Medical Policy

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DESCRIPTION

Stereotactic radiosurgery (SRS) is a method of delivering high doses of precisely targeted ionizing radiation to intracranial lesions. SRS, when used extracranially, is called stereotactic body radiation therapy (SBRT). The technique differs from conventional radiotherapy, which involves exposing large areas of tissue to relatively broad fields of radiation over a longer duration of sessions. SRS and SBRT entail delivering highly focused convergent beams sparing adjacent structures. It may offer a non-invasive alternative to invasive surgery, particularly for patients unable to undergo surgery or for lesions that are difficult to access surgically or are adjacent to vital organs.

Traditional external beam radiation therapy may involve daily treatments for a duration of 6 weeks or longer. The emerging trend in recent years has been toward shorter, more "hypofractionated" courses, such as with SRS and SBRT. Both SRS and SBRT may be completed with one session (single-fraction) or less may require additional sessions (typically no more than 5) over a course of days, referred to as fractionated stereotactic radiotherapy. Fractionation has been made possible by the ability to duplicate the treatment plan from one session to the next. Fractionation of stereotactic radiotherapy aims to optimize the therapeutic ratio; that is the ratio between tumor control and late effects on normal tissues. The main advantage of fractionation is that is allows higher total doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues to each individual, fractionated dose. In addition, some lesions such as large arteriovenous malformations may require more than one procedure to complete the obliteration process.

The main methods of this technology include gamma-ray radiosurgery (Gamma Knife®), most frequently used for intracranial lesions, and linear-accelerator radiosurgery or LINAC (e.g., CyberKnife®). The radiosurgical procedure using SRS or SBRT is preceded by a process of localizing the target with 3-dimensional imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT).

Applications of SRS and SBRT

SRS

The most common applications of SRS include treatment of intracranial malignancies, including primary and metastatic tumors, and benign intracranial tumors such as meningiomas, pituitary adenomas, and acoustic neuromas. SRS has been used for trigeminal neuralgia that is resistant to other therapies. It is also an established treatment for arteriovenous malformations (AVMs). More recently, SRS has been investigated as a treatment of functional disorders, which are defined as conditions having no detectable organic cause. Examples of functional disorders include chronic pain.

Acoustic neuromas are benign tumors originating on the eighth cranial nerve, and they can be seen in association with neurofibromatosis. Although these tumors are benign, they are associated with significant morbidity and even death if their growth compresses vital structures. Treatment options include complete surgical excision using microsurgical techniques, but radiosurgery has also been used extensively, either as a primary treatment or as a treatment of recurrence after incomplete surgical resection. Acoustic neuromas were one of the first indications for SRS, dating back to 1969.

Pituitary adenomas are benign tumors with symptoms that are related to hormone production (i.e., functioning adenomas) or to neurologic symptoms due to their impingement on surrounding neural structures. Treatment options for pituitary adenomas include surgical excision, conventional radiation therapy, or SRS. Surgical excision is typically offered to patients with functioning adenomas, since complete removal of the adenoma leads to more rapid control of autonomous hormone production. The effects of SRS on hormone production are delayed or incomplete. In patients with nonfunctioning adenomas, the treatment goal is to control growth; complete removal of the adenoma is not necessary. Conventional radiation therapy has been used in this setting with an approximate 90% success rate with few complications.

Craniopharyngiomas are benign, however, because of proximity to the optic pathways, pituitary gland, and hypothalamus, may cause severe and permanent damage to such critical structures and can even be life-threatening. Total surgical resection is often difficult.

Because of the rarity of glomus jugulare tumors, a variety of treatment paradigms are currently used. There is no consensus regarding the optimal management to control tumor burden while minimizing treatment-related morbidity.

Arteriovenous malformations consist of a tangled network of vessels in which blood passes from arteries to veins without intervening capillaries. They range in size from small, barely detectable lesions to huge lesions that can occupy an entire hemisphere. SRS incites an inflammatory response in the vessels, which results in ongoing fibrosis with eventual complete obliteration of the lesion over a course of months to years. This latency period is variable, depending on the size of the AVM and the dose distribution of the radiosurgery. During this latency period, there is an ongoing but declining risk of hemorrhage. In contrast, surgical excision provides an immediate effect on the risk of hemorrhage. Total surgical extirpation of the lesion, if possible, is the desired form of therapy to avoid future hemorrhage. However, a small subset of AVMs because of their size or location cannot be excised without serious neurologic sequelae. SRS is an important alternative in these patients.

Trigeminal neuralgia is a disorder of the fifth cranial (i.e., trigeminal) nerve that causes episodes of intense, stabbing pain in the face. Although trigeminal neuralgia is initially treated medically, in a substantial number of cases, drug treatment is either ineffective or the adverse effects become intolerable. Neurosurgical options include microvascular decompression, balloon compression, and rhizotomy. SRS has been investigated as an alternative to these neurosurgical treatments.

Seizure disorders are initially treated medically. Surgical treatment is only considered in those rare instances when the seizures have proven refractory to all attempts at aggressive medical management, when the seizures are so frequent and severe as to significantly diminish quality of life, and when the seizure focus can be localized to a focal

lesion in a region of the brain that is amenable to resection. SRS has been investigated as an alternative to neurosurgical resection. For chronic pain that is refractory to a variety of medical and psychological treatments, there are a variety of surgical alternatives. Neurodestructive procedures include cordotomy, myelotomy, dorsal root entry zone (DREZ) lesions, and stereotactic radiofrequency thalamotomy. SRS targeting the thalamus has been considered an investigative alternative to these neurodestructive procedures.

Intracranial metastases have been considered ideal targets for radiosurgery due to their small spherical size and noninfiltrative borders. Brain metastases are a frequent occurrence, seen in 25–30% of all patients with cancer, particularly in those with lung, breast, or colon cancer or melanoma. Whole-brain radiation treatment (WBRT) is considered the standard of care in the treatment of brain metastases, and the addition of SRS to WBRT has been show to improve survival and local tumor control in selected patients. Stereotactic radiosurgery (SRS) offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single fraction. The idea of deferring WBRT in order to avoid its effects on normal tissues and using SRS alone continues to generate significant discussion and interest. Several trials have been conducted to address this issue.

The treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders.

Melanoma of the uvea (choroid, ciliary body and iris) is the most common primary malignant intraocular tumor in adults. Established treatment modalities include enucleation, local resection, brachytherapy and proton-beam radiotherapy. The main objectives of treating the tumor are to reduce the risk of metastatic spread and to salvage the eye with useful vision if feasible. Treatment selection depends on tumor size and location, associated ocular findings, the status of the other eye, as well as other individual factors, including age, life expectancy, quality of life issues, concurrent systemic diseases and patient expectations.

SBRT

Studies are being conducted to evaluate SBRT for a number of extracranial sites. This approach is being studied to better target lesions (sparing surrounding normal structures) and to shorten the length of time needed to complete the treatments.

Surgical resection is the preferred treatment of hepatocellular carcinoma, although at the time of diagnosis less than 20% of patients are amenable to definitive surgical management due to advanced local disease or comorbidities. These patients may be candidates for local ablative therapies, including radiofrequency ablation and chemoembolization. Radiation may be considered as an alternative to local ablative/embolization therapies or if these therapies fail.

Radiation may be a part of the treatment plan for pancreatic cancer, resectable or unresectable disease, and may be used in the adjuvant or neoadjuvant setting.

Localized renal cell carcinoma is conventionally treated surgically; local ablative methods may also be an option. Preoperative and adjuvant external radiation have not improved survival. However, because renal cell cancer brain metastases, although radioresistant to conventional external radiation, have been responsive to radiosurgery, there is interest in the possibility of treating primary kidney cancer with SBRT.

Metastases from non-small cell lung cancer (NSCLC) to the adrenal gland are common, and systemic treatment is the most frequent therapeutic option. Nevertheless, in patients suffering from an isolated adrenal metastasis, a survival benefit could be achieved after surgical resection.

Oligometastases are defined as isolated sites of metastasis, with the entire burden of disease being recognized as a finite number of discrete lesions that can be potentially cured with local therapies. (1) In general, the indications for SBRT for oligometastases are the same as for metastasectomy. Recently proposed specific criteria for the use of SBRT in patients with oligometastases include: a controlled primary, favorable histology, limited metastatic disease, metachronous appearance of metastases, young age and good performance status. (1)

The management of metastatic solid tumors has historically focused on systemic treatment with palliative intent. However, surgical treatment of oligometastatic disease is now common practice in some clinical settings. (2) Although cure may be possible in some patients with oligometastatic disease, the aim of SBRT in this setting is mainly to achieve local control and delay progression, which also may postpone the need for further treatment.

POLICY

A. Stereotactic radiosurgery (single fraction) and/or stereotactic radiation therapy (multiple fractions) is a viable option for treatment of tumors up to about 5 cm in greatest dimension. There are a number of devices which are designed and licensed for this application. These include GammaKnife, CyberKnife, and radiosurgically configured linear accelerators. This technology is now applied to lesions throughout the body. The following is a current list of appropriate sites and diseases.
    1. Arteriovenous malformations (AVM);
    2. Acoustic neuromas;
    3. Pituitary adenomas (Cushing's disease or acromegaly);
    4. Non-resectable, residual, or recurrent meningiomas
    5. Solitary or multiple brain metastases (initial treatment or treatment of recurrence for patients having good performance status and indolent or no active systemic disease);

6. High-grade gliomas
7. Trigeminal neuralgia refractory to medical management;
8. Jugular foraman schwannomas;
9. Inoperable primary spinal tumors with compression or intractable pain;
10. Recurrent metastatic spinal tumors after prior surgery and conventional radiation therapy.
11. Pulmonary malignancies
    Must meet at least one of the following characteristics:
    a. Medically inoperable early stage non-small cell lung cancer (T1 and T2) 5 cm or less in size
    b. Radioresistant histological subtypes that are not amenable to conventional radiation therapy
    c. Oligometastatic disease (no more than 5 metastases) deep in the parenchyma and not readily accessible by surgery
    d. Metastases near vital structures
    e. Focally persistent or recurrent stage II or III non-small cell lung cancer after prior chemoradiation

B. All other uses of stereotactic radiosurgery are considered **experimental / investigational** including, but not limited to, treatment of chronic pain, treatment of uveal melanoma, psychoneurosis, epilepsy, Parkinson's and other movement disorders, and the treatment of functional disorders other than trigeminal neuralgia. For these applications, there is a lack of studies regarding the safety and effectiveness of radiosurgery in comparison with standard therapies.

RATIONALE

Challenges to an Evidence-Based Approach to Rapidly Evolving Technologies in Radiation Oncology

This policy groups together several different techniques for delivering stereotactic radiosurgery (SRS), i.e., the Gamma Knife®, LINAC devices, and the CyberKnife® device, i.e., an example of image-guided radiotherapy. However, from an evidence-based approach, it is extremely difficult to compare these different devices to determine if one device is superior to another for a particular indication. Controlled trials directly comparing different devices in homogeneous groups of patients are lacking. A limited number of stereotactic radiosurgery options may be available in individual markets, and thus, the choice among devices may be dictated primarily by geography. The following summarizes different variables related to stereotactic radiosurgery and radiotherapy.

- Size of Lesion

In terms of stereotactic radiosurgery, the superiority of one energy source over another depends primarily on the dose distribution capabilities, which in turn depend on the target's volume, location, and shape. For small lesions (i.e., less than 5 cm3), the dose distributions produced by the Gamma Knife are essentially identical to those achievable with LINAC units. When the target lesion is nonspherical or of intermediate size (e.g., between 5 and 25 cm3), LINAC units may have an advantage over Gamma Knife units due to their ability to treat larger lesions without requiring multiple isocenters (which make treatment planning difficult), and the ability to shape the dose using collimated fields. However, when targeting large volumes (i.e., greater than 25 cm3), charged particle units that use a small fixed number of beams have the best ability to shape dose distributions and thus offer some advantages over both LINAC and Gamma Knife units.

- Dose Fractionation

Standard radiobiologic principles suggest that fractionating radiation therapy (i.e., delivery in multiple sessions) will reduce both early and late toxicities to surrounding normal tissues. Radiosurgery (1 treatment) or hypofractionation (limited number of treatments) may be considered when patient movement limits the use of conventional radiation therapy, or may be offered as a convenience to patients, particularly those who require rapid pain relief. These 2 clinical indications are also associated with different outcomes that must be considered as part of an evidence-based analysis. A more basic scientific issue is an underlying understanding of the radiosensitivity of surrounding normal tissues.

- Dose Escalation

Novel forms of radiation therapy have been, and continue to be, proposed as ways to provide dose escalation. In this setting, clinical questions include whether dose escalation provides improved tumor control, which depends on the dose response rate of individual tumor types and whether an increased dose is associated with increased toxicity to surrounding tissues.

- Decreased Toxicity

A variety of novel treatment planning and delivery approaches are designed to reduce toxicity. Evidence of reduced toxicity would require directly comparative studies. Many of the potential benefits of delivery systems have been based on modeling studies or studies with phantoms.

In summary, the lack of comparative studies of different techniques of radiation planning and delivery in homogeneous groups of patients limits any scientific analysis regarding the relative safety and efficacy of different systems for different clinical situations, i.e., reduction of fractionation, dose escalation, reduced toxicity, or a combination of all three. Therefore the scientific evidence is inadequate to permit scientific conclusions regarding the superiority of one device over another. The following discussion focuses on different general applications of stereotactic applications in radiation therapy.

Literature review

This policy was created in 1995 and has been updated annually, most recently through August 15, 2013 with a search of the MEDLINE database. Data on the use of SRS and SBRT consists primarily of case series, registry data and early phase trials. Comparative trials are lacking.

STEREOTACTIC RADIOSURGERY (SRS)

Non-neoplastic conditions

Arteriovenous malformations

Kano and colleagues reported a study to define long-term outcomes and risks of arteriovenous malformation (AVM) management using 2 or more stages of stereotactic radiosurgery (SRS) for symptomatic large-volume lesions unsuitable for surgery. (3) Forty-seven patients with such AVMs underwent volume-staged SRS. Eighteen patients (38%) had had a prior hemorrhage and 21 patients (45%) had undergone prior embolization. The median interval between the first- and second-stage SRS was 4.9 months (range 2.8-13.8 months). The median target volume was 11.5 cm3 (range, 4.0-26 cm3) in the first-stage SRS and 9.5 cm3 in the second-stage SRS. In 17 patients, AVM obliteration was confirmed after 2-4 SRS procedures at a median follow-up of 87 months (range 0.4-209 months). Five patients had near-total obliteration (volume reduction >75% but residual AVM). The actuarial rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at 3, 4, 5, and 10 years, respectively. The 5-year total obliteration rate after the initial staged volumetric SRS was 62% (p=0.001). Sixteen patients underwent additional SRS at a median interval of 61 months (range 33-113 months) after the initial 2-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at 5, 7, and 10 years, respectively. Ten patients sustained hemorrhage after staged SRS, and 5 of these patients died. Three of 16 patients who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the patient who had 2 hemorrhages), the cumulative rates of AVM hemorrhage after SRS were 4.3%, 8.6%, 13.5%, and 36.0% at 1, 2, 5, and 10 years, respectively, corresponding to annual hemorrhage risks of 4.3%, 2.3%, and 5.6% for years 0-1, 1-5, and 5-10 after SRS. Multiple hemorrhages before SRS correlated with a significantly higher risk of hemorrhage after SRS. Symptomatic adverse radiation effects were detected in 13% of patients, but no patient died as a result of an adverse radiation effect. The authors concluded that volume-staged SRS for large AVMs unsuitable for surgery has potential benefit, but often requires more than 2 procedures to complete the obliteration process and that in the future, prospective volume-staged SRS followed by embolization (to reduce flow, obliterate fistulas, and occlude associated aneurysms) may improve obliteration results and further reduce the risk of hemorrhage after SRS.

Trigeminal Neuralgia

A 2011 review article summarizes the literature on the use of SRS for trigeminal neuralgia. (4) The majority of patients with typical facial pain will achieve relief following radiosurgical treatment.

Dhople reports long-term outcomes of SRS for classical trigeminal neuralgia in 112 patients treated between 1996 and 2001. (5) Of these, 67% had no prior invasive operations for trigeminal neuralgia prior to SRS, 13% had 1, 4% had 2, and 16% had greater than or equal to 3. The right side was affected in 56% of cases, predominantly involving V2 (26%), V3 (24%), or

a combination of both (18%) branches. The median age at diagnosis was 56 years, and median age at SRS was 64 years. The median prescription dose of 75 Gy (range, 70-80 Gy) was delivered to the involved trigeminal nerve root entry zone. The authors assessed the degree of pain before and after SRS by using the Barrow Neurological Institute (BNI) pain scale. In total, 102 patients took the survey at least once, for a response rate of 91%. Although not found to alter the conclusions of this study, 7 cases of atypical TN were found, and these patients were removed, for a total of 95 cases herein analyzed. The median follow-up was 5.6 years (range, 13-115 months). Before gamma knife surgery (GKS), 88% of patients categorized their pain as BNI IV or V (inadequate control or severe pain on medication), whereas the remainder described their pain as BNI III (some pain, but controlled on medication). After GKS, 64% reported a BNI score of I (no pain, no medications), 5% had BNI II (no pain, still on medication), 12% had BNI III, and 19% reported a BNI score of IV or V. The median time to response was 2 weeks (range 0-12 weeks), and the median response duration was 32 months (range 0-112 months). Eighty-one percent reported initial pain relief, and actuarial rates of freedom from treatment failure at 1, 3, 5, and 7 years were 60, 41, 34, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment versus those in whom a previous surgical intervention had failed (32 vs. 21 months, $p<0.02$). New facial numbness was reported in 6% of cases.

Epilepsy

A 1998 TEC Assessment (6) cited 2 studies of 11 and 9 patients, respectively, in which radiosurgery was used to treat epilepsy. The subsequent literature search revealed 3 small studies on the use of radiosurgery for medically refractory epilepsy. Regis et al. (7) selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided minimum 2-year follow-up. Seizure-free status was achieved in 13 patients, 2 patients were improved, and 3 patients had radiosurgery-related visual field defects. A study by Schrottner et al. (8) included 26 patients with tumoral epilepsy, associated mainly with low-grade astrocytomas. Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in 6 (3 with generalization) and complex partial in 18 (5 with generalization, 1 gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in 4 patients and none in 7. Whang and Kwon (9) performed radiosurgery in 31 patients with epilepsy associated with non-progressive lesions. A minimum of 1-year follow-up was available in 23 patients, 12 of whom were seizure-free (and 3 of whom had antiseizure medications discontinued), 2 had seizures reduced in frequency, and 9 experienced no change. While the Regis series selected a fairly homogeneous clinical sample, the other 2 studies were heterogeneous. No confirmatory evidence is available on mesial temporal lobe epilepsy. The available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with favorable outcome. There is inadequate reporting of complications associated with radiosurgery. The studies published to date are preliminary in nature. The 1998 TEC Assessment observed that evidence was insufficient to permit conclusions about the effects of radiosurgery on epilepsy. Conclusions about the health outcome effects of radiosurgery await additional studies.

Chronic Pain

The TEC Assessment from 1998 identified 2 reports, with 2 and 47 patients, respectively, who underwent radiosurgical thalamotomy for chronic pain. No new studies were found in the search of recent literature. Thus, the conclusions of the 1998 TEC Assessment have not changed.

Central Nervous System Neoplasms

Acoustic neuromas

In the treatment of acoustic neuromas, the most significant adverse effect is loss of function of the facial and auditory nerve. For example, in a single-institution study, Meijer and colleagues reported on the outcomes of single fraction versus fractionated LINAC-based SRS in 129 patients with acoustic neuromas. (10) Among these patients, 49 were edentate and thus could not be fitted with a relocatable head frame that relies on dental impressions. This group was treated with a single fraction, while the remaining 80 patients were treated with a fractionated schedule. With an average follow-up of 33 months, there was no difference in outcome in terms of local tumor control, facial nerve preservation, and hearing preservation. Chung and colleagues reported on the results of a single-institution case series of 72 patients with acoustic neuromas, 45 of whom received single-fraction therapy and 27 who received fractionated therapy. (11) Patients receiving single-fraction treatment were functionally deaf, while those receiving fractionated therapy had useful hearing in the affected ear. After a median follow-up of 26 months, there was no tumor recurrence in either group. Chang et al. (12) reported that 74% of 61 patients with acoustic neuromas treated with CyberKnife using staged treatment had serviceable hearing maintained during at least 36 months of follow-up.

Craniopharyngioma

Hashizume and colleagues evaluated the results of the use of SRS in 10 patients with craniopharyngioma adjacent to optic pathways. (13) Ten patients (6 men, 4 women) with craniopharyngioma and median age of 56.5 years (range 10-74 years) were treated from 2006 through 2009. Median volume of tumor was 7.9 mL (range 1.1-21 mL). A total dose of 30-39 Gy in 10-15 fractions (median 33 Gy) was delivered to the target. Ten patients were followed up for 9-36 months (median 25.5 months). The response rate was 80% (8/10), and control rate was 100%. Improvement of neurologic symptoms was observed in 5 patients. No serious complications due to SRS were found.

Hasegawa and colleagues determined the limiting dose to the optic apparatus in single-fraction irradiation in patients with craniopharyngioma treated with gamma knife radiosurgery. (14) One hundred patients with 109 craniopharyngiomas treated with radiosurgery were evaluated with a median follow-up period of 68 months. Tumor volume varied from 0.1 to 36.0 (median, 3.3) cm. The actuarial 5- and 10-year overall rates of survival of tumor progression after radiosurgery were 93% and 88%, respectively. The actuarial 5- and 10-year progression-free survival rates were 62% and 52%, respectively.

Among 94 patients in whom visual function was evaluable, only 3 patients developed radiation-induced optic neuropathy, indicating an overall Kaplan-Meier radiation-induced optic neuropathy rate of 5%. Combs and colleagues evaluated the long-term outcome in patients with craniopharyngiomas treated with fractionated stereotactic radiotherapy. (15) A total of 40 patients with craniopharyngiomas were treated between 1989 and 2006. Most patients were treated for tumor progression after surgery. A median target dose of 52.2 grays (Gy) (range 50.4-56 Gy) was applied in a median conventional fractionation of 5 x 1.8 Gy per week. Follow-up examinations included thorough clinical assessment as well as contrast-enhanced magnetic resonance imaging (MRI) scans. After a median follow-up of 98 months (range 3-326 months), local control was 100% at both 5 years and 10 years. Overall survival rates at 5 years and 10 years were 97% and 89%, respectively. A complete response was observed in 4 patients and

partial responses were noted in 25 patients. Eleven patients presented with stable disease during follow-up. Acute toxicity was mild in all patients. Long-term toxicity included enlargement of cysts requiring drainage 3 months after fractionated stereotactic radiotherapy (FSRT). No visual impairment, radionecrosis, or development of secondary malignancies was observed. The authors concluded that long-term outcome of fractionated radiosurgery for craniopharyngiomas is excellent with regard to local control, as well as treatment-related side effects.

Ivan and colleagues conducted a meta-analysis of tumor control rates and treatment-related mortality for patients with glomus jugulare tumors. (16) In this study, the authors assessed data collected from 869 patients with glomus jugulare tumors from the published literature to identify treatment variables that impacted clinical outcomes and tumor control rates. A comprehensive search of the English language literature identified 109 studies that collectively described outcomes for patients with glomus jugulare tumors. Univariate comparisons of demographic information between treatment cohorts were performed to detect differences in the sex distribution, age, and Fisch class of tumors among various treatment modalities. Meta-analyses were performed on calculated rates of recurrence and cranial neuropathy after subtotal resection (STR), gross-total resection (GTR), STR with adjuvant postoperative radiosurgery (STR+SRS), and stereotactic radiosurgery alone (SRS). The authors identified 869 patients who met their inclusion criteria. In these studies, the length of follow-up ranged from 6 to 256 months. Patients treated with STR were observed for 72 ± 7.9 months and had a tumor control rate of 69% (95% confidence interval [CI]: 57-82%). Those who underwent GTR had a follow-up of 88 ± 5.0 months and a tumor control rate of 86% (95% CI: 81%-91%). Those treated with STR+SRS were observed for 96 ± 4.4 months and had a tumor control rate of 71% (95% CI: 53%-83%). Patients undergoing SRS alone had a follow-up of 71 ± 4.9 months and a tumor control rate of 95% (95% CI: 92-99%). The authors' analysis found that patients undergoing SRS had the lowest rates of recurrence of these 4 cohorts, and therefore, these patients experienced the most favorable rates of tumor control ($p<0.01$). Patients who underwent GTR sustained worse rates of cranial nerve (CN) deficits with regard to CNs IX-XI than those who underwent SRS alone; however, the rates of CN XII deficits were comparable.

Brain Metastases

Roos and colleagues examined the randomized evidence to treat brain metastases. (17) A search of MEDLINE, EMBASE, and Cochrane databases for published papers and abstracts on relevant randomized trials was undertaken. Fourteen randomized trials were identified, 11 final reports and 3 abstracts, investigating various combinations of surgery, SRS and whole brain radiation therapy (WBRT). Most of the trials had significant limitations. Surgery and SRS improved local control, maintenance of performance status and survival for favorable prognosis patients with solitary brain metastases relative to WBRT alone, although the absolute survival benefit for the majority was modest. Limited data suggest similar outcomes from surgery and SRS, but few patients were truly suitable for both options. For multiple (2-4) brain metastases, SRS improved local control and functional outcome but not survival. Adjuvant WBRT also improved intracranial control but not survival; however, the neurocognitive risk:benefit ratio of WBRT was controversial. Quality of life data were limited.

Some studies have suggested that use of radiosurgery for brain metastases should be limited to patients with 3 or fewer lesions. A randomized trial compared whole-brain radiation therapy (WBRT) with WBRT plus radiosurgery boost to metastatic foci. (18) It found that the significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure did not

differ among patients with 2, 3, or 4 metastases. Survival also did not depend on the number of metastases. As the number of metastases rises, so does the total volume of tissue receiving high-dose radiation, thus the morbidity risk of radiation necrosis associated with radiosurgery is likely to increase. For a large number of metastases, and for large volumes of tissue, this risk may be high enough to negate the advantage of radiosurgery plus WBRT over WBRT alone seen in patients with 4 or fewer metastases. Stereotactic radiosurgery centers commonly exclude patients with more than 5 metastases from undergoing radiosurgery. (19, 20) It is difficult to identify a specific limit on the number of metastases for which the use of SRS is advantageous. A large number of very small metastases may respond to radiosurgery, as well as a small number of larger metastases.

In a 2010 analysis, a Cochrane review (21) addressed the role for both SRS and whole-brain radiation therapy (WBRT) in patients with small numbers of metastatic lesions (generally no more than 3 or 4 lesions), noted that given the unclear risk of bias in the included studies, the results need to be interpreted with caution. The analysis of all included patients (3 trials) indicated that SRS plus WBRT did not show a survival benefit over WBRT alone; however, performance status and local control were significantly better in the SRS plus WBRT group. In a randomized trial of 58 patients published following the Cochrane review, Chang and colleagues concluded that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. (22)

Aoyama and colleagues recently reported on a randomized trial of SRS plus WBRT versus SRS alone for treatment of patients with 1 to 4 brain metastases. (23) They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS plus WBRT group compared to 76.4% in the group that only received SRS. However, median survival times were not different at 7.5 and 8.0 months, respectively. They also found no differences in neurologic functional preservation. In an accompanying editorial, Raizer commented that either treatment approach is a reasonable first step, recognizing that those who select SRS alone are more likely to need subsequent salvage radiation treatments. (24)

A 2011 review by Park and colleagues on the use of SRS for brain metastases discussed the 2 randomized trials that demonstrated that the addition of single-dose SRS to WBRT improves local tumor control and maintenance of functional status for patients. (25) Also reviewed are 3 recent randomized trials comparing the outcomes for SRS alone versus SRS plus WBRT for limited brain metastases. All 3 trials indicated a lack of detriment in neurocognition or quality of life with the omission of WBRT, despite significantly worsened intracranial tumor control that would require additional salvage therapy in almost all patients.

Uveal melanoma

The literature on the use of SRS for uveal melanoma consists of case series; no studies directly comparing SRS with other, accepted radiation modalities used to treat uveal melanoma (brachytherapy, proton beam) are identified.

A 2012 review article summarizes the literature on the use of SRS for uveal melanoma, with long-term tumor control rates using the Gamma Knife reported to be around 90%. (26) Initial studies using SRS for uveal melanoma reported secondary side effects from radiation to be common; however, more recent studies have reported lower incidences with lower total radiation doses. (26)

The largest study to date consisted of 212 patients with choroidal melanoma, who were not suitable for brachytherapy or resection. (27) Patients in the study received different doses of radiation, ranging from 50 Gy to 70 Gy, in 5 fractions over 7 days. Ophthalmologic examination was performed at baseline and every 3 months in the first 2 years, every 6 months until 5 years, and once a year until 10 years after SRS. The study included measurement of tumor dimension and height using standardized methods, assessment of visual acuity and routine ophthalmologic examinations. Local tumor control was 96% at 5 years, and 93% at 10 years. Thirty-two patients developed metastases, and 22 of these patients died during the follow-up period. Median visual acuity decreased from 0.55 at baseline to hand motion ($p<0.001$). The authors concluded that SRS was sufficient to achieve excellent local tumor control in patients with melanoma of the choroid, and that disease outcome and vision were comparable to that achieved with proton-beam radiotherapy.

Additional case series using SRS for uveal melanoma have suggested that it is a possible eye-sparing option for patients, with outcomes comparable to enucleation or other radiation modalities. (28-30)

Conclusion

Published studies have demonstrated that stereotactic radiosurgery is an accepted and effective method for the treatment of many intracranial lesions/tumors. SRS has been shown to have an advantage over traditional radiation by allowing delivery of higher doses of radiation while minimizing radiation exposure to surrounding normal tissue.

The published literature is insufficient to demonstrate improved outcomes with the use of stereotactic radiosurgery over other accepted radiation modalities in the treatment of uveal melanoma.

STEREOTACTIC BODY RADIATION THERAPY

Spinal tumors

Gerszten and colleagues reported on the outcomes of 115 patients with spinal tumors of varying etiologies, i.e., benign, metastatic, single, or multiple lesions, in a variety of locations, i.e., cervical, thoracic, lumbar, sacral, who were treated with the CyberKnife in a single session. (31) Most patients were treated for pain control and also had received prior external-beam irradiation. The authors point out that radiation therapy of the spinal cord is limited by its low tolerance and that if a radiation dose could be targeted more accurately at the lesions, higher doses could be delivered in a single fraction. They further point out that conventional methods of delivering intensity-modulated radiation therapy (IMRT) are limited due to lack of target immobilization. Axial and radicular pain improved in 74 of the 79 symptomatic patients. There was no acute radiation toxicity or new neurologic deficits. Conventional external-beam radiation therapy (EBRT) typically is delivered over a course of 10 to 20 fractions. In contrast, in this study, only 1 CyberKnife treatment session was used. In a 2005 study, Degen and colleagues reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife. (2) Patients underwent a median of 3 treatments. Pain was improved, as measured by declining mean visual analog scale (VAS) score, and quality of life was maintained during the 1-year study period.

Gerszten et al. recently published results on a series of 500 cases from a single institution (334 tumors had previously undergone external-beam irradiation) using the CyberKnife system. (33) In this series, the maximum intratumoral dose ranged from 12.5 Gy to 25 Gy, with a mean of 20 Gy. Long-term pain improvement occurred in 290 of 336 cases (86%). Long-term radiographic tumor control was demonstrated in 90% of lesions treated with radiosurgery as a primary treatment modality. Twenty-seven of 32 cases (84%) with a progressive neurologic deficit before treatment experienced at least some clinical improvement. Chang et al. reported on Phase I/II results of stereotactic body radiation therapy (SBRT) in 74 spinal lesions in 63 patients (55% had prior irradiation) with cancer. (34) The actuarial 1-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed 2 primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that analysis of the data obtained in their study supports the safety and effectiveness of SBRT in cases of metastatic spinal tumors. They add that they consider it prudent to routinely treat the pedicles and posterior elements using a wide bone margin posterior to the diseased vertebrae because of the possible direct extension into these structures and for patients without a history of radiotherapy, more liberal spinal cord dose constraints than those used in the study.

Conclusion

SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors. The majority of the literature addresses metastases that recur after prior radiation therapy.

Non-small cell lung cancer (NSCLC)
A review by Nguyen et al. (35) cites a number of studies of SBRT for early-stage lung cancer receiving a biologic equivalent dose of 100 Gy or more. Three of the studies cited reported 5-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the 5-year survival was 42%. Koto et al. reported on a Phase II study of 31 patients with stage 1 NSCLC. (36) Patients received 45 Gy in 3 fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the 3-year overall survival was 72%, while disease-free survival was 84%. Five patients developed grade 2 or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported 3-year disease-specific survival rates of 49% for those with stage 1 disease. (37)

Timmerman et al. evaluated the toxicity and efficacy of stereotactic body radiation therapy (SBRT) in a high-risk population of patients with early stage but medically inoperable lung cancer. (38) in a Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction x 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 to 2 weeks. The primary endpoint was 2-year actuarial primary tumor control; secondary endpoints were disease-free survival (i.e., primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% confidence interval [CI]: 84.3-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe

(local) control rate was 90.6% (95% CI: 76.0-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI: 71.0-94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI: 12.3-37.8%). The rates for disease-free survival and overall survival at 3 years were 48.3% (95% CI: 34.4-60.8%) and 55.8% (95% CI: 41.6-67.9%), respectively. The median overall survival was 48.1 months (95% CI: 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients (12.7%; 95% CI: 9.6-15.8%); grade 4 adverse events were reported in 2 patients (3.6%; 95% CI: 2.7-4.5%). No grade 5 adverse events were reported. The authors concluded that patients with inoperable non-small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity.

Hof et al. reported on outcomes (median follow-up 15 months) for 42 patients with stages I and II lung cancer who were not suitable for surgery and who were treated with stereotactic radiotherapy. (39) In this series, at 12 months, overall survival was 75% and disease-free survival was 70%. Better local control was noted with higher doses of radiation.

Ongoing trials

Two Phase 3 trials are ongoing, one comparing surgery with or without internal radiation therapy compared with SBRT in patients with high-risk stage I non-small cell lung cancer (NCT01336894) and one comparing SBRT to conventional radiotherapy for Inoperable early-stage I non-small cell lung cancer (NCT01014130).

Conclusion

Although no comparative data are available, studies have shown that SBRT for patients with stage 1 NSCLC who are not candidates for surgical resection because of comorbid conditions or for those with early-stage disease who refuse surgery, survival rates may be comparable to surgical resection. Therefore, SBRT may be considered medically necessary in patients with stage T1 and T2a NSCLC (not larger than 5 cm in diameter) showing no nodal or distant disease.

Hepatocellular carcinoma (HCC)

Bujold and colleagues reported on sequential Phase I and II trials of SBRT for locally advanced hepatocellular carcinoma. (40) Two trials of SBRT for patients with HCC who were considered to be unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All of the patients had Child-Turcotte-Pugh class A disease. The primary endpoints were toxicity and local control at 1 year, defined as no progressive disease of irradiated HCC by RECIST (Response Evaluation Criteria in Solid Tumors). A total of 102 patients were evaluable (n=50 in trial 1, 2004 to 2007; n=52 in trial 2, 2007 to 2010). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol-related in 25%, and other in 14%, and none in 7%. Fifty-two percent received prior therapies (excluding sorafenib). TNM stage was III in 66% of patients, and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1,913.4 mL). Tumor vascular thrombosis (TVT) was present in 55%, and 12% of patients had extrahepatic disease. Local control at one year was 87% (95% CI: 78% to 93%). Toxicity greater than or equal to grade 3 was seen in 30% of patients. In 7 patients (2 with TVT and progressive disease), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median overall survival was 17.0 months (95% CI: 10.4 to 21.3 months).

Meng and colleagues conducted a systematic review and meta-analysis of transcatheter arterial chemoembolization (TACE) in combination with radiotherapy compared to TACE alone for unresectable HCC using meta-analysis of data from the literature involving available trials. (41) Seventeen trials involving 1,476 patients were identified. Five were RCTs, and 12 were non-randomized controlled clinical trials (RCTs). In terms of quality, 5 RCTs were graded B, and the 12 non-randomized studies were graded C. Results showed that TACE plus radiation therapy (RT) significantly improved survival and tumor response over TACE alone. The authors concluded that considering the strength of the evidence, additional RCTs are needed before combination TACE and RT can be recommended routinely.

A 2012 systematic review conducted by Tao and Yang, assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms. (42) The review included prospective clinical trials published in English. Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included. Treatment was performed in 1-10 fractions to total doses of 18-60 Gy. Most studies that were included reported outcomes for patients with both primary and metastatic disease, without separating out outcome data for primary tumors only. In addition, some studies reported on outcomes for primary liver tumors included cholangiocarciomas. At Indiana University, in a Phase I study, Cardenes et al. treated 17 HCC patients with Child-Turcotte-Pugh (CTP) CTP-A or CTP-B, 1-3 lesions and cumulative tumor diameter less than or equal to 6 cm. Patients with CTP-A were treated in 3 fractions with the dose escalated from 12 to 16 Gy. For patients with CTP-B, the dose was modified to 5 fractions starting at 8 Gy per fraction and was not escalated because 2 patients treated at 3×14 Gy developed grade 3 hepatic toxicity. The 1-year overall survival was 75%, and there were no local failures during the median 24 months of follow-up.

Building upon the Phase I study, 36 patients with CTP-A disease were treated with 3×18 Gy, and 24 patients with CTP-B disease were treated with 5×8 Gy. With this regimen, Andolino et al. reported complete response, partial response, and stable disease for 30%, 40%, and 25% of tumors, respectively. Two-year local control, progression-free survival (PFS), and overall survival (OS) were 90%, 48%, and 67%,respectively, with a median PFS of 20.4 months and OS of 44.4 months.

In an attempt to extend the use of SBRT to larger lesions, Shin et al. treated 6 patients with large tumors (median tumor volume 1,288 mL, range 1,008-1,815 mL) with no worse than CTP-A liver disease and without extrahepatic metastases The 4×8–10 Gy regimen was relatively safe with only one case of grade 3 changes in transaminases. However, 1-year OS was only 33%, in part due to advanced disease. One-year local control and OS rates were 50-100% and 33-100%, respectively. There were 13 cases of radiation-induced liver disease and 4, grade 5; 6, grade 4; and 69, grade 3 adverse events reported.

Andolino et al. evaluated the safety and efficacy of SBRT for the treatment of primary HCC. (43) From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT: 36 Child-Turcotte-Pugh (CTP) Class A and 24 CTP Class B. The median number of fractions, dose per fraction, and total dose was 3, 14 Gy, and 44 Gy, respectively, for those with CTP Class A cirrhosis and 5, 8 Gy and 40 Gy, respectively, for those with CTP Class B. The records of all patients were reviewed, and treatment response was scored according to Response Evaluation Criteria in Solid Tumors v1.1. Toxicity was graded according to the Common Terminology Criteria

for Adverse Events v4.0. Local control (LC), time to progression (TTP), progression-free survival (PFS), and overall survival (OS) were calculated according to the method of Kaplan- Meier. The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The 2-year LC, PFS, and OS were 90%, 48%, and 67%, respectively, with median TTP of 47.8 months. Subsequently, 23 patients underwent transplant, with a median time to transplant of 7 months. There were no greater than or equal to grade 3 nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than 1 grade, and 20% experienced progression in CTP class within 3 months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC less than or equal to 6 cm and that SBRT should be considered when bridging to transplant or as definitive therapy for those ineligible for transplant.

Ibarra et al. evaluated tumor response to SBRT in a combined multicenter database. (44) Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (ICC, n=11) treated with SBRT from 4 academic medical centers were entered into a common database. Statistical analyses were performed for freedom from local progression (FFLP) and patient survival. The overall FFLP for advanced HCC was 63% at a median follow-up of 12.9 months. Median tumor volume decreased from 334.2 to 135 cm (3) ($p<0.004$). The median time to local progression was 6.3 months. The 1- and 2-year OS rates were 87% and 55%, respectively. The incidence of grade 1-2 toxicities, mostly nausea and fatigue, was 39.5%. Grade 3 and 4 toxicities were present in 2 and one patients, respectively.

Price et al. reported the results of a Phase 1/2 trial that evaluated the radiologic response in 26 patients with HCC who were not surgical candidates and were treated with SBRT between 2005 and 2008. (45) Eligibility criteria included solitary tumors less than or equal to 6 cm or up to 3 lesions with sum diameters less than or equal to 6 cm, and well-compensated cirrhosis. All patients had imaging before, at 1 to 3 months, and every 3 to 6 months after SBRT. Patients received 3 to 5 fractions of SBRT. Median SBRT dose was 42 Gray (Gy) (range 24-48 Gy). Median follow-up was 13 months. Per Response Evaluation Criteria in Solid Tumors (RECIST), 4 patients had a complete response (CR), 15 had a partial response (PR), and 7 achieved stable disease (SD) at 12 months. One patient with SD experienced progression marginal to the treated area. The overall best response rate (CR + PR) was 73%. In comparison, by European Association for the Study of the Liver (EASL) criteria, 18 of 26 patients had greater than or equal to 50% nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being greater than 50% in 5 patients. Kaplan-Meier 1- and 2-year survival estimates were 77% and 60%, respectively. SBRT is effective therapy for patients with HCC with an overall best response rate (CR + PR) of 73%.

Louis et al. evaluated the feasibility, tolerance, and toxicity of SBRT in 25 HCC patients who were not eligible for other treatment modalities. (46) All patients had liver cirrhosis with an Eastern Cooperative Oncology Group (ECOG) performance score of less than 2 and pre-treatment Child scores ranging from A5 to B9. A total dose of 45 Gy in 3 fractions of 15 Gy each was prescribed to the 80% isodose line (95% of the planning target volume [PTV] received 45 Gy) and delivered to the target volume over 10-12 days. Overall, the treatment was well-tolerated with 2 grade 3 acute toxicities and no acute grade 4 toxicities. Late toxicity was minimal; all observed late toxicities occurred within the first 6 months of follow-up. Three hepatic recurrences at a distance from the initial target were observed. The actuarial 1- and 2-year local control rate was 95% (95% CI: 69-95%). At a median overall follow-up of 12.7 months (range, 1-24 months), 6 of the

25 (24%) patients have died. Overall actuarial survival at 1 and 2 years was 79% (95% CI: 52-92%) and 52% (95% CI: 19-78%), respectively.

Kwon et al. evaluated the long-term effect of SBRT for primary HCC in 42 patients ineligible for local ablation therapy or surgical resection. (47) Median tumor volume was 15.4 cc (3.0-81.8), and the median follow-up duration was 28.7 months (8.4-49.1). Complete response (CR) for the in-field lesion was initially achieved in 59.6% and partial response (PR) in 26.2% of patients. Hepatic out-of-field progression occurred in 18 patients (42.9%) and distant metastasis developed in 12 (28.6%) patients. Overall 1-year and 3-year survival rates were 92.9% and 58.6%, respectively. In-field progression-free survival (PFS) at 1 and 3 years was 72.0% and 67.5%, respectively. Patients with smaller tumors had better in-field PFS and overall survival (OS) rates (<32 cc vs. ≥32 cc, $p<0.05$). No major toxicity was encountered, but one patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Ongoing trials

One Phase 3 trial is identified that compares the use of transarterial chemoembolization and SBRT for recurrent hepatocellular carcinoma (NCT01327521).

Conclusion

Studies on the use of SBRT for HCC have consisted of heterogenous treatment schedules, treatment planning techniques and patient populations. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71-100% have been reported, it is not clear how SBRT should be used considering the use of established treatment modalities, including systemic therapy, radiofrequency ablation, and chemoembolization. Therefore, the use of SBRT for HCC is considered investigational.

Prostate Cancer

Katz and colleagues compared quality of life (QOL) after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early-stage prostate cancer. (48) QOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC), addressing urinary, sexual and bowel function. The EPIC data from the SBRT group was compared to the surgery group at baseline, 3 weeks, 5, 11, 24 and 36 months (SBRT group) and baseline, 1, 6, 12, 24, and 36 months (surgery group). The largest differences in QOL occurred 1-6 months after treatment, with larger declines in urinary and sexual QOL occurring in the surgery group, but a larger decline in bowel QOL after SBRT. The long-term urinary and sexual QOL declines remained clinically significantly lower for the patients who underwent prostatectomy but not for the SBRT patients.

McBride et al. reported on a multi-institutional experience with SBRT for early-stage, low-risk prostate adenocarcinoma. (49) A total of 4 centers and 45 patients were enrolled in a Phase 1, multi-institutional trial. Thirty-four patients received 7.5 grays (Gy) delivered in 5 fractions, 9 patients received 7.25 Gy delivered in 5 fractions, and 2 patients received other regimens. The variables evaluated were biochemical progression-free survival (bPFS), prostate-specific antigen (PSA) bounce, and toxicities. Health-related quality of life was evaluated using the Sexual Health Inventory for Men (SHIM), American Urological Association (AUA), and Expanded Prostate Cancer Index Composite (EPIC) questionnaires. The median follow-up for surviving patients was 44.5 months (range 0-62 months). The bPFS rate at 3 years was 97.7%. The median PSA declined

from 4.9 ng/mL at diagnosis to 0.2 ng/mL at last follow-up, and the median percentage PSA decline at 12 months was 80%. Nine patients experienced at least 1 PSA bounce ≥0.4 ng/mL, and 4 patients experienced 2 PSA bounces. The median time to first PSA bounce was 11.6 months (range 7.2-18.2 months), and the mean percentage PSA bounce was 1.07 ng/mL. There was one episode of late grade 3 urinary obstruction, and there were 2 episodes of late-grade 3 proctitis. There was a significant late decline in SHIM and EPIC sexual scores and a small, late decline in the EPIC Bowel domain score.

Boike et al. evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer. (50) Eligible patients included those with Gleason score 2 to 6 with prostate-specific antigen (PSA) ≤20, Gleason score 7 with PSA ≤15, ≤T2b, prostate size ≤60 cm (3), and American Urological Association (AUA) score ≤15. Dose-limiting toxicity was defined as grade 3 or worse gastrointestinal (GI)/genitourinary (GU) toxicity by Common Terminology Criteria of Adverse Events (version 3). Patients completed quality-of-life questionnaires at defined intervals. Groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions (45 total patients). The median follow-up is 30 months (range, 3 to 36 months), 18 months (range 0 to 30 months), and 12 months (range 3 to 18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all patients, GI grade ≥2 and grade ≥3 toxicity occurred in 18% and 2%, respectively, and GU grade ≥2 and grade ≥3 toxicity occurred in 31% and 4%, respectively. Mean AUA scores increased significantly from baseline in the 47.5-Gy dose level (p=0.002), as compared with the other dose levels, where mean values returned to baseline. Rectal quality-of-life scores (Expanded Prostate Cancer Index Composite) fell from baseline up to 12 months but trended back at 18 months. In all patients, PSA control was 100% by the nadir + 2 ng/mL failure definition.

Freeman and King presented the outcomes for low-risk prostate cancer patients with a median follow-up of 5 years after SBRT. (51) Between 2003 and 2005, a pooled cohort of 41 consecutive patients from 2 institutions received SBRT for clinically localized, low-risk prostate cancer. Prescribed dose was 35-36.25 Gy in 5 fractions. No patient received hormone therapy. Kaplan-Meier biochemical progression-free survival (defined using the Phoenix method) and Radiation Therapy Oncology Group (RTOG)-toxicity outcomes were assessed. At a median follow-up of 5 years, the biochemical progression-free survival was 93% (95% CI: 84.7% to 100%). Acute side effects resolved within 1-3 months of treatment completion. There were no grade 4 toxicities. No late grade 3 rectal toxicity occurred, and only one late grade 3 genitourinary toxicity occurred following repeated urologic instrumentation.

Jabbari et al. reported PSA nadir and acute and late toxicities with SBRT as monotherapy and post-external-beam radiation therapy (EBRT) boost for prostate cancer using high-dose rate (HDR) brachytherapy fractionation. (52) Thirty-eight patients had been treated with SBRT with a minimum follow-up of 12 months. Twenty of 38 patients were treated with SBRT monotherapy (9.5 Gy × 4 fractions), and 18 were treated with SBRT boost (9.5 Gy × 2 fractions) post-EBRT and androgen deprivation therapy. PSA nadir to date for 44 HDR brachytherapy boost patients with disease characteristics similar to the SBRT boost cohort was also analyzed as a descriptive comparison. SBRT was well-tolerated. With a median follow-up of 18.3 months (range 12.6-43.5), 42% and 11% of patients had acute Grade 2 gastrourinary and gastrointestinal toxicity, respectively, with no Grade 3 or higher acute toxicity to date. Two patients experienced late Grade 3 GU toxicity. All patients are without evidence of biochemical or clinical progression to date, and favorably low PSA nadirs have been observed with a current median PSA nadir of 0.35

ng/mL (range <0.01-2.1) for all patients (0.47 ng/mL, range 0.2-2.1 for the monotherapy cohort; 0.10 ng/mL, range, 0.01-0.5 for the boost cohort). With a median follow-up of 48.6 months (range 16.4-87.8), the comparable HDR brachytherapy boost cohort has achieved a median PSA nadir of 0.09 ng/mL (range 0.0-3.3). The authors concluded that early results with SBRT monotherapy and post-EBRT boost for prostate cancer demonstrated acceptable PSA response and minimal toxicity; PSA nadir with SBRT boost appeared comparable to those achieved with HDR brachytherapy boost.

King and colleagues reported the long-term outcomes of a Phase 2 prospective trial of SBRT for low-risk, biopsy-proven newly diagnosed prostate cancer in 67 patients enrolled between 2003 and 2009. (53) Low-risk was defined as a prebiopsy prostate specific antigen (PSA) of 10 ng/mL or less, a biopsy Gleason grade of 3+3 or 3+4, and a clinical stage T1c or T2a/b. Median patient age was 66 years. Treatment consisted of 36.25 Gy in 5 fractions using SBRT with CyberKnife. Patients who had received prior therapy (e.g. hormonal therapy) were excluded. The endpoints were early and late bladder and rectal toxicities, which were patient self-reported and graded on the Radiation Therapy Oncology Group (RTOG) scale. At baseline, 92% of patients reported no urinary issues and 8% had minor issues. Baseline function for the bowel was 89% with no issues and 11% with minor issues. Median follow-up was 2.7 years (25th-75th percentile, 1.8-4.5 years, maximum 5.9 years). There were no grade 4 toxicities. RTOG grade 1, 2 and 3 bladder toxicities were seen in 23%, 5% and 3% of patients, respectively. The grade 3 toxicities were attributed to dysuria exacerbated by urologic instrumentation. Grade 1, 2 and 3 rectal toxicities were seen in 12.5%, 2% and 0% of patients, respectively. There were 2 PSA, biopsy-proven failures with negative metastatic work-up. The 4-year PSA relapse-free survival was 94% (95% confidence interval [CI]: 85-102%). The authors concluded that significant bladder and rectal toxicities from SBRT for prostate cancer were infrequent.

A separate publication from the same Phase 2 trial outlined above reported sexual function in a subset of patients. (54) A literature review for other radiation modalities assessed by patient self-reported questionnaires served as historical comparison. Using the Expanded Prostate Cancer Index Composite (EPIC)-validated quality-of-life questionnaire, the sexual function of 32 consecutive patients were analyzed at median times of 4, 12, 20 and 50 months after treatment. The median follow-up was 35.5 months (range 12-62 months). The authors concluded that the rates of erectile dysfunction after treatment of prostate cancer with SBRT were comparable to those reported for other modalities of radiotherapy.

Katz and colleagues performed SBRT on 304 patients with clinically localized prostate cancer (211 with high-risk disease, 81 with intermediate-risk and 12 with low-risk disease): Fifty received 5 fractions of 7 Gy (total dose 35 Gy) and 254 received 5 fractions of 7.25 Gy (total dose 36.25 Gy). (55) At a median 30-month (range 26-37 months) follow-up, there were no biochemical failures for the 35-Gy dose level. Acute grade II urinary and rectal toxicities occurred in 4% of patients with no higher grade acute toxicities. At a median 17-month (range: 8-27 months) follow-up, the 36.25-Gy dose level had 2 low- and 2 high-risk patients fail biochemically (biopsy showed 2 low- and 1 high-risk patients were disease-free in the gland). Acute grade II urinary and rectal toxicities occurred in 4.7% and 3.6% of patients, respectively. The authors concluded that the low toxicity was encouraging and that additional follow-up is needed to determine long-term biochemical control and maintenance of low toxicity.

At 6 year follow-up, (56) late urinary grade II complications were seen in 4% of patients treated with 35 Gy and 9% of patients treated with 36.25 Gy. Five late grade III urinary toxicities occurred in patients treated with 36.25 Gy. Late grade II rectal complications were seen in 2% and 5% of patients treated with 35 Gy and 36.25 Gy, respectively. Initially, bowel and urinary QOL scores decreased but returned to baseline levels. There was an overall 20% decrease in the sexual QOL score. For patients who were potent prior to SBRT, 75% remained potent. Actuarial 5-year biochemical recurrence-free survival was 97% for patients with low-risk disease, 90.7% for those with intermediate risk, and 74.1% for high-risk patients.

Ongoing Clinical Trials

A Phase 3 study is active, which is an international, multicenter, randomized study of organ-confined low- and intermediate-risk prostate cancer and is composed of 2 parallel randomization schemes based on applicability of surgery as a treatment for the patient. Patients for whom surgery is a consideration are randomized to either laparoscopic or da Vinci prostatectomy or CyberKnife prostate SBRT. Patients for whom surgery is not a consideration are randomized to either conventionally fractionated radiation therapy or CyberKnife prostate SBRT. Efficacy, toxicity and quality-of-life outcomes will be compared across the pairs in each randomization. (NCT01584258).

A Phase III randomized open multicentre trial (ISRCTN45905321) is ongoing in Sweden comparing 78 Gy of intensity-modulated radiation therapy (IMRT) or 3-dimensional conformal RT (3D-CRT) in 39 2-Gy fractions to 42.7 Gy of SBRT in seven 6.1-Gy fractions, given every other day for men with T1c to T3a prostate cancer and up to 2 of the following risk factors: T3a, Gleason score 7 or higher, and/or PSA higher than 10 but lower than 20 ng/mL.

Conclusion

Limited data on the use of SBRT in prostate cancer consists of single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared to historical controls.

Although studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates, longer term follow up is needed to assess the effect on long-term toxicities, cancer control, and patient survival. Two ongoing randomized trials are comparing SBRT to accepted standard therapy. Therefore, the use of SBRT for prostate cancer is considered investigational.

Pancreatic Cancer

Goyal et al. reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were found not to be candidates for surgical resection. (57) A prospective database of the first 20 consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor was reviewed. Mean radiation dose was 25 Gray (Gy) (range 22-30 Gy) delivered over 1-3 fractions. Chemotherapy was given to 68% of patients in various schedules/timing. Patients had a mean gross tumor volume of 57.2 cm(3) (range 10.1-118 cm(3)) before SBRT. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21% and 38%, respectively ($p<0.05$). Median follow-up was 14.57 months (range 5-23 months). The overall rate of freedom from local progression at 6 and 12 months were 88% and 65% respectively. The probability of overall survival at 6 and 12 months were 89% and 56%,

respectively. No patient had a complication related to fiducial markers placement regardless of modality. The rate of radiation-induced adverse events was: grade 1-2 (11%) and grade 3 (16%). There were no grade 4/5 adverse events seen.

Rwigema et al. assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma. (58) The outcomes of 71 patients treated with SBRT for pancreatic cancer between 2004 and 2009 were reviewed. Forty patients (56%) had locally unresectable disease, 11 patients (16%) had local recurrence following surgical resection, 8 patients (11%) had metastatic disease, and 12 patients (17%) received adjuvant SBRT for positive margins. The median dose was 24 Gy (18-25 Gy), given in a single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meyer survival analyses were used to estimate freedom from local progression (FFLP) and overall survival (OS) rates. The median follow-up among surviving patients was 12.7 months (4-26 months). The median tumor volume was 17 mL (5.1-249 mL). The overall FFLP rates at 6 months/1 year were 71.7%/48.5%, respectively. Among those with macroscopic disease, FFLP was achieved in 77.3% of patients with tumor size less than 15 mL (n=22), and 59.5% for tumor size greater than or equal to15 mL (n=37) (p=0.02). FFLP was achieved in 73% following 24 to 25 Gy, and 45% with 18 to 22 Gy (p=0.004). The median OS was 10.3 months, with 6 month/1 year OS rates of 65.3%/41%, respectively. Grade 1-2 acute and late GI toxicity were seen in 39.5% of patients. Three patients experienced acute grade 3 toxicities. SBRT is feasible, with minimal grade ≥3 toxicity. The overall FFLP rate for all patients was 64.8%, comparable to rates with external-beam radiotherapy.

Chang et al. reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma. (59) Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 gray (Gy) in 1 fraction. Forty-five patients (58%) had locally advanced disease, 11 patients (14%) had medically inoperable disease, 15 patients (19%) had metastatic disease, and 6 patients (8%) had locally recurrent disease. Nine patients (12%) had received prior chemoradiotherapy. Sixteen patients (21%) received between 45 to 54 Gy of fractionated radiotherapy and SBRT. Various gemcitabine-based chemotherapy regimens were received by 74 patients (96%), but 3 patients (4%) did not receive chemotherapy until they had distant failure. The median follow-up was 6 months (range 3-31 months) and, among surviving patients, it was 12 months (range 3-31 months). The overall rates of freedom from local progression (FFLP) at 6 months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs. body/tail, 86%; p=0.52). The progression-free survival (PFS) rates at 6 months and 12 months were 26% and 9%, respectively. The PFS rate at 6 months was superior for patients who had nonmetastatic disease versus patients who had metastatic disease (28% vs. 15%; p=0.05). The overall survival (OS) rates at 6 months and 12 months from SBRT were 56% and 21%, respectively. Four patients (5%) experienced grade 2 or greater acute toxicity. Three patients (4%) experienced grade 2 late toxicity, and 7 patients (9%) experienced grade 3 or greater late toxicity. At 6 months and 12 months, the rates of grade 2 or greater late toxicity were 11% and 25%, respectively.

Conclusion

Combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. The role of SBRT as a radiation technique for pancreatic tumors has not been established, and it is not clear which patients would most likely benefit. Although studies have

shown promising local control rates, there have been no significant changes in patient survival compared to historical data, and some studies have shown unacceptable toxicity and questionable palliative effect. Therefore, the use of SBRT for pancreatic cancer is considered investigational.

Kidney Cancer

A 2012 systematic review on the use of stereotactic radiotherapy for primary renal cell carcinoma identified a total of 126 patients worldwide who had been treated using this modality. (60) A systematic search performed in January 2012 identified 7 retrospective studies and 3 prospective studies that used a wide range of techniques, doses and dose fractionation schedules. Median or mean follow-up ranged from 9 months to 57.5 months. Local control was reported as 93.9% (range 84-100%) and the rate of severe grade 3 or higher adverse events was 3.8% (range 0-19%). The conclusions of the systematic review were that the current literature suggests that stereotactic radiotherapy for renal cell carcinoma can be delivered with good rates of local control and acceptable toxicity but that there is insufficient evidence to recommend a consensus for dose fractionation or technique, and there is a need for further prospective studies.

Beitler et al. reported outcomes in 9 patients with nonmetastatic renal cell carcinoma, 2 of whom had bilateral renal cell cancers. (61) Patients were treated definitively with 40 Gy in 5 fractions using SBRT. With a median follow up of 26.7 months, 4 of the 9 patients were alive. The survivors had a minimum follow-up of 48 months. At presentation, all 4 of the survivors had tumors less than or equal to 3.4 cm in largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Conclusion

The literature on the use of SBRT for renal cell carcinoma consists of very small case series, and no impact on patient outcomes can be derived from these data, nor any comparison made between this treatment modality and more established treatment modalities for renal cell carcinoma. Therefore, the use of SBRT for kidney cancer is considered investigational.

Oligometastases

2012 and 2013 reviews on the use of SBRT for oligometastases summarize the data on local tumor control, and in a limited subset of patients, survival, for various anatomical sites. (1, 2, 62)

A 2012 long-term follow-up of a prospective study was reported on oligometastases treated with SBRT. (63) The authors prospectively analyzed the long-term survival, tumor control outcomes and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with 5 or fewer clinically detectable metastases, from any primary site, metastatic to 1 to 3 organ sites, and treated with SBRT. For patients with breast cancer, the median follow-up was 4.5 years (7.1 years for 16 of 39 patients alive at the last follow-up visit). The 2-year OS, FFDM and local control (LC) rate was 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and LC rate were 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases (p=0.057) and one versus more than one metastasis (p=0.055) were associated with a 4-fold and 3-fold reduced hazard of death, respectively. None of the 17 bone lesions that were from breast cancer recurred after SBRT versus 10 of 68 lesions from other organs that recurred (p=0.095). For patients with non-breast cancers, the median follow-up was 1.7 years (7.3 years for 7 of 82 patients alive at the last follow-up visit). Two-year OS, FFDM, and LC rate were 39%,

28%, and 74%, respectively, and 6-year OS, FFDM, and LC rate were 9%, 13%, and 65%, respectively. For non-breast cancers, a greater SBRT target volume was significantly adverse for OS (p=0.012) and lesion LC (p<0.0001). Patients, whose metastatic lesions demonstrated radiographic progression after systemic therapy but before SBRT, experienced significantly worse OS compared with patients with stable or regressing disease. The authors conclude that select patients with limited metastases treated with SBRT are long-term survivors.

Lung Oligometastases
For isolated or a few lung metastases (including less than 3 or less than 5, according to different selection criteria), the local control probability at 1 year has been reported in the range of 70-100%. (1) In most series, the most common clinical presentation is a single-lung metastasis. It is difficult to accurately evaluate survival estimates and clinical outcomes using SBRT for lung metastases due to an absence of randomized trials and because most Phase 1 and 2 trials included heterogeneous patient populations. (1)

It is also difficult to compare OS data from SBRT with that of historical surgical metastasectomy series, mainly because of the different clinical characteristics of the patients, as most patients referred for SBRT are felt to be inoperable due to medical comorbidities that affect OS outcomes. (1) Data from the International Registry of Lung Metastases reported OS of 70% at 2 years and 36% at 5 years in patients with a single metastasis who underwent surgical metastasectomy. (64)

A systematic review by Siva and colleagues on the use of SBRT for pulmonary oligometastases estimated from the largest studies included in the review a 2-year weighted OS rate of 54.5% (65), ranging from higher rates in a study by Norisha and colleagues of 84% (66) to lower rates, such as 39%, reported from a multi-institutional trial. (67)

Liver Oligometastases
The liver is the most common site of metastatic spread of colorectal cancer (CRC). Data show that surgical resection of limited liver metastases can result in long-term survival in select patients. However, only 10-20% of patients with metastatic CRC to the liver are surgical candidates. In patients who are not considered to be candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are radiofrequency ablation (RFA) and transarterial chemoembolization. Retrospective analyses of RFA for liver metastases from CRC have shown wide variability in 5-year OS rates, ranging from 14% to 55%. (1)

Retrospective series on the use of SBRT has reported local control rates ranging from 57-100%. (1) Prospective studies have reported 1-year OS rates ranging from 61-85% and 2-year OS rates ranging from 30-62%. (1)

One of the larger series that was reported by Chang et al. studied outcomes of SBRT for colorectal liver metastases in a pooled patient cohort from 3 institutions with colorectal liver metastases. (68) Patients were included if they had 1 to 4 lesions, received 1 to 6 fractions of SBRT, and had radiologic imaging 3 months or more post-treatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had 1 or more chemotherapy regimens before stereotactic body radiotherapy, and 27 (42%) patients had 2 or more regimens. The median follow-up was 1.2 years (range, 0.3-5.2 years). The median

dose was 42 gray (Gy; range, 22-60 Gy). One- and 2-year LC rates were 67% and 55%, respectively. One- and 2-year OS rates were 72% and 38%, respectively.

These studies have had relatively short follow-up times, typically less than 18 months. They are also limited by relatively small numbers of patients in the studies and differences in the systemic therapies administered, which may have affected treatment outcomes.

Adrenal Gland Oligometastases
The most frequent primary tumor that metastasizes to the adrenal glands is non-small cell lung cancer. Longer OS times have been reported with resection of clinically isolated adrenal metastases when compared with nonsurgical therapy, which has included locally ablative techniques, embolization and EBRT. Few studies on the use of SBRT in adrenal metastases have been published. Local control rates at 1 year ranging from 55% to 90% have been reported, and 1-year OS rates ranging from 40% to 56% and 2-year OS ranging from 14% to 33%. (1)

Scorsetti et al. described the feasibility, tolerability and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients. (69) Between 2004 and 2010, a total of 34 patients, accounting for 36 adrenal metastatic lesions, were treated with SBRT. All 34 patients were clinically and radiologically evaluated during and after completion of SBRT. The following outcomes were taken into account: best clinical response at any time, local control, time-to-systemic progression, time-to-local progression, overall survival and toxicity. The Kaplan-Meier method was used to estimate survival and factors that could potentially affect outcomes were analyzed with Cox regression analysis. No cases of grade 3or greater toxicity were recorded. At a median follow-up of 41 months (range 12-75 months), 22 patients were alive. Eleven percent of lesions showed complete response, 46% partial response, 36% stable disease and 7% progressed in the treated area. Local failure was observed in 13 cases and actuarial local control rates at 1 and 2 years were 66% and 32%, respectively. Median time-to-local progression was 19 months and median survival was 22 months.

Holy et al. presented initial institutional experiences with SBRT for adrenal gland metastases. (70) Between 2002 and 2009, 18 patients with non-small cell lung cancer and adrenal metastases received SBRT for the metastatic disease. Metastases were isolated in 13 patients and multiple in 5 patients. A median progression-free survival time of 4.2 months was seen in the entire patient group, with an increased PFS of 12 months in the 13 patients with isolated metastasis. After a median follow-up of 21 months, 77% of the patients with isolated adrenal metastasis achieved local control. In these patients, median OS was 23 months.

Casamassima et al. evaluated a retrospective single-institution outcome after hypofractionated SBRT for adrenal metastases. (71) Between 2002 and 2009, 48 patients were treated with SBRT for adrenal metastases. Eight patients were treated with single-fraction SBRT and 40 patients with multi-fraction. Median follow-up was 16.2 months (range 3-63 months). At time of analysis, 20 patients were alive and 28 patients were dead. One- and 2-year actuarial OS rates were 39.7% and 14.5%, respectively. The median interval to local failure was 4.9 months. The actuarial 1-year disease control rate was 9%; the actuarial 1- and 2-year local control rates were both 90%.

Chawla et al. investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands. (72) A retrospective review of 30 patients who had undergone

SBRT for adrenal metastases from various primary sites, including lung (n=20), liver (n=3), breast (n=3), melanoma (n=1), pancreas (n=1), head and neck (n=1), and unknown primary (n=1) was performed. Of the 30 patients, 14 with 5 or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease. Sixteen patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Twenty-four patients had more than 3 months of follow-up with serial computed tomography. Of these 24 patients, 1 achieved a complete response, 15 achieved a partial response, 4 had stable disease, and 4 developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. Local control was poor, and most patients developed widespread metastases shortly after treatment, with 1-year survival, local control, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed grade 2 or greater toxicity.

Ongoing Clinical Trials

An active randomized clinical Phase III trial is testing the efficacy of radiofrequency ablation and stereotactic body radiotherapy SBRT in the treatment of colorectal carcinoma liver metastases. Primary endpoint is local progression-free survival.

Conclusion

Systemic therapy is most frequently the preferred therapy for patients with liver metastases, but surgical excision or local tumor ablation strategies are often considered for patients with limited disease.

The role of SBRT in metastases to the liver is not clear. The optimal dose and fractionation is not known, nor is there consensus on the maximum size or number of lesions suitable to SBRT. The literature on the use of SBRT in liver metastases is limited by the small numbers of patients in the studies, retrospective analyses, and the inclusion of mixed tumor types in the local control and survival analyses. Therefore, the use of SBRT for hepatic metastases is considered investigational.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 3 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review for September 2013. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Support for the use of SBRT for HCC, prostate cancer and oligometastases and SRS for uveal melanoma was mixed.

In response to requests, input was received from 6 physician specialty societies (8 reviewers) and 4 academic medical centers, for a total of 12 reviewers, while this policy was under review for October 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of

appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was general agreement with the policy statements for the use of stereotactic radiosurgery in treating the neoplasms/conditions listed in the policy statements. In addition, there was support to expand the policy statements on the use of stereotactic radiosurgery to include craniopharyngiomas and glomus jugulare tumors.

There was general support for the use of SBRT in spinal tumors and early-stage NSCLC and support to expand the use in the spine to include metastatic radioresistant tumors. Support for the use in primary and metastatic lesions of the liver, pancreas, adrenal and kidney was mixed. There was little support for the use of SBRT in prostate cancer.

In response to requests, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review for December 2008. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The input uniformly supported use of this technology in the treatment of NSCLC and spinal tumors after prior radiation therapy. There was also support for use in some patients with liver (metastatic and primary) cancer and as first-line treatment of spinal tumors. There was little support for its use in cases of prostate cancer.

Summary

Stereotactic radiosurgery is an established safe and effective treatment modality for many benign and malignant intracranial tumors/conditions. Improved outcomes using stereotactic body radiation therapy have also been demonstrated in patients with early-stage non-small cell lung cancer who are not considered to be candidates for resection. The literature and input from clinical vetting support its use in spinal tumors that have been previously irradiated and in radioresistant metastases to the spine.

There is insufficient evidence or clinical support for the use of stereotactic radiation therapy/stereotactic body radiation therapy to treat other conditions including, but not limited to, uveal melanoma and extracranial tumors except for lung and spinal tumors as outlined above, and seizures.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines.

NCCN guidelines for the treatment of central nervous system tumors (v.2.2013) recommends, as category 2A, stereotactic radiosurgery for certain benign and malignant brain tumors, limited (1-3) metastatic lesions as category 2A if used alone; category 1 if with whole brain radiation for 1 metastasis, for multiple (>3) metastatic lesions category 2A, certain metastatic spinal tumors and primary spinal cord tumors if re-irradiating (category 2A).

For primary non-small cell lung cancer, NCCN guidelines (v2.2013) recommend SBRT for inoperable early-stage disease. (category 2A).

For prostate cancer, NCCN guidelines (v.2.2013) state that SBRT requires longer follow-up and prospective multi-institutional data to evaluate longer term results.

For hepatocellular carcinoma, NCCN guidelines (v.2.2012) state that radiation therapy (conformal or stereotactic) is one of the options to consider in patients with unresectable HCC with local disease (category 2B).

For colon cancer metastatic to the liver (colon cancer guidelines v3.2013), NCCN considers radiation in highly selected cases in which the patient has a limited number of metastases (category 3) or in the setting of a clinical trial.

For pancreatic adenocarcinoma (v1.2013), NCCN recommends that SBRT only be utilized as part of a clinical trial.

For the treatment of primary kidney cancer (v1.2013), NCCN guidelines do not address the use of SBRT.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment (Effective 01-01-2013)
61781	Stereotactic computer-assisted (navigational) procedure; cranial, intradural (list separately in addition to code for primary procedure)
61782	Stereotactic computer-assisted (navigational) procedure; cranial, extradural (list separately in addition to code for primary procedure)
61783	Stereotactic computer-assisted (navigational) procedure; spinal (list separately in addition to code for primary procedure)
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)

61800 Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
63620 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
77371 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesion(s) consisting of 1 session; multi-source Cobalt 60 based
77372 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesion(s) consisting of 1 session; linear accelerator based
77373 Stereotactic body radiation therapy, treatment delivery per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77432 Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session)
77435 Stereotactic body radiation therapy, treatment management, per treatment course, to one or more lesions, including image guidance, entire course not to exceed 5 fractions
G0173 Linear accelerator based stereotactic radiosurgery, complete course of therapy in one Session
G0251 Linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum five sessions per course treatment.
G0339 Image-guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment.
G0340 Image-guided robotic linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions; maximum five sessions per course of treatment.

DIAGNOSIS

162.3 Malignant neoplasm of upper lobe, bronchus or lung
162.4 Malignant neoplasm of middle lobe, bronchus or lung
162.5 Malignant neoplasm of lower lobe, bronchus or lung
162.8 Malignant neoplasm of other parts of bronchus or lung
162.9 Malignant neoplasm of bronchus and lung, unspecified
171.0 Malignant neoplasm of connective and other soft tissue, head, face and neck (schwannoma)
190.0 Malignant neoplasm of eyeball, except conjunctiva, cornea, retina, and choroid
190.1 Malignant neoplasm of Orbit
190.2 Malignant neoplasm of Lacrimal gland
190.3 Malignant neoplasm of Conjunctiva
190.4 Malignant neoplasm of Cornea
190.5 Malignant neoplasm of Retina
190.6 Malignant neoplasm of Choroid
190.7 Malignant neoplasm of Lacrimal duct
190.8 Malignant neoplasm of eye, Other specified sites of eye
190.9 Malignant neoplasm of eye, part unspecified
191.0 Malignant neoplasm of cerebrum, except lobes and ventricles

191.1 Malignant neoplasm of frontal lobe
191.2 Malignant neoplasm of temporal lobe
191.3 Malignant neoplasm of parietal lobe
191.4 Malignant neoplasm of occipital lobe
191.5 Malignant neoplasm of ventricles
191.6 Malignant neoplasm of cerebellum NOS
191.7 Malignant neoplasm of brain stem
191.8 Malignant neoplasm of other parts of brain
191.9 Malignant neoplasm of brain, unspecified
192.1 Malignant neoplasm of cerebral meninges
192.2 Malignant neoplasm of spinal cord
192.3 Malignant neoplasm of spinal meninges
198.3 Secondary malignant neoplasm of brain and spinal cord
198.4 Secondary malignant neoplasm of other parts of nervous system(meninges)
225.1 Benign neoplasm of cranial nerves (acoustic neuroma)
225.2 Benign neoplasm of cerebral meninges
225.3 Benign neoplasm of spinal cord
225.4 Benign neoplasm of spinal meninges
227.3 Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)
237.5 Neoplasm of uncertain behavior, brain and spinal cord
237.6 Neoplasm of uncertain behavior, meninges
253.0 Disorders of the pituitary gland and its hypothalamic control; acromegaly and gigantism
255.0 Cushing's syndrome
350.1 Trigeminal neuralgia
747.81 Anomalies of cerebrovascular system (arteriovenous malformation)

ICD-10 Diagnosis *(Effective October 1, 2014)*
C34.11 Malignant neoplasm of upper lobe, right bronchus or lung
C34.12 Malignant neoplasm of upper lobe, left bronchus or lung
C34.2 Malignant neoplasm of middle lobe, bronchus or lung
C34.31 Malignant neoplasm of lower lobe, right bronchus or lung
C34.32 Malignant neoplasm of lower lobe, left bronchus or lung
C34.81 Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82 Malignant neoplasm of overlapping sites of left bronchus and lung
C34.91 Malignant neoplasm of unspecified part of right bronchus or lung
C34.92 Malignant neoplasm of unspecified part of left bronchus or lung
C47.0 Malignant neoplasm of peripheral nerves of head, face and neck
C49.0 Malignant neoplasm of connective and soft tissue of head, face and neck
C69.01 Malignant neoplasm of right conjunctiva
C69.02 Malignant neoplasm of left conjunctiva
C69.11 Malignant neoplasm of right cornea
C69.12 Malignant neoplasm of left cornea
C69.21 Malignant neoplasm of right retina
C69.22 Malignant neoplasm of left retina
C69.31 Malignant neoplasm of right choroid
C69.32 Malignant neoplasm of left choroid
C69.41 Malignant neoplasm of right ciliary body
C69.42 Malignant neoplasm of left ciliary body

C69.51 Malignant neoplasm of right lacrimal gland and duct
C69.52 Malignant neoplasm of left lacrimal gland and duct
C69.61 Malignant neoplasm of right orbit
C69.62 Malignant neoplasm of left orbit
C69.81 Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82 Malignant neoplasm of overlapping sites of left eye and adnexa
C69.91 Malignant neoplasm of unspecified site of right eye
C69.92 Malignant neoplasm of unspecified site of left eye
C70.0 Malignant neoplasm of cerebral meninges
C70.1 Malignant neoplasm of spinal meninges
C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1 Malignant neoplasm of frontal lobe
C71.2 Malignant neoplasm of temporal lobe
C71.3 Malignant neoplasm of parietal lobe
C71.4 Malignant neoplasm of occipital lobe
C71.5 Malignant neoplasm of cerebral ventricle
C71.6 Malignant neoplasm of cerebellum
C71.7 Malignant neoplasm of brain stem
C71.8 Malignant neoplasm of overlapping sites of brain
C71.9 Malignant neoplasm of brain, unspecified
C72.0 Malignant neoplasm of spinal cord
C72.1 Malignant neoplasm of cauda equina
C79.31 Secondary malignant neoplasm of brain
C79.32 Secondary malignant neoplasm of cerebral meninges
C79.49 Secondary malignant neoplasm of other parts of nervous system
D32.0 Benign neoplasm of cerebral meninges
D32.1 Benign neoplasm of spinal meninges
D33.3 Benign neoplasm of cranial nerves
D33.4 Benign neoplasm of spinal cord
D35.2 Benign neoplasm of pituitary gland
D35.3 Benign neoplasm of craniopharyngeal duct
D42.0 Neoplasm of uncertain behavior of cerebral meninges
D42.1 Neoplasm of uncertain behavior of spinal meninges
D43.0 Neoplasm of uncertain behavior of brain, supratentorial
D43.1 Neoplasm of uncertain behavior of brain, infratentorial
D43.4 Neoplasm of uncertain behavior of spinal cord
E22.0 Acromegaly and pituitary gigantism
E24.0 Pituitary-dependent Cushing's disease
E24.2 Drug-induced Cushing's syndrome
E24.3 Ectopic ACTH syndrome
E24.8 Other Cushing's syndrome
E34.4 Constitutional tall stature
G50.0 Trigeminal neuralgia
Q28.2 Arteriovenous malformation of cerebral vessels
Q28.3 Other malformations of cerebral vessels

REVISIONS

09-25-2007	Created two policies from the one Stereotactic Radiosurgery policy entitled: 1. Stereotactic Radiosurgery other than CyberKnife ▪ Policy section the same as previous Stereotactic Radiosurgery policy 2. Stereotactic Radiosurgery and Radiotherapy – CyberKnife ▪ In Policy section added the following indication: 12. Pulmonary malignancies with at least one of the following characteristics: a. Medically inoperable early stage non-small cell lung cancer (T1 and T2) 5 cm or less in size b. Radioresistant histological subtypes that are not amenable to conventional radiation therapy c. Oligometastatic disease (no more than 5 metastases) deep in the parenchyma and not readily accessible by surgery d. Metastases near vital structures e. Focally persistent or recurrent stage II or III non-small cell lung cancer after prior chemoradiation
06-26-2008	Created one policy entitled Stereotactic Radiosurgery and Radiotherapy from two policies: 1. Stereotactic Radiosurgery other than CyberKnife, and 2. Stereotactic Radiosurgery and Radiotherapy – CyberKnife The policy language was combined into one policy.
01-01-2009	In Coding section: ▪ Removed CPT code 61793 as code was deleted by CPT for 2009. ▪ Added new 2009 CPT codes 61796, 61797, 61798, 61799, 61800, 63620, 63621.
06-16-2009	In Policy section: ▪ On #5 added "indolent or" to read, "Solitary or multiple brain metastases (initial treatment or treatment of recurrence for patients having good performance status and indolent or no active systemic disease)" ▪ On #12 removed "(e.g. CyberKnife)" In Coding section: ▪ Added CPT code 61795. ▪ Added Diagnosis codes 132.3, 162.4, 162.5, 162.8, 162.9
02-25-2011	In Coding section: ▪ Added CPT codes 61781, 61782, 61783 ▪ Removed CPT code 61795
01-15-2013	In the Coding section: ▪ Added CPT code 32701 (Effective 01-01-2013)
03-27-2014	Updated Description section.
	In Policy section: ▪ Removed Item A, 9, "Uveal melanoma" ▪ In Item B, added "treatment of uveal melanoma" to read "All other uses of stereotactic radiosurgery are considered experimental / investigational including, but not limited to, treatment of chronic pain, treatment of uveal melanoma,..."
	Added Rationale section.

	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.

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