranial nerves.¹⁴ As such, many skull base meningiomas are suitable for SRS, whereas open surgery in this region can be associated with a high risk of cranial nerve, brainstem, and vascular damage.^{9,11} Four main indications exist for which SRS may be considered as a primary or secondary treatment strategy for skull base meningiomas including patients unfit for surgery, small or residual cavernous sinus, and recurrent meningiomas (► **Table 1**).

Patients Unfit for Surgery

Meningiomas frequently occur in elderly patients whose preexisting medical conditions may heighten surgical or anesthetic risks.^{2,9,12,13,15-18} In young patients, the primary treatment goal is complete lesion destruction by surgery, surgery plus SRS, or SRS alone because this provides better long-term outcomes than conservative management. However, depending on the life expectancy due to age and certain medical conditions, halting the tumor progression is a reasonable goal in elderly patients. In addition, elderly patients unfit to receive general anesthesia due to preexisting medical conditions can benefit greatly from treatment with radiosurgery. Furthermore, radiosurgery can be a primary treatment option in patients unwilling to undergo surgery.

Small or Residual Skull Base Meningiomas

For small (average diameter < 3 cm) or residual skull base meningiomas, SRS leads to excellent long-term control.^{3,9,11,13,17-25} Additionally, meningiomas associated with no or minimal surrounding edema, no elevated intra-

cranial pressure, or no neurologic deficits are suitable for radiosurgery. For large skull base meningiomas (average diameter > 3 cm) or those in critical locations, SRS has been reported to provide rates of durable tumor control and low morbidity comparable with those reported with fractionated radiotherapy (FRT) and may thus be a safe treatment modality either following STR or as primary treatment in patients with significant comorbidity. Several series have demonstrated that skull base benign meningiomas with a tumor volume of at least 10 cm³ are associated with higher rates of recurrence, increased edema, and permanent neurologic deficits, suggesting that these tumors should first undergo STR to relieve mass effect and thereafter undergo SRS. Tumor debulking by surgical resection before radiosurgery results in the advantage of treating a smaller tumor volume with SRS.

Cavernous Sinus Meningiomas

Meningiomas located in and around the cavernous sinus are difficult to resect because of the high risk of neurovascular damage, particularly if they involve the cranial nerves, internal carotid artery (ICA), or pituitary.^{4,9,11,15,20} Radiosurgery, because of its excellent tumor control rate and minimal rate of morbidity, has been shown to be an effective and safe treatment. Due to the high surgical morbidity and effectiveness of radiosurgery, primary SRS should be considered for cavernous sinus meningiomas with diameters < 3 cm. However, a distinction needs to be made between “holocavernous” meningiomas and meningiomas of the lateral wall of the cavernous sinus, in which the latter are eminently surgically resectable.

Recurrent Meningioma

Patients with recurrent or residual skull base meningiomas after aggressive resection should receive SRS rather than undergo open resection.^{2,8,13,16,21} For instance, in cases where a small amount of residual tumor of the cerebello-pontine angle needs to be left unresected to preserve facial function and hearing, SRS can be used to treat the residual portion.

In addition to these indications, several other situations may be considered suitable for SRS on an individual case basis. The optimal treatment for petroclival meningiomas

Table 1 Indications

	Treatment	Indications	Reference
Patients unfit for surgery	Primary	Elderly patients with preexisting conditions Patients unfit to receive general anesthesia	2,9,12,13,15-18
Small or residual meningioma	Primary Secondary	Small, neurologically asymptomatic (average diameter < 3 cm) Small, neurologically symptomatic (average diameter < 3 cm) Large (average diameter > 3 cm) Involvement of critical structures	3,9,11,13,17-25
Cavernous sinus meningioma	Primary	Holocavernous Cranial nerves, intracranial artery, or pituitary involvement	4,9,11,15,20
Recurrent meningioma	Primary	Recurrence or residual following aggressive resection	2,8,13,16,21

remains controversial, with some authors arguing for primary resection for small tumors with adjuvant radiosurgery to decrease recurrence because reoperation is technically challenging.²¹ Others propose that even initial gross total resection is only possible in a minority of cases and therefore SRS alone is the preferred initial treatment strategy.²⁰ Petroclival meningiomas are almost always medial to the fifth cranial nerve and closely adhere to the brainstem arachnoid mater. However, in our experience, debulking the tumor is possible with anterior or posterior petrosal approaches, or a combination of both. Any residual tumor is treated with radiosurgery to prevent growth and recurrence.²⁰

Foramen magnum meningiomas that involve the vertebral artery or cranial nerves should also undergo partial resection, with the residual tumor either observed (in young healthy patients) or targeted with SRS (especially in older patients).²¹ For recurrent foramen magnum meningiomas, radical surgery is not always possible, with surgery potentially resulting in morbidity of the ninth and tenth cranial nerves and an extended hospital stay. In these cases, SRS is preferable due to very low risk. Finally, radiosurgery can be used to treat malignant meningiomas, although some consider FRT to be a better treatment option for these higher grade meningiomas.^{16,22,26,27} SRS is thus an effective primary alternative to surgical resection of small to moderate size benign basal meningiomas, and as adjuvant therapy to reduce the risk of tumor recurrence and morbidity in STRs.^{1,2,9}

Contraindications

In contrast to the variety of indications for SRS, there are only a few relative contraindications to SRS for skull base meningiomas. In the era of increased MRI availability, incidentally identified small asymptomatic tumors should be treated conservatively.¹³ The long natural history of benign meningiomas, which can extend to ≥ 10 years, suggests that routine clinical and radiologic follow-up can be recommended for elderly or medically infirm patients in whom a meningioma is unlikely to cause significant acute morbidity or mortality.^{8,28}

When the risk of SRS is unacceptably high, such as in large tumors or those within 2 to 4 mm of critical structures (e.g., the optic apparatus or brainstem), another modality, such as stereotactic radiotherapy (SRT), is a potentially better treatment option.^{2,3,5,11,16,29} Small basal meningiomas (average diameter < 3 cm) presenting with neurologic symptoms may benefit from immediate surgical decompression followed by SRS for residual tumor.^{9,11,13,25,27} Surgical resection is recommended for patients with increasing neurologic deficit, with particular concern given to rapidly progressive vision loss, due to compression of the brain, brainstem, or optic apparatus. Patients with pretreatment edema should also undergo surgery because the risk of worsening edema and permanent neurologic sequelae are greater with SRS than with primary surgical resection. SRS for lesions with volumes > 10 cm³ has been associated with lower tumor control rates and higher morbidity, with post-SRS complications reaching up to 13%.^{14,29,30} Patients with atypical findings on imaging should first undergo surgery to obtain a histologic diagno-

sis.¹⁶ This prevents the possibility of an incorrect diagnosis, which has been reported in up to 2% of cases treated with radiosurgery.

Radiosurgical Planning

When planning treatment with SRS, MRI is most useful for defining the tumor, but CT allows for direct measurement of tissue photon attenuation, which is necessary for calculating the precise dose needed.¹¹ Thus for small to midsized meningiomas, the combined use of CT/MRI is best because it provides the most information for optimum management.

The prescription dose should take into account tumor volume, proximity to organs at risk, and previous irradiation.^{12,20} Given that cranial base meningiomas are located in a region that includes critical structures (e.g., cranial nerves, the brainstem, small and large vessels, venous sinuses, and the cochlea), careful planning is needed to deliver a conformal isodose that completely covers the tumor while minimally affecting surrounding structures.^{10,12,25}

Median radiation doses of 12, 12.6, and 13 Gy to skull base meningiomas have been correlated with 5-year progression-free survival (PFS) rates of 98.5%, 97.9%, and 93%, respectively.^{8,11,29} One study found a tumor control rate of 98% at 7 years with the use of 14 to 15 Gy.³¹ Kreil et al⁸ and Nicolato et al³² reported low complication rates of 2.5 to 4% with marginal doses of 12 to 14 Gy; Iwai et al reported a 6% incidence of complications and a 10-year PFS of 86% in patients treated with doses of 8 to 12 Gy.⁵ Taken together, these findings suggest that the dose at the tumor margin should be 18 Gy for meningiomas < 1 cm in diameter, 16 Gy for tumor diameters between 1 and 3 cm, and 12 to 14 Gy for tumor diameters > 3 cm.^{11,20} Small tumors receive a higher dose to the margin because of the steeper falloff of radiation at smaller volumes.¹² Given that invasion of the dural tail usually occurs 1 to 2 mm beyond the tumor, the first several millimeters of adjacent dura should also be targeted.¹¹

Partially irradiated tumors are more likely to recur. Shin et al reviewed radiosurgical treatment of cavernous sinus meningiomas and found that although tumors targeted with a marginal dose ≥ 14 Gy showed local control of 100%, those treated with only 10 to 12 Gy had a local control of 80%.³³ In another study, doses < 12 Gy were associated with general meningioma control failure, whereas doses > 16 Gy were associated with increased edema without improved local tumor control, with anterior skull base and parasagittal meningioma at particular risk.²⁹ Kondziolka and colleagues also found that margin doses > 15 Gy do not provide better tumor control.¹³ Thus it appears that margin doses between 12 and 16 Gy provide the best balance of excellent tumor control with acceptable toxicity.^{5,11,29} In addition to these general considerations, specific considerations relating to nervous tissue, brainstem, and vessels must be taken into account when planning radiosurgical intervention.

Cranial Nerves

Different classes of cranial nerves have distinct tolerances for radiation.²⁵ For instance, special sensory nerves (e.g., the

optic nerve) are able to tolerate doses < 8 to 10 Gy with marginal risks, whereas somatic efferent nerves (e.g., the oculomotor nerve) can tolerate doses > 20 Gy.^{2,5,8,10-12,25} The trigeminal nerve has a threshold of 19 Gy for injury, and the seventh and eighth cranial nerves in the setting of meningioma should not be subjected to a radiation dose > 12 Gy.^{2,11,20,34} Morita et al observed rates of trigeminal nerve dysfunction of 13% and 7% with doses > 19 Gy and < 19 Gy, respectively, to Meckel's cave.³⁴ Small beam collimators should therefore be used for the auditory canal and for the portion of the cavernous sinus near the optic nerve or chiasm.²⁵ Meningiomas in the posterior fossa should receive a maximum of 12 to 16 Gy.²⁰

Due to the tenuous nature of the optic apparatus and increased risks for neurologic injury associated with surgical resection, upfront SRS may provide superior vision preservation for meningiomas either involving or neighboring the optic apparatus.^{3,5,15,17,21} Radiosurgery may be used to treat lesions within 2 mm of the optic apparatus after the tumor burden is reduced or as a standalone therapy if the unresected lesion is of similar size.¹⁶ Maximum radiation doses of 8 to 10 Gy are commonly used for the optic structures.²⁰ Radiation-induced optic neuropathy may be avoided with radiation doses to the visual pathways of up to 10 Gy.^{2,5,25,34} However, with doses of 10 to 15 Gy, the incidence of radiation-induced optic neuropathy is as high as 26.7%, and at doses \geq 15 Gy, the incidence rises to 77.8%. Incidence of radiation-induced optic complications is reportedly between 1.1% and 1.3% for optic nerve doses < 12 Gy and < 8 Gy with a 13-Gy margin dose, respectively.^{25,35}

Brainstem

The brainstem can tolerate a maximum dose of 15 Gy, although such a dose risks damage to the acoustic and facial nerves.²⁰ Thus high marginal radiation doses are restricted to meningiomas of the cerebellopontine angle and petroclival regions. Preservation of brainstem function is more easily achieved when there is space between the tumor and lateral brainstem surface. Patients who are asymptomatic and without brainstem compression are well suited to radiosurgical treatment, in which the tumor may slowly regress off the brainstem surface with treatment.²⁵ A study of the natural history of skull base meningiomas demonstrates that after a mean follow-up of 7 years, only 28% of patients (11 of 40) experienced new or worsening cranial neuropathies.²⁸ None of the 23 patients (58%) who presented with concerning brainstem compression at diagnosis were found to develop hemiparesis, long tract signs, or intracranial hypertension. Furthermore, only 18% of patients (7 of 40) demonstrated radiographic tumor growth, although radiographic progression was poorly correlated with neurologic progression. The benign and indolent natural history of skull base meningiomas suggests that conservative management through observation is indicated in many of these asymptomatic cases.

Vessels at the Skull Base

Vascular complications following radiosurgery, including ischemia and hemorrhage, occur in 1.1 to 2.3% of cases.³⁶

Radiation doses > 25 Gy increase the risk of occlusion; hemorrhage likely results from vessel stress caused by rapid shrinkage of tumor postradiation. Stafford et al reported permanent neurologic deficits as a result of ICA injury (stenosis and occlusion) in 2 of 66 patients (3%) with cavernous sinus meningiomas treated by > 25 Gy SRS.³⁵ Vascular injury in the cavernous sinus is rare but has been reported to occur up to 60 months after treatment.³⁰

Safety

Although SRS is associated with a lower incidence of permanent neurologic deficits compared with microsurgical resection, several safety considerations must be taken into account.⁹ Neurologic symptoms after radiosurgery usually occur within the first 2 to 3 years and are more common after treatment of cavernous sinus and petroclival meningiomas.^{13,23} Significant toxicity occurs in < 5% of cases.⁹ Factors affecting the potential toxicity of radiosurgery include prior or concomitant therapy (including SRT, chemotherapy, and/or surgery), host factors (e.g., age or comorbidities), and idiosyncratic reactions.³⁴

The most common adverse effect of SRS is edema as a result of brain invasion, venous congestion, blood-brain barrier breakdown, and release of inflammatory cytokines from damaged tumor cells after exposure to high doses of radiation.²³ Edema occurs more frequently with small meningiomas, whereas large tumors may be associated with edema if they are subjected to even low radiation doses.^{20,23} In a study of 50 skull base meningiomas, 6% had perilesional edema; 2% of these were symptomatic.¹⁸ Factors that make a patient more prone to developing posttreatment edema are (1) presence of a previous neurologic deficit, (2) tumor volume > 10 cm³, (3) prescription dose > 16 Gy, (4) age > 60 years, (5) no previous surgery, (6) perilesional edema before radiosurgery, and (7) tumors in the anterior skull base.^{1,23,29} Given that peritumoral edema tends to occur after ~3 months, if a second irradiation will be administered, it should be done at least 3 months after the first.

The risk of radiosurgical failure is increased for tumors of higher World Health Organization grade and for those patients who have undergone prior surgery.^{22,36} Recurrent tumor growth after failed SRS, which can occur long periods (up to 14 years) after treatment, tends to be aggressive, and therefore it has been suggested that all patients should be followed > 10 years after radiosurgery.³⁷ One benefit of SRS is that additional radiosurgery for the treatment of tumor recurrence can be offered without the additional risks of treatment-related morbidity.²⁴

The risk of radiation-induced tumors, especially in patients with benign lesions, is a potential but uncommon safety consideration.^{14,27} The risk for SRS for skull base meningiomas, however, is low (< 1 in 1000) due to the restricted volume of radiation exposure and small number of exposures.^{14,27} Malignant transformation after radiosurgery may more commonly result from the natural course of the disease rather than radiosurgery itself.⁵ Aftercare of radiosurgical management of benign meningiomas should include surveillance with MRI at 6 and 12 months, and annually thereafter.¹¹

Patients who have had near-total resection are considered low risk for recurrence, and, as such, they may undergo imaging every 2 years after 5 years without recurrence.

Efficacy

SRS approaches surgical resection in terms of efficacy.⁹ The incidence of neurologic improvement or stability after SRS ranges from 62 to 96% in the literature.^{2,8,11,16,29} Pollock and Stafford reported that nearly a third of patients presenting with cavernous sinus meningioma-associated cranial neuropathies showed improvement in the cranial nerve.³⁸ Roche and colleagues reported that SRS, unlike surgery, provides the advantage of oculomotor nerve recovery in petroclival or cavernous sinus meningiomas.³⁹ Radiosurgery for skull base meningiomas using the gamma knife system has demonstrated control rates of 82 to 100% at > 6 years, with a 0 to 27% incidence of new neurologic deficits. Similar studies using LINAC have yielded comparable tumor control rates of 92 to 100% with neurologic complications in the range of 4.7 to 24%.² These PFS rates are similar to those for completely resected meningiomas in small to moderate size asymptomatic meningiomas, as well as for basal meningiomas.^{1,3}

Primary Surgical Resection versus Stereotactic Radiosurgery

Surgical resection has been compared with SRS as a primary treatment in two retrospective series. Linskey and colleagues evaluated 74 meningiomas, in which 38 (51%) were treated with SRS and 35 (47%) with surgery.²⁷ Radiosurgery resulted in a tumor control rate of 97%, with one recurrence during follow-up, and a 5% incidence of permanent morbidity, compared with a 93% control rate and 8.5% morbidity for the surgery group. Pollock and colleagues studied 188 small benign meningiomas treated with either resection (126 tumors) or radiosurgery alone (62 tumors).³⁶ The 7-year PFS for radiosurgery and Simpson grade I resection were equivalent (95% and 96%, respectively); recurrence was more common in the surgical group (12% versus 2%). Radiosurgery may stabilize rather than improve preoperative symptoms, whereas surgery may be more likely to improve symptoms because it can relieve mass effect more quickly and completely.²⁷ Nevertheless, SRS may be an appropriate primary treatment for certain skull base meningiomas.¹¹

Surgical resection is associated with higher rates of morbidity and recurrence in skull base meningiomas due to the critical location of these tumors. As such, it is difficult to achieve a cure with surgery without a significant risk of potentially permanent neurologic sequelae. Radiosurgery is effective at controlling tumor growth and poses minimal morbidity compared with surgery.

Both primary and adjunctive SRS achieve good tumor control and low morbidity rates. Immediate surgical decompression of cranial nerves with tumor debulking followed by radiosurgical therapy of the residual lesion is synergistic and should be considered in appropriate cases. Adjunctive SRS markedly decreases morbidity rates that would otherwise accompany primary surgical resection.

Stereotactic Radiosurgery for Residual or Recurrent Meningiomas

In an effort to minimize morbidity associated with surgery, radical surgical resection should be replaced with subtotal surgical resection. However, this decision should always be based on intraoperative judgment guided by tumor texture, dissection planes, and neighboring structures, rather than preplanned. The residual lesion can then be safely targeted with SRS. Davidson and colleagues noted 44% of 36 patients showed neurologic improvement after radiosurgery for residual or recurrent benign meningiomas of the skull base after one or more surgical procedures.⁹ The PFS rate was 100% at 5 years and 94.7% at 10 years.

Postoperative enhancement can make defining the residual tumor on imaging a challenge.¹¹ For this reason, adjuvant SRS should be performed several weeks after surgical resection. Subach et al analyzed 62 cases of petroclival meningiomas treated with radiosurgery, of which 63% had undergone at least one prior resection.⁴⁰ Neurologic improvement was seen in 21%, 13% worsened, and new cranial nerve deficits developed within 2 years of SRS in 8%. Jung et al reported a 5-year tumor progression rate of 40% in patients in whom petroclival meningiomas were subtotally resected.⁴¹

Recurrence of basal meningiomas after surgery are not uncommon. However, recurrence can be reduced or even avoided by administering radiosurgery.⁶ Recurrence can occur many years after treatment, and therefore extended follow-up > 10 years should be undertaken in all patients.³⁷

Atypical and Malignant Meningiomas

Atypical and malignant meningiomas have high rates of recurrence, progression, morbidity, and mortality, regardless of the treatment modality.^{22,26} Recurrence rates for atypical meningiomas (AMs) have been reported to be as high as 3 to 40%. Five-year overall survival rates range from 59 to 76% in patients with AMs and between 0% and 59% in patients harboring malignant meningiomas.

SRS has been associated with varying survival rates based on the grade of tumor treated.^{22,37} Harris and colleagues reported the 5-year progression-free survival rates of 83% and 72% for atypical and malignant meningiomas, respectively.⁴² Other studies report 5-year local control rates of 40 to 77% for AMs, and 0 to 26% for malignant meningiomas.^{15,22,26,31,43} More favorable outcomes have been achieved in small tumors and in young patients.^{16,22,26} AMs in older patients or exhibiting volumes > 8 cm³ are less amenable to radiosurgical treatment.

Higher radiation doses may be necessary to achieve better tumor control in patients with atypical or malignant meningiomas. Ojemann et al reported 2-year and 5-year survival rates of 75% and 0%, respectively, for patients with malignant meningiomas treated with doses < 15 Gy. Those treated with doses > 15 Gy had 2-year and 5-year survival rates of 69% and 50%, respectively.²⁶ Three of the 22 patients in Ojemann's study experienced recurrence of the same lesion, and all 3 had been treated with doses of ≤ 18 Gy.

Conclusions

SRS is of particular benefit for these patients in whom cranial base meningiomas cannot be completely resected without a high risk of new or worsening neurologic deficits because SRS provides excellent long-term tumor control with minimal treatment-related morbidity. Radiosurgery has been shown to be effective as primary treatment for small and medium-size asymptomatic meningiomas, recurrent tumors, as an adjunct to surgical resection, and for patients with risk factors precluding open surgical resection. Meningiomas that are asymptomatic, nongrowing, and do not involve critical neurovascular structures may be effectively managed with routine clinical and radiologic follow-up. SRS is also considered to be relatively safe for patients with certain large skull base meningiomas, following surgical debulking. Whereas radiosurgery is a first-line treatment option for most holocavernous sinus meningiomas, petroclival meningiomas, which tend to be larger at presentation, should be debulked as a primary treatment in most cases. SRS is limited by tumor size and the proximity of pathology to critical structures, particularly the optic apparatus. Surgical resection is recommended as the primary treatment for meningiomas that are either symptomatic or $> 10 \text{ cm}^3$ in volume, followed by SRS for any residual tumor.

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