Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual Surgery, Policy No. 214

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites

Effective: August 1, 2019

Next Review: July 2020
Last Review: July 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) are radiotherapy techniques that use highly focused radiation beams to treat both neoplastic and non-neoplastic conditions, in contrast to traditional external radiation beam therapy, which involves the use of relatively broad fields of radiation over a number of sessions that may occur over weeks to months.

MEDICAL POLICY CRITERIA

I. Stereotactic radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Body Radiotherapy (SABR), may be considered **medically necessary** for initial treatment or treatment of recurrence for any of the following indications:

   A. Hemangioblastoma of the spine

   B. Hemangiopericytoma outside of intracranial, skull base, or orbital sites

C. Hepatic tumor (primary or metastatic) as palliative or curative treatment when both of the following are met:
    1. Absence or minimal extra hepatic disease; and
    2. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

D. Hepatocellular carcinoma when all of the following criteria are met:
    1. Five or fewer hepatic lesions; and
    2. Size of largest lesion is 6 cm diameter or less; and
    3. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

E. Lung metastases when both of the following criteria are met:
    1. Five or fewer metastatic lung lesions; and
    2. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

F. Non-small cell lung cancer (NSCLC), primary (node negative, tumor stage T1a, T1b, T2a, T2b)

G. Oligometastases when the following criteria are met:
    1. Five or fewer metastatic lesions; and
    2. Primary is controlled, stable, or expectation of the same; and
    3. Metastases are limited to one to three organs; and
    4. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

H. Osteosarcoma, metastatic when all of the following criteria are met:
    1. Five or fewer metastatic lesions; and
    2. Karnofsky performance score greater than or equal to 60 or an ECOG score less than or equal to 2 (See Policy Guidelines).

I. Pancreatic adenocarcinoma, locally advanced, borderline resectable, inoperable (See Policy Guidelines) or local recurrence after resection

J. Paraganglioma

K. Prostate cancer, low- to intermediate-risk (See Policy Guidelines) when all of the following criteria are met:
    1. Stage less than T3a; and
    2. PSA less than or equal to 20; and
    3. Gleason Score less than 8.

L. Renal cell cancer, inoperable primary, when a urological surgeon has documented inoperability

M. Spinal or paraspinal tumors (primary or metastatic)

II. Stereotactic radiosurgery and stereotactic body radiation therapy (also known as Stereotactic ablative body radiotherapy) are considered **investigational** for all other indications outside of intracranial, skull base, or orbital sites, including but not limited to: Tumors, primary, of the following sites: cervix, endometrium, esophagus, hemangiomas, large bowel, ovaries, rectum, and small bowel

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

For the purposes of this policy, neoplasm is defined as "an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer)."[1]

PERFORMANCE STATUS MEASUREMENT

Performance status is frequently used in oncology practice as a variable in determining prognosis and management strategies. Either the Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) Performance Status scoring systems may be used.

Karnofsky Performance Status

100	Normal, without symptoms
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance; able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated
20	Very sick; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly

ECOG Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Pancreatic Adenocarcinoma Resectability

See Appendix II. for the National Comprehensive Cancer Network definition of resectability for pancreatic adenocarcinoma.

Prostate Cancer Risk

The National Comprehensive Network (NCCN) Clinical Practice Guideline for Prostate Cancer defines low risk prostate cancer as T1-T2a, Gleason score less than or equal to six/Gleason grade one, and PSA less than 10ng/mL.[2] Intermediate risk is defined as T2b-T2c or Gleason score of seven/Gleason grade group two or three, or PSA 10-20ng/ml.

FRACTIONATION

Fractionated stereotactic radiotherapy refers to when SRS or SBRT are performed in 1-10 treatments focused upon a specific site. SRS is commonly delivered in 1-5 fractions and SBRT or SABR is commonly delivered in 1-5 fractions but may be delivered in as many as 10 fractions.

DOSE CONSTRAINT REFERENCES

Radiation Therapy Oncology Group (RTOG) Radiation Dose Constraints

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/RTOG

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)

Available from: https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/QUANTEC

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History/Physical and Chart notes, including requirements as outlined by the policy criteria, as applicable to the indication for treatment.
- As applicable, documentation of sites, size and count of lesions
- As applicable, documented ECOG score or Karnofsky performance score
- As applicable, absent or minimal extra hepatic disease for extracranial site treatment
- For prostate cancer, PSA and Gleason score.

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
2. Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid, Medicine, Policy No. 164
3. Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, and Pelvis, Medicine, Policy No. 165
4. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
5. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213

BACKGROUND

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) rely on three-dimensional imaging to localize the therapy target. SRS and SRBT have been used for a range

of malignant and non-malignant conditions. Because they are more targeted than traditional external radiation therapy, SRS and SRBT are often used for treatment at sites that are difficult to reach via surgery, located close to other vital structures, or subject to movement within the body. The term SBRT will be used to describe treatment also referred to as stereotactic ablative body radiotherapy (SABR).

SRS and SBRT (or SABR) employ similar technological "stereotactic" sophistication with elements of advanced pretreatment imaging for localization of target(s), patient immobilization, control of breathing associated tumor movement, focally targeted treatment planning, and daily image guidance to ensure precise delivery of high daily doses of radiation. As commonly used in the medical literature, SRS refers to intracranial treatments and SBRT refers to extracranial treatments. Alternatively, SRS and SBRT may be defined independent of whether treatment is directed to intra or extra cranial tumors volumes. According to this definition, when such treatment is given as a single fraction, it may be referred to as SRS, and when it is delivered in 2-10 fractions it may be referred to as SBRT or SABR.

The fractionation used for SRS and SBRT is referred to as “hypofractionated” because it is fewer treatments than those used for conventional external beam radiotherapy.” 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 it 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.

SRS and SBRT can be administered by several types of devices that are distinguished by their source of radiation, including particle beams (e.g., proton), gamma radiation from cobalt-60 sources, or high-energy photons from linear accelerator (LINAC) systems. The Gamma Knife and linear accelerator systems (including the Cyberknife®) are similar in concept; both use multiple photon radiation beams that intersect at a stereotactically determined target, thus permitting higher doses of radiation delivery with sparing of surrounding normal tissues. The differences between the two relate to how the energy is produced (i.e., through decaying cobalt-60 in the gamma knife devices, or from x-rays in the linear accelerator system) and the number of energy sources used (i.e., multiple energy sources in the gamma knife versus one in the linear accelerator system).

IMAGE-GUIDED RADIOSURGERY OR RADIOTHERAPY

Image-guided radiosurgery or radiotherapy is a relatively new development collectively describing units with real-time image guidance systems. Examples include the Cyberknife® device, BrainLAB Novalis®, TomoTherapy®, and LINAC with computerized tomography (CT).

REGULATORY STATUS

Several devices that use cobalt 60 radiation (gamma ray devices) for SRS have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The most commonly used gamma ray device is the GammaKnife (Elekta; approved May 1999). Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by the FDA through the 510(k) premarket notification process including the Novalis Tx®

(Novalis, Westchester, IL); the TrueBeam STx (Varian Medical Systems, Palo Alto, CA, approved December 2012); and the CyberKnife® System (Accuray, Inc.; approved December 1998). LINAC-based devices may be used for intracranial and extracranial lesions.

Note: Particle radiation can also be used without stereotactic guidance. In this setting, the use of particles is referred to as proton, helium, or neutron radiation *therapy*. Proton or helium ion radiation therapies (RT), intraocular RT for age-related macular degeneration, and electromagnetic navigation bronchoscopy for placement of fiducial markers are considered in separate medical policies. See cross-reference section below.

EVIDENCE SUMMARY

The selection of variables used in the delivery of SRS and SBRT is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins All of these variables depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Trials that allow direct comparison of all of the possible variables involved in selecting specific SRS and SBRT methods do not broadly exist making it difficult to draw comparative effectiveness conclusions. Further, for many rare conditions, large comparative studies are unlikely. The evidence below will focus on indications with criteria and investigational indications.

Please note that the evidence review below does not compare specific radiation planning and delivery techniques.

Spinal Tumors

In 2017, Huo performed a systematic review of SRS for the spine. The authors found local control rates at a 12-18 months to be between 80.5 and 95%.[3] They found that with strict quality assurance, efficacious results can be obtained but that a number of contraindications to spine SBRT should be avoided, including spinal instability, poor performance status, and high-grade epidural disease.

Jawad (2016) evaluated 594 spinal tumors treated with SBRT at eight different institutions. 24% of cases had preexisting vertebral compression fractures.[4] At a median follow up of 10.1 months, 80% of patients had local tumor control. At the last imaging follow-up was (median 8.8 months after SBRT), 3% had new vertebral compression fractures and 2.7% had progressive vertebral compression fractures.

Sahgal (2013) evaluated rates of vertebral compression fractures after SBRT in 252 patients with 410 spinal segments treated with SBRT.[5] Fifty-seven fractures were observed (13.9% of spinal segments treated), with 27 *de novo* fractures and 30 cases of existing fracture progression. Most fractures occurred relatively early posttreatment, with a median and mean time to fracture of 2.46 months and 6.33 months, respectively. Radiation dose per fraction, baseline vertebral compression fracture, lytic tumor, and baseline spinal misalignment were predictive of fracture risk.

Gerszten (2007) published results on a series of 500 cases from a single institution (334 tumors had previously undergone external beam irradiation) using the CyberKnife system.[6] 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 (2007) reported on phase one/two results of SBRT in 74 spinal lesions in 63 patients (55% had prior irradiation) with cancer.[7] The actuarial one-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed two 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.

Gerszten (2004) 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.[8] Most patients were treated for pain control and also had prior EBRT. The authors point out that radiotherapy 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 EBRT typically is delivered over a course of 10 to 20 fractions. In contrast, in this study, only one CyberKnife treatment session was used. In a 2005 study, Degen (2005) reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife.[9] Patients underwent a median of three treatments. Pain was improved, as measured by declining mean visual analog scale (VAS) score, and quality of life was maintained during the one-year study period.

Section Summary

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

Non-Small-Cell Lung Cancer

Systematic Reviews

In 2014, Zheng reported results from a systematic review and meta-analysis comparing survival after SBRT with survival after surgical resection for the treatment of stage I NSCLC.[10] The authors included 40 studies reporting outcomes from SBRT, including 4850 patients, and 23 studies reporting outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at one, three, and five years were 83.4%, 56.6%, and 41.2%, respectively. The mean unadjusted OS rates at one, three, and five years were 92.5%, 77.9%, and 66.1%, respectively, with lobectomy, and 93.2%, 80.7%, and 71.7% with limited lung resections. After adjustment for surgical eligibility (for the 27 SBRT studies that reported surgical eligibility) and age, in a multivariable regression model,

the treatment modality (SBRT vs surgical therapy) was not significantly associated with OS (p=0.36).

A review by Nguyen (2008)[11] 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 five-year survival was 42%. Koto reported on a phase two study of 31 patients with stage one NSCLC.[12] 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 three-year OS was 72%, while disease-free survival was 84%. Five patients developed grade two or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported three-year disease-specific survival rates of 49% for those with stage one disease.[13]

Nonrandomized Comparative Studies

Numerous nonrandomized, comparative studies have compared SBRT with surgery for NSCLC. A few of them used matching and are therefore are the strongest methodologically of this group. Lam (2018) performed a matched analysis of cases in the National Cancer Database of stage 1a and 1b NSCLC treated with primary RF ablation or SBRT.[14] A total of 4,454 SBRT- and 335 RF-treated patients were included. There were significantly more comorbidities (p<0.001) and unplanned readmission within 30 days (p<0.001) in the RF ablation group. A multivariate Cox regression analysis of OS for the unmatched groups showed no significant difference (p=0.285). In the matched groups, no difference was found with one-, three- and five-year OS of 85.5%, 54.3%, and 31.9% in the SBRT group vs 89.3%, 52.7%, and 27.1% in the RF ablation group (p=0 .835).

von Reibnitz (2018) analyzed 497 patients with early-stage NSCLC (T1-T2N0M0) treated with conventional radiation (n=127) or SBRT (n=398).[15] Median follow-up was 24.4 months. The Kaplan-Meier method was used to estimate OS and the Cox regression model was used to compare between groups. Propensity score matched analysis was performed using seven patient and clinical variables: age, gender, Karnofsky performance status (KPS), histology, T stage, biologically equivalent dose (BED), and history of smoking. Three-year local failure and OS rates were 38.9% for conventional radiation and 13.6% for SBRT (p<0.001) and 38.9% for conventional radiation and 53.1% for SBRT, respectively. Propensity score matching indicated a statistically significant improvement of OS for SBRT (p=0.0497).

Two matched analyses used the SEER (Surveillance, Epidemiology, and End Results) database to identify patients. Yu (2015) identified elderly patients with stage I NSCLC who received either SBRT or surgery from 2007 to 2009.[16] Propensity matching was used to select two surgery patients for each SRS patient. A total of 367 SBRT patients were matched with 711 surgery patients. Early mortality at three months was significantly better for the SBRT group compared to the surgery group (2.2% vs 6.1%, p=0.005). However, late mortality at 24 months was significantly worse for the SBRT group (40.1%) compared with the surgery group (22.3%; p<0.001). Across the 24-month follow-up, patients in the SBRT group had fewer complications (incidence rate ratio, 0.74; 95% CI, 0.64 to 0.87). A similar study was performed by Ezer (2015),[17] and the two studies likely had overlapping populations. A total of 362 patients with stage I or II NSCLC and negative lymph nodes were matched with patients who received limited resection. There was no difference in OS for the SBRT patients compared with the surgery patients (HR=1.19; 95% CI, 0.97 to 1.47). Complications were less common in

patients undergoing SBRT (14% of total) compared with patients undergoing resection (28%; p<0.001).

In a matched-cohort study design, Crabtree (2014) retrospectively compared outcomes between SBRT and surgical therapy in patients with stage one NSCLC.[18] Four hundred fifty-eight patients underwent primary surgical resection, and 151 were treated with SBRT. Surgical and SBRT patients differed significantly on several baseline clinical and demographic characteristics, with SBRT patients having an older mean age, higher comorbidity scores, a greater proportion of peripheral tumors, and worse lung function at baseline. For the surgical group, three-year OS and disease-free survival (DFS) were 78% and 72%, respectively. Of note, among the 458 patients with clinical stage I lung cancer, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, three-year and five-year OS were 66% and 43%, respectively. For patients without occult nodal disease, three- and five-year OS were 80% and 68%, respectively. For the SBRT group, three-year OS and DFS were 47% and 42%, respectively.

In a propensity score-matched analysis, 56 patients were matched based on clinical characteristics, including age, tumor size, ACE comorbidity score, forced expiratory volume in one second (FEV_1) percent, and tumor location (central vs peripheral). In the final matched comparison, three-year OS was 52% versus 68% for SBRT and surgery, respectively (p=0.05), while DFS was 47% versus 65% (p=0.01). Two-, three-, four-, and five-year local recurrence-free survival for SBRT was 91%, 91%, 81%, and 40%, respectively, versus 98%, 92%, 92%, and 92% for surgery (p=0.07).

Jeppeson (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).[19] The study included 100 subjects treated with SBRT and 32 treated with conventional radiotherapy. At baseline, the SBRT-treated patients had smaller tumor volume, lower FEV_1, and a greater proportion of T1 stage disease. Median OS was 36.1 months versus 24.4 months for SBRT and conventional radiotherapy, respectively (p=0.015). Local failure-free survival rates at one year were 93% in the SBRT group versus 89% in the conventional radiotherapy group and at five years 69% versus 66%, SBRT and conventional radiotherapy, respectively (p=0.99).

Port (2014) compared SBRT with wedge resection for patients with clinical stage IA NSCLC using data from a prospectively maintained database.[20] One hundred sixty-four patients were identified, 99 of whom were matched based on age, sex, and tumor histology. Thirty-eight patients underwent a wedge resection only, 38 patients underwent a wedge resection with brachytherapy, and 23 patients had SBRT. SBRT patients were more likely to have local or distant recurrences than surgically-treated patients (9% vs 30%, p=0.016), but there were no differences between the groups in disease-free three-year survival (77% for wedge resection vs 59% for SBRT, p=0.066).

Varlotta (2013) compared surgical therapy (n=132 with lobectomy, n=48 with sublobar resection) with SBRT (N=137) in the treatment of stage I NSCLC.[21] Mortality was 54% in the SBRT group, 27.1% in the sublobar resection group, and 20.4% in the lobar resection group. After matching for pathology, age, sex, tumor diameter, aspirin use, and Charlson Comorbidity Index, patients with SBRT had lower OS than patients treated with either wedge resection (p=0.003) or lobectomy (p<0.000).

Noncomparative Studies

Raman (2018) reported an institutional prospective database review of 180 central and 26 ultracentral lung tumors.[22] Most patients received 60 Gy in eight fractions or 48 Gy in four fractions. Rates of toxicity were 8.4% for grade 2 or higher in the central group an d7.9 in the ultracentral group. No grade 4 or 5 toxicities were reported. The two-year cumulative rates of local, regional, and distant failure were 3.3% vs 0 (p=0.36), 9.1% vs 5.0% (P = .5), and 17.7% vs 18.7% (P = .63) in the central and ultracentral groups, respectively.

A report of a seven-year follow-up of 65 patients treated with SBRT for medically inoperable, clinical stage I NSCLC was published in 2017 by Sun.[23] A dose of 50 Gy was delivered in four fractions. Recurrence occurred in 27.7% of patients at a median of 14.5 months following SBRT. Five- and seven-year estimated local, regional, and distant recurrence were 8.1, 10.9, and 11.0%, and 8.1, 13.6, and 13.8%, respectively. Five- and seven-year estimated OS were 55.7 and 47.5% and PFS were 49.5 and 38.2%, respectively. Three patients experienced grade 3 treatment-related adverse events, but there were no reported grade 4 or 5 adverse events.

In a 2017 study of 71 patients undergoing SBRT for stage I NSCLC by Miyakawa, dose escalation was used with the goal of attaining improved local control of large tumors.[24] Doses used were 48, 50, and 52 Gy for tumors with a longest diameter of < 1.5 cm, 1.5-3 cm, and > 3 cm, respectively. OS and PFS at the median follow-up of 61 months for living patients (44 months for all patients) were 65% and 55%, respectively. The cumulative incidence of local recurrence was 15% at five years.

In a 2015 multicenter study, Nagata evaluated SBRT with four fractions in patients (n=164) with T1N0M0 non-small cell lung cancer.[25] The median age of the study population was 78-years old. The three-year overall survival for the 100 inoperable patients was 59.9%. Grade three and four toxicities were observed in 10 and two patients, respectively. The three-year overall survival for the 64 operable patients was 76.5%. There were five patients with Grade three toxicities.

A retrospective database study (n=3,147) by Nanda (2015) evaluated patients aged 70 years or older with early stage (T1-T3N0M0) NSCLC for three years.[26] Overall survival was compared between stereotactic body radiotherapy alone and no treatment. SBRT was associated with improved survival in elderly patients who have concurrent comorbid conditions compared with no treatment.

Timmerman (2007) evaluated the toxicity and efficacy of SBRT in a high-risk population of patients with early stage but medically inoperable lung cancer.[27] in a phase two North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small-cell tumors (<5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction $\times$ 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 to two weeks. The primary end point was two-year actuarial primary tumor control; secondary end points were DFS (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and OS. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors, 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only one patient had primary tumor failure; the estimated three-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had recurrence within the involved lobe; the three-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2%

(95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the three-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates for DFS and OS at three years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade three adverse events were reported in seven patients (12.7%; 95% CI, 9.6% to 15.8%); grade four adverse events were reported in two patients (3.6%; 95% CI, 2.7% to 4.5%). No grade five adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at three years, high rates of local tumor control, and moderate treatment-related morbidity.

In 2014, Stanic reported additional analysis of pulmonary toxicity in participants from the Timmerman study.[28] During two-year follow-up pulmonary function test results were collected. Mean percentage of predicted FEV1 and DLCO declines were 5.8% and 6.3%, respectively. There was no significant decline of oxygen saturation. Baseline pulmonary function testing was not predictive of any pulmonary toxicity following SBRT. Whole lung V5, V10, V20 and mean dose to the whole lung were almost identical between patients who developed pneumonitis and patients who were pneumonitis-free. Poor baseline pulmonary function testing did not predict decreased overall survival. Patients with poor baseline pulmonary function testing as a reason for medical inoperability had higher median and overall survivals than patients with normal baseline pulmonary function testing but with cardiac morbidity.

Hof (2007) 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.[29] In this series, at 12 months, OS was 75% and DFS was 70%. Better local control was noted with higher doses of radiation.

In a prospective evaluation of 185 medically inoperable patients with early (T1-T2N0M0) NSCLC treated with SBRT, Allibhai (2014) evaluated the influence of tumor size on outcomes.[30] Over a median follow-up of 15.2 months, tumor size (maximum gross tumor diameter) was not associated with local failure but was associated with regional failure (p=0.011) and distant failure (p=0.021). Poorer OS (p=0.001), DFS (p=9.001), and cause-specific survival (p=0.005) were also significantly associated with tumor volume more significant than diameter.

Harkenrider (2014) reported outcomes after SBRT for 34 patients with unbiopsied lung cancer, with estimated rates of two-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.[31]

Section Summary

Although no randomized data are available, studies have shown that SBRT for patients with stage one 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 with surgical resection.

Hepatic Tumors

Systematic Reviews

Frakulli (2019) performed a systematic review SBRT for the treatment of advanced cholangiocarcinoma.[32] Studies were included if they analyzed at least 10 patients with

advanced cholangiocarcinoma. A total of 10 studies with 231 patients met inclusion criteria. Nine of the 10 showed moderate to serious risk of bias, as calculated by the ROBINS-I risk of bias tool. Median follow up was 15 months (range: 7.8-64.0 months). Pooled one- and two-year OS was 58.3% (95% CI: 50.2-66.1%) and 35.5% (95% CI: 22.1-50.1%), respectively. Pooled local control at one-year was 83.4%, (95% CI: 76.5-89.4%). There was one treatment-related death.

A 2012 systematic review conducted by Tao and Yang, assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms.[33] 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 to 10 fractions to total doses of 18 to 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 including cholangiocarciomas. At Indiana University, in a phase I study, Cardenes (2010) treated 17 HCC patients with Child-Turcotte-Pugh (CTP) CTP-A or CTP-B, one to three lesions and cumulative tumor diameter of 6 cm or less.[34] Patients with CTP-A were treated in three 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 two patients treated at 3 $\times$ 14 Gy developed grade three hepatic toxicity. The one-year OS was 75%, and there were no local failures during the median 24 months of follow-up.

Meng (2009) conducted a systematic review and meta-analysis of transcatheter arterial chemoembolization (TACE) in combination with radiotherapy compared with TACE alone for unresectable hepatocellular carcinoma (HCC) using meta-analysis of data from the literature involving available trials.[35] Seventeen trials involving 1476 patients were identified. Five were RCTs, and 12 were non-RCTs. In terms of quality, five RCTs were graded B, and the 12 nonrandomized studies were graded C. Results showed that TACE plus radiotherapy 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 radiotherapy can be routinely recommended.

Nonrandomized Comparative Studies

All studies identified for review were retrospective reports.

Nakano (2018) reported results of a retrospective analysis of 281 patients with one to three small (≤3 cm in diameter) hepatocellular carcinoma tumors who were treated with curative intent via surgical resection or SBRT.[36] The surgical resection group on average was younger, had more tumors, and had better hepatic function than those in the stereotactic body radiotherapy group ($p<0.05$). The five-year OS rate was 75.2% vs 47.8% ($P = .0149$) in the surgical resection and SBRT groups, respectively. The five-year disease-free survival rate was 33.8% vs 16.4% ($p=0.0512$) in the surgical resection and SBRT groups, respectively. According to the multivariate analysis, surgical resection was a significant favorable factor for OS and disease-free survival.

Parikh (2018) secondary analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to compare SBRT with RFA as primary treatment for early-stage HCC.[37] A total of 408 patients treated with RFA and 32 with SBRT were included. Ninety-day hospitalization and one-year mortality were not significantly different between groups. Overall

survival was significantly better in the RFA group (p<0.001). In a multivariate analysis, advanced age, higher stage, decompensated cirrhosis, and treatment with SBRT (HR 1.80; 95%CI: 1.15-2.82) were associated with worse survival, but in the propensity score adjusted analysis, survival and costs were similar between the two groups.

Su (2017) retrospectively compared the efficacy of SBRT and liver resection for small HCC (less than or equal to 5 cm).[38] A total of 117 patients with small HCCs with one or two nodules were included, with 82 receiving SBRT and 35 undergoing liver resection. No significant differences between groups were found in OS or PFS. Prior to propensity score matching, the one-, three-, and five-year OS was 96.3%, 81.8%, and 70.0% in the SBRT treated patients and 93.9%, 83.1%, and 64.4% in the resection patients, respectively (p=0.558). One-, three-, and five-year PFS in the SBRT and resection groups were 100%, 91.8%, and 74.3% and 96.7%, 89.3%, and 69.2%, respectively. Hepatotoxicity was also similar between groups.

In 2016, Wahl reported on single U.S. site experience with 224 patients with nonmetastatic HCC accumulated between 2004 and 2012.[39] Radiofrequency ablation (RFA) was used to treat 161 patients and 249 lesions with a freedom from local progression (FFLP) rate at one year of 83.6% and two years of 80.2%. SBRT was used to treat 63 patients with 83 lesions with a FFLP rate of 97.4% at one year and 83.8% at two years.

In an attempt to extend the use of SBRT to larger lesions, Shin (2010) treated six patients with large tumors (median tumor volume, 1288 mL; range, 1008-1815 mL) with no worse than CTP-A liver disease and without extrahepatic metastases.[40] The 4×8–10 Gy regimen was relatively safe with only one case of grade three changes in transaminases. However, one-year OS was only 33%, in part due to advanced disease. One-year LC and OS rates were 50% to 100% and 33% to 100%, respectively. There were 13 cases of radiation-induced liver disease and four, grade five; six, grade four; and 69, grade three adverse events reported.

The effect of SBRT in conjunction with TACE was reported in the following retrospective studies.

Sapir (2018) assessed 209 patients that underwent TACE (n=84) or SBRT (n=125) for HCC at a single institution.[41] Baseline differences between the groups included age (SBRT 65 versus TACE 61; p=0.01), tumor size (SBRT 2.3 cm versus TACE 2.9 cm; p<0.01), and frequency of liver transplantation (SBRT 8% versus TACE 18%; p=0.01). However, there were no significant differences in number of tumors treated per patient, underlying liver disease, or baseline liver function. One- and two-year local control were significantly different between treatment groups (SBRT 97 and 91% versus TACE 47 and 23%, respectively). Toxicities grades 3 and higher were reported in 8% of the SBRT group and 13% of the TACE group.

Cai (2018) included 121 patients with primary hepatocellular carcinoma in a retrospective comparison of transarterial chemoembolization (TACE), gamma knife, and a combination of the two.[42] The TACE alone group included 46 patients, the gamma knife alone group 36 patients, and the combination group 39 patients. Statistically significant differences were reported for overall survival rates between the three groups at 6, 12, and 18 months (TACE alone 50%, 34.8%, and 28.3%; gamma-knife alone 36.1%, 30.6%, and 16.7%; TACE and gamma-knife combined 84.6%, 71.8%, 61.5%). However, there was no significant difference between groups in overall survival at 24 months. (p=0.117). Median survival time for the TACE, gamma knife, and combination groups was seven months, three months, and 20 months, respectively, with the differences reported as significant. There were also statistically

significant differences reported in leukopenia, but not in thrombocytopenia, anemia, nausea, vomiting, or liver function lesions.

In 2015, Jacob evaluated HCC lesions 3 cm or more and compared TACE alone (n=124) with TACE plus SBRT (n=37) from 2008 to 2013.[43] Sorafenib, the tyrosine kinase inhibitor (TKI), was used by 36.1% of the TACE alone group and 41.9% in the combination therapy group. Both groups had received pre- and posttreatment chemotherapy. Local recurrence was significantly decreased in the TACE plus SBRT group (10.8%) in comparison with the TACE-only group (25.8%) (CI, not reported, p=0.04). After censoring for liver transplantation, OS was found to be significantly increased in the TACE plus SBRT group (33 months) compared with the TACE-only group (20 months) (CI, not reported, p=0.02). Chronic HCV infection was the cause of HCC in most patients in both groups.

In 2016, Su, reported on a single-site experience with 77 HCC lesions greater than 5 cm treated with SBRT followed by TACE and 50 patients who had SBRT alone.[44] The patients who had SBRT alone either refused TACE or had hepatic arteriovenous fistulas precluding TACE. The median follow-up was 20.5 months and median tumor size was 8.5 cm (range, 5.1-21.0 cm). The PFS and local relapse-free survival did not differ significantly between groups.

In 2014, Zhong reported on a single-site experience with 72 of 1086 HCC patients consecutively treated with SBRT between 2006 and 2012.[45] These patients had lesions 10 cm or larger and incomplete ablation with prior TACE. The median total dose of 35.6 Gy was delivered over 12 to 14 days with a fractional dose of 2.6 to 3.0 Gy at 6 fractions per week. A complete response (CR) achieved in 6 (8.3%), partial response (PR) in 51 (70.8%), stable disease (SD) in 9 (12.5%) and progressive disease (PD) in 6 patients (8.3%) within a median follow-up of 18 months.

Noncomparative Studies

Scorsetti (2015) published a single center case series study with 43 patients (63 HCC lesions). Median follow-up was eight months (range 3-43 months).[46] Median OS was 18 months +/-5.8 months. Actuarial local control was 64.4% +/-11.5% at 24 months. Overall survival was correlated with local control and gross tumor volume less than 5 cm. No radiation induced liver disease was reported. Several patients experienced significant toxicity (≥ Grade three).

Bujold (2013) reported on sequential phase one and two trials of SBRT for locally advanced HCC.[47] 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 CTP class A disease. The primary end points were toxicity and LC at one year, defined as no progressive disease of irradiated HCC by Response Evaluation Criteria in Solid Tumors (RECIST). A total of 102 patients were evaluable (n=50 in trial one from 2004-2007; n=52 in trial two from 2007-2010). 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, 1.3-1913.4 mL). Tumor vascular thrombosis (TVT) was present in 55% and 12% of patients had extrahepatic disease. LC at one year was 87% (95% CI, 78% to 93%). Toxicity of grade three or more was seen in 30% of patients. In 7 patients (two with TVT and progressive disease), death was possibly related to treatment (1.1-7.7 months after SBRT). Median OS was 17.0 months (95% CI, 10.4 to 21.3 months).

Andolino (2011) evaluated the safety and efficacy of SBRT for the treatment of primary HCC.[48] From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT: 36 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 RECIST v1.1. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0. LC, time to progression (TTP), PFS, and OS were calculated according to Kaplan-Meier method. The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The two-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 grade three or greater nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than one grade, and 20% experienced progression in CTP class within three months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC of 6 cm or less and that SBRT should be considered when bridging to transplant or as definitive therapy for those ineligible for transplant.

Ibarra (2012) evaluated tumor response to SBRT in a combined multicenter database.[49] Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (ICC, n=11) treated with SBRT from four 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 one- and two-year OS rates were 87% and 55%, respectively. The incidence of grade one to two toxicities, mostly nausea and fatigue, was 39.5%. Grade three and four toxicities were present in two and one patients, respectively.

Price (2012) reported the results of a Phase one/two 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.[50] Eligibility criteria included solitary tumors of 6 cm or less or up to three lesions with sum diameters of 6 cm or less, and well-compensated cirrhosis. All patients had imaging before, at one to three months, and every three to 6 months after SBRT. Patients received three to five fractions of SBRT. Median SBRT dose was 42 Gy (range, 24-48 Gy). Median follow-up was 13 months. Per RECIST, four 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 50% or more nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being greater than 50% in five patients. Kaplan-Meier one- and two-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 (2010) evaluated the feasibility, tolerance, and toxicity of SBRT in 25 HCC patients who were not eligible for other treatment modalities.[51] All patients had liver cirrhosis with an Eastern Cooperative Oncology Group performance score of less than two and pretreatment Child scores ranging from A5 to B9. A total dose of 45 Gy in three 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 to 12 days. Overall, the treatment was well tolerated with two grade three acute toxicities and no acute grade four toxicities. Late toxicity

was minimal; all observed late toxicities occurred within the first six months of follow-up. Three hepatic recurrences at a distance from the initial target were observed. The actuarial one- and two-year LC rate was 95% (95% CI, 69% to 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 one and two years was 79% (95% CI, 52% to 92%) and 52% (95% CI, 19% to 78%), respectively.

Kwon (2010) evaluated the long-term effect of SBRT for primary HCC in 42 patients ineligible for local ablation therapy or surgical resection.[52] 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). 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 one-year and three-year survival rates were 92.9% and 58.6%, respectively. In-field PFS at one and three years was 72.0% and 67.5%, respectively. Patients with smaller tumors had better in-field PFS and 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.

Yoon (2013) reported outcomes for 93 patients with primary nonmetastatic HCC treated with SBRT at a single institution.[53] The median follow-up was 25.6 months. OS at one and three years was 86% and 53.8%, respectively. The main cause of treatment failure was intrahepatic (i.e., out-of-field) metastases. At one and three years, LC rates were 94.8% and 92.1%, respectively, and distant metastasis-free survival rates were 87.9% and 72.2%, respectively. However, intrahepatic recurrence-free survival rates at one and three years were 51.9% and 32.4%, respectively.

Jung (2013) reported rates of radiation-induced liver disease in patients with HCC treated with SBRT for small (<6 cm), nonmetastatic HCC that was not amenable to surgery or percutaneous ablative therapy.[54] Ninety-two patients were included, 17 of whom (18.5%) developed grade two or worse radiation-induced liver disease within three months of SBRT. In multivariable analysis, Child-Pugh class was the only significant predictor of radiation-induced liver injury. The one- and three-year survival rates were 86.9% and 54.4% respectively; with the median survival of 53.6 months. The presence of radiation-induced liver disease was not associated with survival.

Bridge to Transplantation

The increasing prevalence of chronic liver conditions progressing to HCC such as HCV infection and alcoholic cirrhosis has led to interest in the use of SBRT and other liver-directed therapies as bridge therapy to transplantation for persons who are on organ waitlists.

Sapisochin (2017) performed an intention-to-treat analysis to examine the safety and efficacy of SBRT as a bridge to liver transplantation for HCC. A total of 379 patients were treated with SBRT (n=36), TACE (n=99), or RFA (n=244). The dropout rate was not significantly different between groups (p=0.7). The numbers of patients transplanted per group were 30, 79, and 203 in the SBRT, TACE, and RFA groups, respectively. The one-, three-, and five-year actuarial survival from time of listing was not significantly different between groups and the values reported ranged from 83-86%, 72-75%, and 56-61%, respectively. The one-, three-, and five-year survival from the time of transplant was also not significantly different between groups (83%, 75% and 75% in the SBRT group, 96%, 75% and 69% in the TACE group, and 95%, 81% and 73% in the RFA group, p=0.7).

Section Summary

The current evidence base is largely heterogenous and includes mostly prospective cohort studies that report outcomes for patients with HCC. Many of the studies were conducted on patients eligible for transplant or who were not eligible for other treatment modalities. Local control and overall survival among the study participants were generally over 70% at one-three-years follow-up. Studies reported a reduction in these outcomes after two-three years follow-up. Multiple studies reported better outcomes when tumors were 6 cm or less. It is important to note that multiple studies reported severe adverse events (≥ grade three) after SBRT for a small number of study participants. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant.

Prostate Cancer

Systematic Reviews

Linney and Barrett (2018) performed a systematic review of the literature on the use of SBRT for early-stage prostate cancer. Sixteen articles met inclusion criteria. The range of reported biochemical progression-free survival rates was 77.1 to 100% for SBRT and 55 to 98% for conventionally fractionated EBRT. Rates of grades 1, 2, and 3 acute genitourinary toxicity were reported as 13.3 to 71%, 12 to 25% and 0 to 3% for SBRT and 28.7 to 51.9%, 15.6 to 41.4%. and 1.1 to 8.1% for EBRT, respectively. Authors noted a lack of randomized trials and long-term follow-up.

Nonrandomized Comparative Studies

In 2014, Yu compared toxicities after treatment with either SBRT (N=1335) or IMRT (N=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries.[55] The authors identified early stage prostate cancer patients aged 66 to 94 years treated from January 2008 to June 2011 who received either IMRT (N=53,841) or SBRT (N=1335) as primary treatment. SBRT patients were matched in a 2:1 manner based on potential confounders. SBRT was associated with higher rates of genitourinary (GU) toxicity. By six months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity versus 12.6% of IMRT patients (odd ratio [OR]=1.29; 95% CI, 1.05 to 1.53; p=0.009). By 12 months posttreatment, 27.1% of SBRT versus 23.2% of IMRT patients had a claim indicative of GU toxicity (OR=1.23; 95% CI, 1.03 to 1.43; p=0.01), and by 24 months after treatment initiation, 43.9% of SBRT versus 36.3% of IMRT patients had a claim indicative of GU toxicity (OR=1.38;95% CI, 1.12 to 1.63; p=0.001). At six months posttreatment, there was increased gastrointestinal (GI) toxicity for patients treated with SBRT, with 5.8% of SBRT patients having had a claim indicative of GI toxicity versus 4.1% of IMRT patients (OR=1.42; 95% CI, 1.00 to 1.85; p=0.02), but at 12 and 24 months posttreatment, there were no significant differences in GI toxicity between groups.

Katz (2012) compared quality of life (QOL) after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early stage prostate cancer.[56] 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 with the surgery group at baseline, three 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 one to six 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.

Noncomparative Studies

Multiple cohort studies have report outcomes for patients treated with a standard dose of SRS or SBRT, or for groups of patients treated with SRS or SBRT at escalating doses.[57-70] Other noncomparative studies have reported on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence[71] and rectal tolerance[72] and health-related QOL outcomes.[73]

Section Summary

Data on the use of SBRT in prostate cancer consists primarily of single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared with historical controls and a few looking at recurrence-free survival with a follow-up of three years or longer. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates and relatively high rates of biochemical recurrence-free survival.

Pancreatic Cancer

This section will focus on systematic reviews, comparative studies and larger case series.

Zaorsky (2019) reported a systematic review of SBRT with varying doses for nonmetastatic pancreatic cancer.[74] A total of 15 studies met inclusion criteria and included 508 patients. Median follow-up was nine months. Local control rates were 60% to 83%. Acute and late grade 3+ toxicity were 3.5% and 5%, respectively. There were no significant differences in local control at one year or acute toxicity between biologically equivalent doses (calculated with an α/β of 10) <70 Gy versus ≥70 Gy.

Buwenge (2018) published a systematic review that evaluated the impact of SBRT on pain reduction.[75] Fourteen studies were identified, seven prospective and seven retrospective. Of these, 12 reported the percentage of pain relief in 190 patients. In these studies, global overall response rate to pain in patients with pain at presentation (complete and partial) was 84.9%, and heterogeneity was high. Acute and late toxicity (grade ≥3) rates were 3.3%-18.0% and 6.0%-8.2%, respectively.

A 2017 systematic review from Petrelli evaluated the safety and efficacy of SBRT for the treatment of pancreatic cancer. Nineteen studies, with a total of 1009 patients, including nonrandomized and single-center series with mixed populations, were analyzed.[76] No publication bias was identified, but the heterogeneity among studies was substantial. A meta-analysis calculated the OS rate at one year and the median OS to be 51.6% and 17 months, respectively. The rate of acute severe toxicity ranged from 0% to 36%. The authors concluded that no evidence supports the claim that SBRT results in better outcomes than conventional RT, but there are benefits of SBRT, including shorter treatment time.

Park (2017) published a retrospective review of patients treated with SBRT (n=44) or IMRT (n-226) for unresectable stage I-III pancreatic adenocarcinoma.[2] Baseline characteristics were analyzed and only age was found to be significantly different between groups. There were no significant differences in OS, local or distant failure, or subsequent resection. Acute grade 2+ gastrointestinal toxicity, grade 2+ fatigue, and grade 3+ hematologic toxicity were significantly

different between groups, with IMRT associated with higher levels (p=0.008, p<0.0001, p=0.001, respectively).

In 2017, Zhong published a retrospective database analysis comparing conventional fractionated radiotherapy (CFRT) with SBRT for locally advanced primary pancreatic carcinoma.[77] Using a large hospital-based registry, the National Cancer Data Base (NCDB), clinical outcomes were described in 10,534 cases (CFRT in 7819, SBRT in 631) diagnosed and treated between 2004 and 2012. To minimize the treatment selection bias, a propensity score matching method was used. A logistic regression model predicting CFRT treatment vs SBRT treatment was used to calculate propensity scores for covariates of interest. The covariates chosen were ones found to be significant in the multivariate analysis or ones thought to be clinically significant and included the following: patient age, AJCC clinical T and N staging, chemotherapy use, Charlson-Deyo comorbidity score, year of diagnosis, and receipt of definitive surgery. In the multivariate analysis, treatment with SBRT was associated with significantly improved OS with a hazard ratio of 0.84 (95% CI, 0.75 to 0.93; p<.001). With matched propensity score analysis, a total of 988 patients were analyzed, with 494 patients in each cohort. The median follow-up time was 26 months. After propensity matching as described above, SBRT usage continued to be associated with significantly improved OS with a median survival of 13.9 months vs 11.6 months (p<0.001). Kaplan-Meier curves for the propensity-matched groups demonstrate a significantly better OS curve for the SBRT cohort (p=0.001) with two-year OS rates of 21.7% and 16.5% for the SBRT and CFRT groups, respectively (p=0.001).

Goyal (2012) reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were found not to be candidates for surgical resection.[78] 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 Gy (range, 22-30 Gy) delivered over one to three fractions. Chemotherapy was given to 68% of patients in various schedules/timing. Patients had a mean gross tumor volume (GTV) of 57.2 cm^3 (range, 10.1-118 cm^3) before SBRT. The mean total GTV reduction at three and six 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 OS 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 one to two (11%) and grade three (16%). There were no grade four or five adverse events seen.

Rwigema (2011) assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma.[79] 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 FFLP and 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 six months/one year were 71.7% to 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 of 15 mL or more (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 six-month/one-year OS rates of 65.3% to

41%, respectively. Grade one and two acute and late GI toxicity were seen in 39.5% of patients. Three patients experienced acute grade three toxicities. SBRT is feasible, with minimal grade three or more toxicity. The overall FFLP rate for all patients was 64.8%, comparable with rates with EBRT.

Chang (2009) reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma.[80] Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 Gy in one 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 three patients (4%) did not receive chemotherapy until they had distant failure. The median follow-up was six months (range, 3-31 months) and, among surviving patients, it was 12 months (range, 3-31 months). The overall rates of 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 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 OS rates at 6 months and 12 months from SBRT were 56% and 21%, respectively. Four patients (5%) experienced grade two or greater acute toxicity. Three patients (4%) experienced grade two late toxicity, and seven patients (9%) experienced grade three or greater late toxicity. At 6 months and 12 months, the rates of grade two or greater late toxicity were 11% and 25%, respectively.

Section Summary

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. However, studies have shown promising LC rates, and outcomes are comparable to other forms of EBRT but with shorter treatment time.

Renal Cell Carcinoma

Siva (2018) retrospectively evaluated 223 patients who received single- or multi-fraction SBRT for primary RCC.[81] Average maximum tumor dimension was 43.6 mm (SD 27.7 mm) Grade 1 and 2 toxicity were reported in 35.6% of patients and grade 3 and 4 toxicities were reported in 1.3%. The rates of LC at two and four years were 97.8% and 97.8%, respectively. Cancer-specific survival, and progression-free survival were 95.7%, and 77.4%, respectively, at two years and 91.9%, and 65.4%, respectively, at four years.

A 2017 systematic review by Prins assessed options for the treatment of T1 renal cell carcinoma (RCC) for patients where surgery is not the treatment of choice.[82] Treatment options assessed included active surveillance, radiofrequency ablation, cryoablation, microwave ablation, and SBRT. PRISMA criteria were used to assess the literature and a total of 73 articles with methodological quality between 2b and 4 met inclusion criteria. No RCTs were identified. The authors concluded that all of the assessed treatment modalities were options for patients unfit to undergo invasive treatment, but that due to the quality of available studies was low.

Siva (2017) assessed the use of SBRT for unresectable RCC in a prospective interventional study.[83] A total of 37 patients with T1a, T1b, and T2a disease were included to a median of 24 months. Thirty-three patients and 34 kidneys received all prescribed SBRT fractions, representing 89% feasibility. Twenty-six patients experienced treatment-related grade 1-2 toxicities, one patient experienced grade 3 toxicity, and no grade 4-5 toxicities were reported. Six patients (18%) reported no toxicity. Two-year overall survival was 92% and two-year freedom from distant progression was 89%. There were no cases of local progression at two years. The decrease in mean glomerular filtration rate from 55 mL/min at baseline to 44 mL/min at one and two years was statistically significant ($p<0.001$). Authors concluded that SBRT for primary RCC was feasible and well-tolerated.

In 2016, Yamamoto reported on 14 patients (11 males, 3 females) who received SBRT for RCC at a single site between April 2010 and February 2014.[84] The dose constraints for planning organ at risk volume of 10-fraction SBRT were 30 Gy for patients who retained both kidneys and 26 Gy in patients with single kidneys. Significant renal atrophic change was observed at a median observation interval of 16.9 months (range, 12.0-21.8 months). No patient experienced worsening of hypertension or required hemodialysis.

In 2015, Taunk reported a systematic review and clinical opinion on the use of SBRT for spinal metastases from RCC.[85] Important clinical outcomes discussed include the rates of vertebral compression fracture which ranged from 11% to 39% from heterogeneous studies. Preexisting mechanical instability of the spine and prior radiation therapy may be risk factors for fracture.

A 2012 systematic review by Siva on the use of stereotactic radiotherapy for primary RCC identified a total of 126 patients worldwide who had been treated using this modality.[86] A systematic search performed in January 2012 identified seven retrospective studies and three 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. LC was reported as 93.9% (range, 84%-100%) and the rate of severe grade three 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 RCC can be delivered with good rates of LC 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 (2004) reported outcomes in nine patients with nonmetastatic RCC, two of whom had bilateral RCCs.[87] Patients were treated definitively with 40 Gy in 5 fractions using SBRT. With a median follow-up of 26.7 months, four of the nine patients were alive. The survivors had a minimum follow-up of 48 months. At presentation, all four of the survivors had tumors of 3.4 cm or less in largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Ranck (2013) reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT.[88] For patients with five or fewer metastatic lesions, all lesions were treated; in patients with greater than five lesions, rapidly-growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of two lesions per patient. The two-year lesion-control rate was reported as 91.4% in the 12 patients who underwent treatment for all metastases, over a median follow-up of 21.3 months. However, in these patients, two-year freedom from new metastases was 35.7%. OS was 85% at two years. No patients who underwent treatment at all lesion sites died.

Section Summary

The literature on the use of SBRT for RCC consists of very small case series, which generally report high rates of LC. However, little evidence about the impact on patient outcomes can be derived from these data, nor any comparison made between this treatment modality and more established treatment modalities for RCC.

Oligometastases

In 2019, the Canadian Agency for Drugs and Technology in Health (CADTH) published a rapid response report addressing the clinical effectiveness and cost-effectiveness of SBRT for oligometastatic cancer.[89] Four publications met inclusion criteria, including three retrospective cohort studies and one economic evaluation. None of the included studies of clinical effectiveness found a significant difference in overall survival or progression-free survival following SBRT compared with other treatments. One study reported that local control of adrenal metastases was superior following real-time tumor-tracking radiotherapy compared to SBRT. The report concluded that the evidence was of limited quality and may not improve overall survival rates compared to other cancer treatments.

Vilela (2018) performed a systematic review of the safely and effectiveness of SBRT for oligometastatic recurrent prostate cancer.[90] Fourteen studies met inclusion criteria and included 661 patients. A total of 899 lesions were treated, 561 nodal, 336 bone, 2 liver. Androgen deprivation therapy-free survival and median progression free survival were between one and three years. Among the studies with a low risk of bias, local control varied between 82 to 100%. Acute and late grade 2 toxicity were reported in 2.4% and 1.1% of patients, respectively. One case of acute and two cases of late grade 3 toxicity were reported.

In a 2018 systematic review, Petrelli analyzed the efficacy of SBRT to treat colorectal cancer liver oligometastases.[91] Eighteen studies met inclusion criteria. A total of 656 patients were included in the random-effect model pooled-analysis. Pooled one- and two-year survival were 67.18% (95% CI, 42.1-92.2) and 56.5% (95% CI, 36.7-76.2), respectively. Median PFS was 11.5 months and median OS was 31.5 months. The pooled one-year and two-year LC were 67% (95% CI, 43.8-90.2) and 59.3% (95% CI, 37.2-81.5), respectively. Reported mild to moderate and severe liver toxicity were 30.7% and 8.7%.

Kobiela (2018) published a systematic review of local control in colorectal cancer liver and lung oligometastases following treatment with SBRT.[92] A total of 15 studies met inclusion criteria. One-year LC ranged from 50% to 100% for liver metastases and 62% to 92% for lung metastases. Two-year LC ranged from 32% to 91% for liver metastases and 53% to 92% for lung metastases.

A number of studies were published in 2018 that evaluated the safety and efficacy of SBRT of oligometastases. Most addressed lung[93-97] or liver[98-100] metastases, although some addressed both[101] and others addressed adrenal[102,103], bone[104-106], and other sites[107,108]. The largest and those that are prospective or comparative are discussed below.

A 2018 retrospective study published by Franzese compared SBRT with microwave ablation. Data from 135 patients with liver metastases were extracted and analyzed. Median follow-up time was 24.5 months (2.4-95.8). The one-year freedom from local progression was significantly longer in the SBRT group than the microwave ablation group (SBRT group 91%; 95% CI 81-95; versus the microwave ablation group 84%; 95% CI 0.72-0.91). The likelihood of local relapse was lower in the SBRT-treated group (adjusted hazard ratio 0.31; 95%CI 0.13-0.70, p = 0.005).

Andratschke (2018) published a pooled analysis of the as part of the German society for radiation oncology (DEGRO) stereotactic body radiotherapy (SBRT) initiative to analyze the patterns of care of SBRT for liver oligometastases.[109] Data from 474 patients with 623 liver oligometastases treated with SBRT from 17 German and Swiss centers were analyzed. Primaries were mostly colorectal and breast. Median follow-up time was 15 months. The control rate of treated metastases at one and two years was 77% and 64%, respectively. When only tumors treated with biological equivalent dose (BED) was greater than 150 Gy EQD2Gy, the control rate was 83% and 70%, respectively.

Siva (2018) prospectively analyzed 33 patients receiving SBRT for oligometastatic prostate cancer.[110] Lesions were bone, nodal, or mixed (one patient). One grade 3 adverse event was reported. One-year local and distant progression-free survival were 97% (95% CI 91 to 100) and 58% (95% CI 43 to 77), respectively. Two-year local and distant progression-free survival were 93% (95% CI 84 to 100) and 39% (95% CI 25 to 60), respectively.

Franzese (2018) reported outcomes in 270 patients receiving SBRT for a maximum of five colorectal cancer metastases.[111] Most lesions were in the lung (48.5%) or liver (36.4%). Most patients (73.7%) received systemic treatment before SBRT. Median follow-up was 23 months. Rates of LC and OS were 95% and 88.5% respectively at one year, 73% and 56.6% respectively at three years, and 73% and 37.2% respectively at five years. Median progression-free survival was 8.6 months.

Sharma (2018) retrospectively reviewed 206 patients with 327 inoperable pulmonary oligometastases.[112] Primary sties included colorectal carcinoma, lung carcinoma, melanoma, sarcoma, and breast carcinoma. Median follow-up was 26 months. Rates of OS at two and five years were 63% and 30%, respectively. Median survival was 33 months.

The 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 anatomic sites.[113-115] The review conclusions are summarized below by type of oligometastases.

A 2012 long-term follow-up of a prospective study was reported by Milano (2012) on oligometastases treated with SBRT.[116] The authors prospectively analyzed the long-term survival, tumor control outcomes, and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with five or fewer clinically detectable metastases, from any primary site, metastatic to one to three organ sites, and treated with SBRT. For patients with breast cancer, the median follow-up was 4.5 years (7.1 years for 16/39 patients alive at the last follow-up visit). The two-year OS, FFDM and 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 four-fold and three-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 post 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 nonbreast cancers, a greater SBRT target volume was significantly adverse for OS (p=0.012) and lesion LC (p<0.001). 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.

In 2015, Scorsetti published a case series with 82 elderly patients (111 total metastases) with oligometastases (16 localized to the abdomen, 50 liver, 45 lungs).[117] Median age was 79 years of age. The majority of patients (n=64) had a single lesion and 18 had two-four lesions. Local response was reported for 87 lesions and local progression was reported for 24 lesions. Two-year local control findings were 76.3% +/- 4.4% and overall survival was 72.0% +/- 5.6%. Disease-specific survival was 81.6% +/- 4.9% at two years. Treatment related Grade toxicity was reported. Grade two-three toxicity was reported in five patients, Grade one toxicity in seven patients, and no toxicity in 85.4% of patients.

Lung Oligometastases

For isolated or a few lung metastases (including <3 or <5, according to different selection criteria), the LC probability at one year has been reported in the range of 70% to 100%.[113] The overall survival varied widely after two-years (21%-84%) among the studies. In most case 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 one and two trials included heterogeneous patient populations.[113]

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.[113] Data from the International Registry of Lung Metastases reported OS of 70% at two years and 36% at five years in patients with a single metastasis who underwent surgical metastasectomy.[118]

A systematic review by Siva (2010) on the use of SBRT for pulmonary oligometastases estimated from the largest studies included in the review a two-year weighted OS rate of 54.5%,[119] ranging from higher rates in a study by Norisha (2008) of 84%[120] to lower rates, such as 39%, reported from a multi-institutional trial.[121]

The following studies were published after the publication of the Siva systematic review.

Qiu (2018) retrospectively analyzed a total of 65 colorectal cancer patients with lung metastases, of which fifteen had oligometastases.[122] When SBRT treatment occurred, 64.6% of patients had lung-only involvement and 69.2 and 33.8% of patients had received prior systemic therapy and lung-directed therapy, respectively. Median OS was 20.3 months, median progression-free survival was 5.7 months, and median local failure-free survival was 15.4 months. Distant progression developed in 98% of patients.

Osti (2013) reported outcomes from a prospective cohort study of SBRT for lung oligometastases.[123] Sixty-six patients with lung oligometastases were included, most (61%) with a single pulmonary nodule. For the primary end point of LC, over a median follow-up of 14 months, LC at one year and two years was 89.1% and 82.1%, respectively. OS at one and two years was 76.4% and 31.2%, respectively, while PFS at one and two years was 53.9% and 22%, respectively. Two cases of grade three toxicity (pneumonitis) occurred.

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% to 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 RFA and transarterial chemoembolization. Retrospective analyses of RFA for liver metastases from CRC have shown wide variability in five-year OS rates, ranging from 14% to 55%.[113]

Retrospective series on the use of SBRT have reported LC rates ranging from 57% to 100% (median follow-up ranged 10 months – 4.3 years), as reported in a review by Alongi.[113] Prospective studies have reported one-year OS rates ranging from 61% to 85% and two-year OS rates ranging from 30% to 62%.[113] Another systematic review by Tree concluded similar findings evaluating similar studies.[115] In addition, the review concluded that the rate of adverse events was low with less than 5% of patients experiencing severe toxicity (grade three or more).

In one of the larger series, McPartlin (2017) assessed 60 patients, of whom 82% received previous chemotherapy, 23% previously underwent focal liver treatment, and 38% had extrahepatic disease at the time of SBRT.[124] Only one acute toxicity greater than grade 2 was reported. Median overall survival was 16.0 months and local control rate per lesion at one and four years was 49.8% and 26.2%, respectively.

Chang (2011) studied outcomes of SBRT for colorectal liver metastases in a pooled patient cohort from three institutions with colorectal liver metastases.[125] Patients were included if they had one to four lesions, received one to six fractions of SBRT, and had radiologic imaging three months or more posttreatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had one or more chemotherapy regimens before stereotactic body radiotherapy, and 27 (42%) patients had two or more regimens. The median follow-up was 1.2 years (range, 0.3-5.2 years). The median dose was 42 Gy (range, 22-60 Gy). One- and two-year LC rates were 67% and 55%, respectively. One- and two-year OS rates were 72% and 38%, respectively.

In 2012, Lanciano reported on the single-center experience with SBRT to treat patients with metastases from multiple primary sites.[126] The patients were heavily pretreated with 87% having had prior systemic chemotherapy for treatment of liver metastases or liver tumor and 37% having had prior liver-directed therapy. These therapies included surgical resection, chemoembolization, RFA, photodynamic therapy, or previous external-beam radiation. There were four patients who had more than one prior liver-directed treatment. In 2014, Yuan reported on the single-site experience of a cohort of patients with liver metastases from multiple primary sites; 56% of whom had received prior systemic therapy.[127] Patients were considered to have a favorable prognosis with primary tumors originating from the colon, breast, or stomach, as well as sarcomas. In this group, the median overall survival was not reached and the one-year and two-year overall survival rates were 89.6% and 72.2%, respectively.

These studies have had relatively short follow-up times, typically less than two years. They are also limited by relatively small numbers of patients in the studies and differences in the systemic therapies administered, which may affect treatment outcomes. Adrenal Gland Oligometastases

The most frequent primary tumor that metastasizes to the adrenal glands is NSCLC. 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. LC rates at one year ranging from 55% to 90% have been reported, and one-year OS rates ranging from 40% to 56% and two-year OS ranging from 14% to 33%.[113]

Scorsetti (2012) described the feasibility, tolerability and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients.[128] 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, LC, time-to-systemic progression, time-to-local progression, OS 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 three or 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 CR, 46% PR, 36% SD, and 7% progressed in the treated area. Local failure was observed in 13 cases and actuarial local control rates at one and two years were 66% and 32%, respectively. Median time-to-local progression was 19 months and median survival was 22 months.

Holy (2011) presented initial institutional experiences with SBRT for adrenal gland metastases.[129] Between 2002 and 2009, 18 patients with NSCLC and adrenal metastases received SBRT for the metastatic disease. Metastases were isolated in 13 patients and multiple in five patients. A median PFS 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 LC. In these patients, median OS was 23 months.

Casamassima (2012) retrospectively evaluated a single-institution's outcomes after hypofractionated SBRT for adrenal metastases.[130] 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 multiple fractions. 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 two-year actuarial OS rates were 39.7% and 14.5%, respectively. The median interval to local failure was 4.9 months. The actuarial one-year disease control rate was 9%; the actuarial one- and two-year LC rates were both 90%.

Chawla (2009) investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands.[131] 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 five 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 three months of follow-up with serial computed tomography. Of these 24 patients, one achieved CR, 15 achieved PR, four had SD, and four developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. LC was poor, and most patients developed widespread metastases

shortly after treatment, with one-year survival, LC, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed grade two or greater toxicity.

Ahmed (2013) reported outcomes from a single-center's experience with SBRT for treatment of metastases to the adrenal glands.[132] Thirteen patients were included, most with lung primary tumors (n=9), with the remainder having kidney (n=2), skin (n=2), bladder (n=1), colon (n=1), and liver (n=1) as primary sites. Eleven patients (84.6%) had received prior chemotherapy since being diagnosed with metastatic disease, and one patient had undergone previous SBRT to bilateral psoas muscle metastases before adrenal SBRT. At the time of analysis, 8 of 13 patients were alive. The median follow-up time for living patients was 12.3 months (range, 3.1-18 months). Median survival for the five patients who died was 6.9 months (range, 2.1-15.2 months). Of the 12 patients who had evaluation for LC and distant control, 11 (91.6%) had some local response to therapy, but distant failure occurred in six patients at a median of 2.5 months posttreatment, leading to a one-year distant control estimate of 55%. In exploratory analysis, there was no difference between lung primary tumor and other primary tumor sites in terms of OS or distant control. Acute toxicity included grade two nausea in two patients, grade two abdominal pain in one patient, grade one fatigue in five patients, and grade one diarrhea in one patient.

Bone Oligometastases

Napieralska (2014) reported a series 48 cases of prostate cancer bone metastases (in 32 patients) treated with SBRT primarily for pain control.[133] The size of the treated lesions ranged from 0.7 to 5.5 cm (mean, three dimension), and 31 (65%) of the treated metastases were located in the spine. At three-month follow-up, 17 patients had complete pain relief, two had partial pain relief, and two had no pain reduction. At the end of the follow-up period, complete pain relief was observed in 28 patients and partial pain relief in 16 patients.

Spinal Oligometastases

A small number of case series have been published evaluating the use of SBRT for the treatment of spinal metastases. Many are summarized in the included systematic reviews addressing oligometastases. A 2017 systematic review by Myrehaug focused on SBRT for reirradiation of spinal metastases.[134] The included studies reported one-year local control rates between 66% and 90%. The authors concluded that SBRT for spinal metastases is safe and effective, but the evidence is limited to low-quality data. A few studies have been published since the publication of the systematic reviews.[135,136] The case series are heterogenous and some include studies with mixed primary sites. The studies consistently report local control rates of 77%-93% with a median follow-up ranging from 6-21 months. Data is lacking regarding longer-term follow-up and overall survival.[114,115]

Section Summary

The evidence for the use of SBRT to treat oligometastases is generally limited to case series with heterogenous study populations. However, the evidence consistently reports a high rate of tumor control for isolated or few metastases (≤ 3 or ≤ 5). The local tumor control is good and reported at one-year to be in the range of 70% to 100%. The overall survival varied widely after two-years (21%-84%) among the studies. Although some adverse events were reported, the overall rates for adverse events were low.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Network (NCCN) provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers.[137]

Cancer Site	Tumor Type	Recommendation	Version
Bone	Osteosarcoma – metastatic disease	Consider SRS to allow high-dose therapy while maximizing normal tissue sparing (category 2A)	2.2019
CNS	Adult intracranial and spinal ependymoma – spine or brain reoccurrence	• Resection with limited radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A) • If unresectable, radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A) • If progression, radiotherapy; consider use of SRS if geometrically favorable (category 2A)	1.2019
CNS	Primary spinal cord tumors	If recurrence, radiotherapy including SRS if surgery is not possible (category 2A)	1.2019
CNS	Limited Brain Metastases, primary treatment	• For newly diagnosed or stable systemic disease or reasonable systemic treatment options exist, SRS (preferred) or WBRT. SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances.	1.2019
CNS	Metastatic spine tumors	• If spinal cord compression, fracture or spinal cord instability, consider surgical stabilization or vertebral augmentation followed by RT (recommend SRS if oligometastases and radioresistant) • If no spinal cord compression, no fracture or spinal instability, RT (preferred) or chemotherapy or surgery. Consider surgery or SRS if deterioration during RT, intractable pain, or tumor progression (recommend SRS if oligometastases and radioresistant) (category 2A). • If progressive disease or recurrent disease and if previously treated with RT or surgery and RT, consider surgery or SRS (recommend SRS if oligometastases and radioresistant). Consider re-irradiation if recurrent. • If progressive disease or recurrent disease and previously treated with chemotherapy, consider RT (recommend SRS if oligometastases and radioresistant) (category 2A). • If spinal cord compression, steroids, followed by: o primary RT (recommend SRS if oligometastases and radioresistant) or o surgery, followed by RT or o In the absence of clinical myelopathy, primary chemotherapy if chemosensitive tumor	1.2019

Cancer Site	Tumor Type	Recommendation	Version
Colon	Metastatic to liver or lung	In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic sites can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or SBRT.	2.2019
Hepatobiliary	Hepatocellular carcinoma	• Principles of locoregional therapy includes recommendations for SBRT • If unresectable and not a liver transplant candidate, consider external beam radiation therapy among other options (category 2B) • If inoperable by performance status or comorbidity and local disease with minimal or no extrahepatic disease, consider external beam radiation therapy among other options (category 2B) • Principles of locoregional therapy indicate that SBRT may be considered as an alternative to the techniques listed elsewhere in the recommendations. • Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain	2.2019
Kidney	Non-clear cell and clear cell renal cell carcinoma	Metastasectomy or SBRT or ablative techniques for oligometastatic disease (category 2A)	1.2020
Lung	Non-small-cell lung cancer – Stage IA, IB, IIB	If negative mediastinal nodes and medically inoperable, definitive RT including stereotactic ablative radiotherapy (category 2A)	5.2019
Lung	Non-small-cell lung cancer – Locoregional recurrence, resectable	Resection (preferred) or external beam RT or SABR	5.2019
Lung	Non-small-cell lung cancer – Stage IV, metastatic disease to single site, brain or adrenal.	• Brain metastasis: Surgical resection followed by WBRT or SRS (category 2A) or SRS alone (category 2A)If brain or adrenal metastasis and T1-2, N0-1 or T3, N0 disease: consider stereotactic ablative radiotherapy of lung lesion (category 2A) or chemotherapy followed by surgical resection of lung lesion or stereotactic ablative radiotherapy of lung lesion (category 2A)	5.2019
Pancreas	Pancreatic adenocarcinoma – Locally advanced	• If good performance status, in selected patients, locally advanced without systemic metastases, induction chemotherapy followed by chemoradiation or SBRT in selected patients who are not candidates for combination chemotherapy (category 2A) • As second-line therapy following disease progression, clinical trial (preferred) or chemotherapy or SBRT if not previously given and if primary site is the sole site of progression (category 2A) • In selected patients who are not candidates for combination chemotherapy, chemoradiation or SBRT (category 2A)	2.2019

Cancer Site	Tumor Type	Recommendation	Version
Pancreas	Pancreatic adenocarcinoma - Local recurrence after resection	• Clinical trial (preferred) or Systemic chemotherapy +/- chemoradiation or SBRT (if not previously done) or SBRT or Palliative and best supportive care (category 2A)	2.2019
Prostate	Prostate cancer	• SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise • In patients with unfavorable intermediate risk or high risk, prophylactic nodal radiation can be considered. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered when delivering longer courses of EBRT would present a medical or social hardship. • SBRT can be considered, and enrollment on clinical trials is encouraged for oligometastatic disease where durable local control is desirable.	2.2019
Skin	Melanoma – metastatic	• Brain metastases: SRS either as adjuvant or primary treatment or WBRT (category 2A) • Ablative treatment for intact extracranial metastases – higher doses utilizing conformal techniques such as stereotactic body radiation therapy (SBRT) may offer more durable control. SBRT may be considered for selected patients with oligometastasis. (category 2A)	2.2019
Soft tissue sarcoma – extremity, superficial trunk, head/neck	Sarcoma – synchronous stage IV	• If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A) • If disseminated metastases: SBRT as a palliative option (category 2A)	2.2019
Soft tissue sarcoma – extremity, superficial trunk, head/neck	Sarcoma – recurrent disease with metastases	• If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A) • If disseminated metastases: SBRT as a palliative option (category 2A) • If isolated regional disease or nodes: consider SBRT (category2A)	2.2019
Thyroid	Papillary, follicular, or Hurthle cell carcinoma – structurally persistent/recurrent locoregional or distant metastatic disease not amenable to radioactive iodine	• Iodine-refractory unresectable locoregional recurrent/persistent disease or iodine-refractory soft tissue metastases (eg lung, liver, muscle) excluding CNS metastases: consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies when available to metastatic lesions if progressive and/or symptomatic • CNS metastases: for solitary lesions, either neurosurgical resection or SRS is preferred (category 2A)	1.2019

NCCN Categories

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.

AMERICAN COLLEGE OF CHEST PHYSICIANS

Non-Small-Cell Lung Cancer

- In patients with stage I or II NSCLC with no medical contraindications to operative intervention, surgical resection is recommended (grade 1B-strong recommendation based on moderate evidence)[138]
- In patients with stage I NSCLC who cannot tolerate lobectomy or segmentectomy:[138]
  - SBRT and wedge resection are recommended over no treatment (Grade 2C).
  - SBRT is favored over wedge resection in these cases unless surgical resection may provide the benefit of definitive histologic analysis and nodal information that will result in a change in the patient's management.
  - SBRT is also favored in these patients if adequate surgical margin is unlikely with wedge resection.

- For high-risk stage I NSCLC tumors <5 cm, SBRT is preferred over conventional fractionated RT for definitive treatment when normal dose constraints can be respected.[139]
- For tumors within 2 cm of the proximal bronchial tree, a modified SBRT treatment schedule is suggested to decrease treatment-related toxicity.[139]
- For second primary lung cancer, SRS is an emerging technology, particularly when there is limited pulmonary reserve.[138]

Lung Cancer

- In lung cancer patients with 1-3 brain metastases, stereotactic radiosurgery (SRS) alone is the recommended initial therapy (Grade 1A). [140]

AMERICAN HEART ASSOCIATION SCIENTIFIC STATEMENT

In 2017, the American Heart Association and American Stroke Association published a scientific statement on the management of brain arteriovenous malformations (AVMs).[141] The statement concludes that the available literature supports the use of SRS for small- to moderate volume brain AVMs that are generally 12 cm^3 of less in volume or located in deep or eloquent regions of the brain.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Non-Small-Cell Lung Cancer

- For patients with T1-2, N0 non-small cell lung cancer who are medically operable, ASTRO makes the following recommendations related to the use of SBRT:[142]
  - "For patients with "standard operative risk" (i.e., with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial."

- “For patients with “high operative risk” (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a a potential alternative to surgery are encouraged. Patients should be informed that while SBRG may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established.”

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The ASCO guideline addresses the management of brain metastases for patients with human epidermal growth factor receptor 2 (HER2) -positive advanced breast cancer.[143] ASCO makes the following recommendations:

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (SRS), SRS (WBRT), and FSRT for metastases 3 to 4 cm.
- For metastases 3 to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.

A 2016 ASCO guideline addresses the treatment of locally advanced, unresectable pancreatic cancer.[144] ASCO makes the following evidence-based recommendations:

- “Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria: Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, a favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy. There is no clear evidence to support one regimen over another, and physicians may offer therapy on the basis of extrapolation from data derived from studies in the metastatic setting. For some patients, conformal radiation therapy (CRT) or stereotactic body radiotherapy (SBRT) may be offered up front on the basis of patient and physician preference.” (evidence quality intermediate)
- “A short course of palliative radiotherapy (conventional RT or SBRT) may be offered to patients with LAPC who meet the following criteria: prominent local symptoms, such as abdominal pain and/or worsening jaundice and/or gastrointestinal (GI) bleeding; local infiltration into the GI tract causing impending gastric outlet or duodenal obstruction; and patient preference.” (evidence quality intermediate)

SUMMARY

Hepatic Tumors

There is enough evidence to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) improve health outcomes for patients with hepatic tumors. Therefore, the use of SRS and SBRT for the treatment of hepatic tumors (primary or metastatic) may be considered medically necessary when policy criteria are met.

For all other tumors or indications when policy criteria is not met, there is not enough research to show improved health outcomes with stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). Therefore, all other indications for the use of SRS or SBRT for hepatic tumors are considered investigational.

Hepatocellular Carcinoma

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) improve health outcomes in patients with less than five tumors and less than 6 centimeters in diameter. Therefore, SRS and SBRT for the treatment of HCC may be considered medically necessary when policy criteria are met.

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for hepatocellular carcinoma (HCC) when the criteria are not met. Therefore, the use of SRS and SBRT for all other indications for HCC is considered investigational.

Lung Metastases

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) improve health outcomes for people with lung metastases (e.g., local control and acceptable treatment-related toxicity) in a select group of patients with a limited number of metastases. Therefore, the use of SRS or SBRT for lung metastases may be considered medically necessary when policy criteria are met.

Outside this subgroup, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with lung metastases. Therefore SRS and SBRT of lung metastases are considered investigational when policy criteria are not met.

Oligometastases

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with oligometastases with a limited number of metastases. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for oligometastatic disease in certain scenarios. Therefore, SRS and SBRT for the treatment of oligometastatic disease may be considered medically necessary when policy criteria are met.

Outside this subgroup when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with oligometastases. Therefore, the use of SRS and SBRT for oligometastases when policy criteria are not met are considered investigational.

Osteosarcoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with osteosarcoma. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for osteosarcoma metastatic disease. Therefore, SRS and SBRT for the treatment of osteosarcoma metastatic disease may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with osteosarcoma. Therefore, the use of SRS and SBRT for osteosarcoma when policy criteria are not met are considered investigational.

Pancreatic Adenocarcinoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with pancreatic adenocarcinoma that is locally advanced, borderline resectable, inoperable, or locally recurrent after resection. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for pancreatic adenocarcinoma in these scenarios. Therefore, SRS and SBRT for the treatment of pancreatic adenocarcinoma may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with pancreatic adenocarcinoma. Therefore, the use of SRS and SBRT for pancreatic adenocarcinoma when policy criteria are not met are considered investigational.

Primary Non-Small Cell Lung Cancer

Non-comparative studies have consistently shown that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for patients with non-small cell lung cancer (NSCLC), node negative, tumor stage T1a, T1b, T2a, or T2b, have survival rates comparable to patients who have undergone surgical resection. In addition, clinical practice guidelines recommend the use of SRS or SBRT for NSCLC. Therefore, SRS and SBRT may be considered medically necessary for patients with NSCLC, when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with NSLC. Therefore, SRS and SBRT for NSCLC are considered investigational when policy criteria are not met.

Prostate Cancer

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) may improve health outcomes for people with prostate cancer. Clinical guidelines based on research cautiously recommend SRS or SBRT for people with prostate cancer. Therefore, the use of SRS or SBRT for prostate cancer may be considered medically necessary.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with prostate cancer. Therefore, SRS and SBRT for prostate cancer are considered investigational when policy criteria are not met.

Renal Cell Carcinoma

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with inoperable primary renal cell carcinoma. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for renal cell carcinoma in these scenarios. Therefore, SRS and SBRT for the treatment of renal cell carcinoma may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with renal cell carcinoma. Therefore, the use of SRS and SBRT for renal cell carcinoma when policy criteria are not met are considered investigational.

Spinal and Vertebral Body Tumors (Primary or Metastatic)

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) lead to improved net health outcomes in patients with spinal or vertebral body tumors and especially in patients that have received prior radiation therapy. In addition, there is expert clinical consensus on the benefits of SBRT in this population. Therefore, SRS and SBRT may be considered medically necessary for the treatment of primary and salvage treatment of local recurrence after previous irradiation when policy criteria are met.

Other Indications

For all other tumors or indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) leads to improved health outcomes. Therefore, SRS and SBRT are considered investigational when policy criteria are not met.

REFERENCES

1. NCI Dictionary of Cancer Terms [cited 6/18/2019]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neoplasm
2. Park, JJ, Hajj, C, Reyngold, M, et al. Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer. *Acta oncologica (Stockholm, Sweden)*. 2017 Jun 29:1-8. PMID: 28661823
3. Huo, M, Sahgal, A, Pryor, D, Redmond, K, Lo, S, Foote, M. Stereotactic spine radiosurgery: Review of safety and efficacy with respect to dose and fractionation. *Surgical neurology international*. 2017;8:30. PMID: 28303210
4. Jawad, MS, Fahim, DK, Gerszten, PC, et al. Vertebral compression fractures after stereotactic body radiation therapy: a large, multi-institutional, multinational evaluation. *Journal of neurosurgery Spine*. 2016 Jun;24(6):928-36. PMID: 26895526

5. Sahgal, A, Atenafu, EG, Chao, S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013 Sep 20;31(27):3426-31. PMID: 23960179
6. Gerszten, PC, Burton, SA, Ozhasoglu, C, Welch, WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)*. 2007 Jan 15;32(2):193-9. PMID: 17224814
7. Chang, EL, Shiu, AS, Mendel, E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *Journal of neurosurgery Spine*. 2007 Aug;7(2):151-60. PMID: 17688054
8. Gerszten, PC, Ozhasoglu, C, Burton, SA, et al. CyberKnife frameless stereotactic radiosurgery for spinal lesions: clinical experience in 125 cases. *Neurosurgery*. 2004 Jul;55(1):89-98; discussion -9. PMID: 15214977
9. Degen, JW, Gagnon, GJ, Voyadzis, JM, et al. CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. *Journal of neurosurgery Spine*. 2005 May;2(5):540-9. PMID: 15945428
10. Zheng, X, Schipper, M, Kidwell, K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *International journal of radiation oncology, biology, physics*. 2014 Nov 1;90(3):603-11. PMID: 25052562
11. Nguyen, NP, Garland, L, Welsh, J, Hamilton, R, Cohen, D, Vinh-Hung, V. Can stereotactic fractionated radiation therapy become the standard of care for early stage non-small cell lung carcinoma. *Cancer Treat Rev*. 2008 Dec;34(8):719-27. PMID: 18657910
12. Koto, M, Takai, Y, Ogawa, Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol*. 2007 Dec;85(3):429-34. PMID: 18022720
13. Kupelian, PA, Komaki, R, Allen, P. Prognostic factors in the treatment of node-negative nonsmall cell lung carcinoma with radiotherapy alone. *International journal of radiation oncology, biology, physics*. 1996 Oct 1;36(3):607-13. PMID: 8948345
14. Lam, A, Yoshida, EJ, Bui, K, Fernando, D, Nelson, K, Abi-Jaoudeh, N. A National Cancer Database Analysis of Radiofrequency Ablation versus Stereotactic Body Radiotherapy in Early-Stage Non-Small Cell Lung Cancer. *Journal of vascular and interventional radiology : JVIR*. 2018 Sep;29(9):1211-7 e1. PMID: 30061058
15. von Reibnitz, D, Shaikh, F, Wu, AJ, et al. Stereotactic body radiation therapy (SBRT) improves local control and overall survival compared to conventionally fractionated radiation for stage I non-small cell lung cancer (NSCLC). *Acta oncologica (Stockholm, Sweden)*. 2018 Nov;57(11):1567-73. PMID: 29873277
16. Yu, JB, Soulos, PR, Cramer, LD, Decker, RH, Kim, AW, Gross, CP. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. *Cancer*. 2015 Jul 15;121(14):2341-9. PMID: 25847699
17. Ezer, N, Veluswamy, RR, Mhango, G, Rosenzweig, KE, Powell, CA, Wisnivesky, JP. Outcomes after Stereotactic Body Radiotherapy versus Limited Resection in Older Patients with Early-Stage Lung Cancer. *J Thorac Oncol*. 2015;10(8):1201-6. PMID: 26200275
18. Crabtree, TD, Puri, V, Robinson, C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or

stereotactic radiation therapy. *The Journal of thoracic and cardiovascular surgery*. 2014 Apr;147(4):1183-91; discussion 91-2. PMID: 24507980
19. Jeppesen, SS, Schytte, T, Jensen, HR, Brink, C, Hansen, O. Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: an updated retrospective study on local failure and survival rates. *Acta oncologica (Stockholm, Sweden)*. 2013 Oct;52(7):1552-8. PMID: 23902274
20. Port, JL, Parashar, B, Osakwe, N, et al. A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer. *The Annals of thoracic surgery*. 2014 Oct;98(4):1152-9. PMID: 25085557
21. Varlotto, J, Fakiris, A, Flickinger, J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. *Cancer*. 2013 Apr 19. PMID: 23605504
22. Raman, S, Yau, V, Pineda, S, et al. Ultracentral Tumors Treated With Stereotactic Body Radiotherapy: Single-Institution Experience. *Clinical lung cancer*. 2018 Sep;19(5):e803-e10. PMID: 30007498
23. Sun, B, Brooks, ED, Komaki, RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer*. 2017 Aug 15;123(16):3031-9. PMID: 28346656
24. Miyakawa, A, Shibamoto, Y, Baba, F, et al. Stereotactic body radiotherapy for stage I non-small-cell lung cancer using higher doses for larger tumors: results of the second study. *Radiat Oncol*. 2017;12(1):152. PMID: 28893300
25. Nagata, Y, Hiraoka, M, Shibata, T, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. *International journal of radiation oncology, biology, physics*. 2015 Dec 1;93(5):989-96. PMID: 26581137
26. Nanda, RH, Liu, Y, Gillespie, TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: A National Cancer Data Base analysis. *Cancer*. 2015 Dec 1;121(23):4222-30. PMID: 26348268
27. Timmerman, RD, Park, C, Kavanagh, BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. *J Thorac Oncol*. 2007 Jul;2(7 Suppl 3):S101-12. PMID: 17603304
28. Stanic, S, Paulus, R, Timmerman, RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *International journal of radiation oncology, biology, physics*. 2014 Apr 1;88(5):1092-9. PMID: 24661663
29. Hof, H, Muenter, M, Oetzel, D, Hoess, A, Debus, J, Herfarth, K. Stereotactic single-dose radiotherapy (radiosurgery) of early stage nonsmall-cell lung cancer (NSCLC). *Cancer*. 2007 Jul 1;110(1):148-55. PMID: 17516437
30. Allibhai, Z, Taremi, M, Bezjak, A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *International journal of radiation oncology, biology, physics*. 2013 Dec 1;87(5):1064-70. PMID: 24210082
31. Harkenrider, MM, Bertke, MH, Dunlap, NE. Stereotactic Body Radiation Therapy for Unbiopsied Early-stage Lung Cancer: A Multi-Institutional Analysis. *American journal of clinical oncology*. 2014 Aug;37(4):337-42. PMID: 23660597

32. Frakulli, R, Buwenge, M, Macchia, G, et al. Stereotactic body radiation therapy in cholangiocarcinoma: a systematic review. *The British journal of radiology*. 2019 May;92(1097):20180688. PMID: 30673295
33. Tao, C, Yang, LX. Improved radiotherapy for primary and secondary liver cancer: stereotactic body radiation therapy. *Anticancer research*. 2012 Feb;32(2):649-55. PMID: 22287758
34. Cardenes, HR, Price, TR, Perkins, SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2010 Mar;12(3):218-25. PMID: 20231127
35. Meng, MB, Cui, YL, Lu, Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol*. 2009 Aug;92(2):184-94. PMID: 19042048
36. Nakano, R, Ohira, M, Kobayashi, T, et al. Hepatectomy versus stereotactic body radiotherapy for primary early hepatocellular carcinoma: A propensity-matched analysis in a single institution. *Surgery*. 2018 Aug;164(2):219-26. PMID: 29801728
37. Parikh, ND, Marshall, VD, Green, M, et al. Effectiveness and cost of radiofrequency ablation and stereotactic body radiotherapy for treatment of early-stage hepatocellular carcinoma: An analysis of SEER-medicare. *Journal of medical imaging and radiation oncology*. 2018 Oct;62(5):673-81. PMID: 29877615
38. Su, TS, Liang, P, Liang, J, et al. Long-Term Survival Analysis of Stereotactic Ablative Radiotherapy Versus Liver Resection for Small Hepatocellular Carcinoma. *International journal of radiation oncology, biology, physics*. 2017 Jul 1;98(3):639-46. PMID: 28581406
39. Wahl, DR, Stenmark, MH, Tao, Y, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34(5):452-9. PMID: 26628466
40. Shin, YJ, Kim, MS, Yoo, SY, et al. Pilot study of stereotactic body radiotherapy for huge hepatocellular carcinoma unsuitable for other therapies. *Tumori*. 2010 Jan-Feb;96(1):65-70. PMID: 20437860
41. Sapir, E, Tao, Y, Schipper, MJ, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. *International journal of radiation oncology, biology, physics*. 2018 Jan 1;100(1):122-30. PMID: 29066120
42. Cai, Y, Chang, Q, Xiao, E, Shang, QL, Chen, Z. Transcatheter arterial chemoembolization (TACE) combined with gamma-knife compared to TACE or gamma-knife alone for hepatocellular carcinoma. *Medicine (Baltimore)*. 2018;97(22):e10890. PMID: 29851811
43. Jacob, R, Turley, F, Redden, DT, et al. Adjuvant stereotactic body radiotherapy following transarterial chemoembolization in patients with non-resectable hepatocellular carcinoma tumours of >/= 3 cm. *HPB (Oxford)*. 2015;17(2):140-9. PMID: 25186290
44. Su, TS, Lu, HZ, Cheng, T, et al. Long-term survival analysis in combined transarterial embolization and stereotactic body radiation therapy versus stereotactic body radiation monotherapy for unresectable hepatocellular carcinoma >5 cm. *BMC Cancer*. 2016;16(1):834. PMID: 27809890
45. Zhong, NB, Lv, GM, Chen, ZH. Stereotactic body radiotherapy combined with transarterial chemoembolization for huge (>/=10 cm) hepatocellular carcinomas: A clinical study. *Mol Clin Oncol*. 2014;2(5):839-44. PMID: 25054055

46. Scorsetti, M, Comito, T, Cozzi, L, et al. The challenge of inoperable hepatocellular carcinoma (HCC): results of a single-institutional experience on stereotactic body radiation therapy (SBRT). *Journal of cancer research and clinical oncology*. 2015 Jul;141(7):1301-9. PMID: 25644863
47. Bujold, A, Massey, CA, Kim, JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013 May 1;31(13):1631-9. PMID: 23547075
48. Andolino, DL, Johnson, CS, Maluccio, M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *International journal of radiation oncology, biology, physics*. 2011 Nov 15;81(4):e447-53. PMID: 21645977
49. Ibarra, RA, Rojas, D, Snyder, L, et al. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. *Acta oncologica (Stockholm, Sweden)*. 2012 May;51(5):575-83. PMID: 22263926
50. Price, TR, Perkins, SM, Sandrasegaran, K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer*. 2012 Jun 15;118(12):3191-8. PMID: 22025126
51. Louis, C, Dewas, S, Mirabel, X, et al. Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results. *Technology in cancer research & treatment*. 2010 Oct;9(5):479-87. PMID: 20815419
52. Kwon, JH, Bae, SH, Kim, JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer*. 2010;10:475. PMID: 20813065
53. Yoon, SM, Lim, YS, Park, MJ, et al. Stereotactic body radiation therapy as an alternative treatment for small hepatocellular carcinoma. *PloS one*. 2013;8(11):e79854. PMID: 24255719
54. Jung, J, Yoon, SM, Kim, SY, et al. Radiation-induced liver disease after stereotactic body radiotherapy for small hepatocellular carcinoma: clinical and dose-volumetric parameters. *Radiat Oncol*. 2013;8:249. PMID: 24160910
55. Yu, JB, Cramer, LD, Herrin, J, Soulos, PR, Potosky, AL, Gross, CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014 Apr 20;32(12):1195-201. PMID: 24616315
56. Katz, A, Ferrer, M, Suarez, JF. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat Oncol*. 2012;7:194. PMID: 23164305
57. Boyer, MJ, Papagikos, MA, Kiteley, R, Vujaskovic, Z, Wu, J, Lee, WR. Toxicity and quality of life report of a phase II study of stereotactic body radiotherapy (SBRT) for low and intermediate risk prostate cancer. *Radiat Oncol*. 2017 Jan 13;12(1):14. PMID: 28086825
58. Jeong, BK, Jeong, H, Ha, IB, et al. Stereotactic Body Radiation Therapy for Low- to Intermediate-risk Prostate Adenocarcinoma. *Journal of Korean medical science*. 2015 Jun;30(6):710-5. PMID: 26028922
59. McBride, SM, Wong, DS, Dombrowski, JJ, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: Preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer*. 2011 Dec 13;118(15):3681-90. PMID: 22170628

60. King, CR, Freeman, D, Kaplan, I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol*. 2013 Nov;109(2):217-21. PMID: 24060175
61. Boike, TP, Lotan, Y, Cho, LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011 May 20;29(15):2020-6. PMID: 21464418
62. Jabbari, S, Weinberg, VK, Kaprealian, T, et al. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. *International journal of radiation oncology, biology, physics*. 2012 Jan 1;82(1):228-34. PMID: 21183287
63. Freeman, DE, King, CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. *Radiat Oncol*. 2011;6:3. PMID: 21219625
64. King, CR, Brooks, JD, Gill, H, Presti, JC, Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *International journal of radiation oncology, biology, physics*. 2012 Feb 1;82(2):877-82. PMID: 21300474
65. Katz, AJ, Santoro, M, Ashley, R, Diblasio, F, Witten, M. Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urol*. 2010;10:1. PMID: 20122161
66. Katz, AJ, Santoro, M, Diblasio, F, Ashley, R. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. *Radiat Oncol*. 2013 May 13;8(1):118. PMID: 23668632
67. Wiegner, EA, King, CR. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. *International journal of radiation oncology, biology, physics*. 2010 Oct 1;78(2):442-8. PMID: 20137864
68. Bolzicco, G, Favretto, MS, Satariano, N, Scremin, E, Tambone, C, Tasca, A. A single-center study of 100 consecutive patients with localized prostate cancer treated with stereotactic body radiotherapy. *BMC Urol*. 2013;13:49. PMID: 24134138
69. Park, Y, Park, HJ, Jang, WI, Jeong, BK, Kim, HJ, Chang, AR. Long-term results and PSA kinetics after robotic SBRT for prostate cancer: multicenter retrospective study in Korea (Korean radiation oncology group study 15-01). *Radiat Oncol*. 2018;13(1):230. PMID: 30470253
70. Meier, RM, Bloch, DA, Cotrutz, C, et al. Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer: Survival and Toxicity Endpoints. *International journal of radiation oncology, biology, physics*. 2018 Oct 1;102(2):296-303. PMID: 30191864
71. Chen, LN, Suy, S, Wang, H, et al. Patient-reported urinary incontinence following stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer. *Radiat Oncol*. 2014;9:148. PMID: 24966110
72. Kim, DW, Cho, LC, Straka, C, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *International journal of radiation oncology, biology, physics*. 2014 Jul 1;89(3):509-17. PMID: 24929162
73. King, CR, Collins, S, Fuller, D, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *International journal of radiation oncology, biology, physics*. 2013 Dec 1;87(5):939-45. PMID: 24119836
74. Zaorsky, NG, Lehrer, EJ, Handorf, E, Meyer, JE. Dose Escalation in Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Meta-Analysis. *American journal of clinical oncology*. 2019 Jan;42(1):46-55. PMID: 29965809

75. Buwenge, M, Macchia, G, Arcelli, A, et al. Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. *J Pain Res*. 2018;11:2169-78. PMID: 30323651
76. Petrelli, F, Comito, T, Ghidini, A, Torri, V, Scorsetti, M, Barni, S. Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials. *International journal of radiation oncology, biology, physics*. 2017 Feb 01;97(2):313-22. PMID: 28068239
77. Zhong, J, Patel, K, Switchenko, J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer*. 2017 Sep 15;123(18):3486-93. PMID: 28493288
78. Goyal, K, Einstein, D, Ibarra, RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *The Journal of surgical research*. 2012 May 15;174(2):319-25. PMID: 21937061
79. Rwigema, JC, Parikh, SD, Heron, DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *American journal of clinical oncology*. 2011 Feb;34(1):63-9. PMID: 20308870
80. Chang, DT, Schellenberg, D, Shen, J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009 Feb 1;115(3):665-72. PMID: 19117351
81. Siva, S, Louie, AV, Warner, A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer*. 2018 Mar 1;124(5):934-42. PMID: 29266183
82. Prins, FM, Kerkmeijer, LGW, Pronk, AA, et al. Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for Small Renal Masses, a Systematic Review. *Journal of endourology*. 2017 Oct;31(10):963-75. PMID: 28741377
83. Siva, S, Pham, D, Kron, T, et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. *BJU international*. 2017 Nov;120(5):623-30. PMID: 28188682
84. Yamamoto, T, Kadoya, N, Takeda, K, et al. Renal atrophy after stereotactic body radiotherapy for renal cell carcinoma. *Radiat Oncol*. 2016;11:72. PMID: 27229710
85. Taunk, NK, Spratt, DE, Bilsky, M, Yamada, Y. Spine Radiosurgery in the Management of Renal Cell Carcinoma Metastases. *J Natl Compr Canc Netw*. 2015;13(6):801-9; quiz 9. PMID: 26085394
86. Siva, S, Pham, D, Gill, S, Corcoran, NM, Foroudi, F. A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. *BJU international*. 2012 Dec;110(11 Pt B):E737-43. PMID: 23107102
87. Beitler, JJ, Makara, D, Silverman, P, Lederman, G. Definitive, high-dose-per-fraction, conformal, stereotactic external radiation for renal cell carcinoma. *American journal of clinical oncology*. 2004 Dec;27(6):646-8. PMID: 15577450
88. Ranck, MC, Golden, DW, Corbin, KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. *American journal of clinical oncology*. 2013 Dec;36(6):589-95. PMID: 22868242
89. Stereotactic Body Radiotherapy for Oligometastatic Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottowa: CADTH; 2019 Feb. (CADTH Rapid Response Report). [cited 6/18/2019]; Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1071%20Stereotactic%20Body%20Radiotherapy%20Final.pdf

90. Vilela, RA, Navarro, NF, Faria, ET, et al. Use of stereotactic body radiation therapy for oligometastatic recurrent prostate cancer: A systematic review. *Journal of medical imaging and radiation oncology*. 2018 Oct;62(5):692-706. PMID: 29808571
91. Petrelli, F, Comito, T, Barni, S, Pancera, G, Scorsetti, M, Ghidini, A. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. *Radiother Oncol*. 2018 Dec;129(3):427-34. PMID: 29997034
92. Kobiela, J, Spychalski, P, Marvaso, G, et al. Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review. *Critical reviews in oncology/hematology*. 2018 Sep;129:91-101. PMID: 30097241
93. Khadige, M, Salleron, J, Marchesi, V, Oldrini, G, Peiffert, D, Beckendorf, V. Cyberknife((R)) stereotactic radiation therapy for stage I lung cancer and pulmonary metastases: evaluation of local control at 24 months. *J Thorac Dis*. 2018;10(8):4976-84. PMID: 30233872
94. Mihai, A, Mu, Y, Armstrong, J, et al. Patients with colorectal lung oligometastases (L-OMD) treated by dose adapted SABR at diagnosis of oligometastatic disease have better outcomes than patients previously treated for their metastatic disease. *Journal of radiosurgery and SBRT*. 2017;5(1):43-53. PMID: 29296462
95. Dohopolski, MJ, Horne, Z, Clump, D, Burton, SA, Heron, DE. Stereotactic Body Radiation Therapy for Pulmonary Oligometastases Arising from Non-lung Primaries in Patients Without Extrapulmonary Disease. *Cureus*. 2018 Feb 7;10(2):e2167. PMID: 29644155
96. Osti, MF, Agolli, L, Valeriani, M, et al. 30 Gy single dose stereotactic body radiation therapy (SBRT): Report on outcome in a large series of patients with lung oligometastatic disease. *Lung cancer (Amsterdam, Netherlands)*. 2018 Aug;122:165-70. PMID: 30032826
97. Mazzola, R, Fersino, S, Ferrera, G, et al. Stereotactic body radiotherapy for lung oligometastases impacts on systemic treatment-free survival: a cohort study. *Med Oncol*. 2018;35(9):121. PMID: 30076479
98. Gandhidasan, S, Ball, D, Kron, T, et al. Single Fraction Stereotactic Ablative Body Radiotherapy for Oligometastasis: Outcomes from 132 Consecutive Patients. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2018 Mar;30(3):178-84. PMID: 29224900
99. He, X, Zhang, P, Li, Z, et al. Curative-intent radiotherapy in patients with oligometastatic lesions from colorectal cancer: A single-center study. *Medicine (Baltimore)*. 2018;97(40):e12601. PMID: 30290630
100. Scorsetti, M, Comito, T, Clerici, E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. *Radiat Oncol*. 2018;13(1):234. PMID: 30477560
101. Nakamura, M, Hashimoto, N, Mayahara, H, et al. Additional chemotherapy improved local control and overall survival after stereotactic body radiation therapy for patients with oligo-recurrence. *Radiat Oncol*. 2018;13(1):75. PMID: 29688858
102. Buergy, D, Rabe, L, Siebenlist, K, et al. Treatment of Adrenal Metastases with Conventional or Hypofractionated Image-guided Radiation Therapy - Patterns and Outcomes. *Anticancer research*. 2018;38(8):4789-96. PMID: 30061250
103. Celik, E, Semrau, R, Baues, C, Trommer-Nestler, M, Baus, W, Marnitz, S. Robot-assisted Extracranial Stereotactic Radiotherapy of Adrenal Metastases in Oligometastatic Non-small Cell Lung Cancer. *Anticancer research*. 2017;37(9):5285-91. PMID: 28870966

104. Erler, D, Brotherston, D, Sahgal, A, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. *Radiother Oncol*. 2018 May;127(2):304-9. PMID: 29706460
105. Fanetti, G, Marvaso, G, Ciardo, D, et al. Stereotactic body radiotherapy for castration-sensitive prostate cancer bone oligometastases. *Med Oncol*. 2018;35(5):75. PMID: 29671075
106. Loi, M, Klass, ND, De Vries, KC, et al. Pain flare, complexity and analgesia in bone oligometastases treated with stereotactic body radiation therapy. *European journal of cancer care*. 2018 Nov;27(6):e12915. PMID: 30246916
107. Loi, M, Duijm, M, Baker, S, et al. Stereotactic body radiotherapy for oligometastatic soft tissue sarcoma. *Radiol Med*. 2018;123(11):871-8. PMID: 29923086
108. Iftode, C, D'Agostino, GR, Tozzi, A, et al. Stereotactic Body Radiation Therapy in Oligometastatic Ovarian Cancer: A Promising Therapeutic Approach. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. 2018 Oct;28(8):1507-13. PMID: 30036231
109. Andratschke, N, Alheid, H, Allgauer, M, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. *BMC Cancer*. 2018;18(1):283. PMID: 29534687
110. Siva, S, Bressel, M, Murphy, DG, et al. Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial. *European urology*. 2018 Oct;74(4):455-62. PMID: 30227924
111. Franzese, C, Comito, T, Toska, E, et al. Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy. *Radiother Oncol*. 2018 Nov 7. PMID: 30414754
112. Sharma, A, Duijm, M, Oomen-de Hoop, E, et al. Survival and prognostic factors of pulmonary oligometastases treated with stereotactic body radiotherapy. *Acta oncologica (Stockholm, Sweden)*. 2018 Oct 3:1-7. PMID: 30280633
113. Alongi, F, Arcangeli, S, Filippi, AR, Ricardi, U, Scorsetti, M. Review and uses of stereotactic body radiation therapy for oligometastases. *The oncologist*. 2012;17(8):1100-7. PMID: 22723509
114. Corbin, KS, Hellman, S, Weichselbaum, RR. Extracranial oligometastases: a subset of metastases curable with stereotactic radiotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013 Apr 10;31(11):1384-90. PMID: 23460715
115. Tree, AC, Khoo, VS, Eeles, RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol*. 2013 Jan;14(1):e28-37. PMID: 23276369
116. Milano, MT, Katz, AW, Zhang, H, Okunieff, P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *International journal of radiation oncology, biology, physics*. 2012 Jul 1;83(3):878-86. PMID: 22172903
117. Scorsetti, M, Clerici, E, Navarria, P, et al. The role of stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic disease in the elderly. *The British journal of radiology*. 2015 Sep;88(1053):20150111. PMID: 26183933
118. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. *The Journal of thoracic and cardiovascular surgery*. 1997 Jan;113(1):37-49. PMID: 9011700
119. Siva, S, MacManus, M, Ball, D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol*. 2010 Jul;5(7):1091-9. PMID: 20479693

120. Norihisa, Y, Nagata, Y, Takayama, K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. *International journal of radiation oncology, biology, physics*. 2008 Oct 1;72(2):398-403. PMID: 18374506
121. Rusthoven, KE, Kavanagh, BD, Cardenes, H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009 Apr 1;27(10):1572-8. PMID: 19255321
122. Qiu, H, Katz, AW, Chowdhry, AK, et al. Stereotactic Body Radiotherapy for Lung Metastases from Colorectal Cancer: Prognostic Factors for Disease Control and Survival. *American journal of clinical oncology*. 2018 Jan;41(1):53-8. PMID: 26270442
123. Osti, MF, Carnevale, A, Valeriani, M, et al. Clinical outcomes of single dose stereotactic radiotherapy for lung metastases. *Clinical lung cancer*. 2013 Nov;14(6):699-703. PMID: 23886798
124. McPartlin, A, Swaminath, A, Wang, R, et al. Long-Term Outcomes of Phase 1 and 2 Studies of SBRT for Hepatic Colorectal Metastases. *International journal of radiation oncology, biology, physics*. 2017 Oct 1;99(2):388-95. PMID: 28871989
125. Chang, DT, Swaminath, A, Kozak, M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer*. 2011 Sep 1;117(17):4060-9. PMID: 21432842
126. Lanciano, R, Lamond, J, Yang, J, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. *Frontiers in oncology*. 2012;2:23. PMID: 22645716
127. Yuan, ZY, Meng, MB, Liu, CL, et al. Stereotactic body radiation therapy using the CyberKnife((R)) system for patients with liver metastases. *Onco Targets Ther*. 2014;7:915-23. PMID: 24959080
128. Scorsetti, M, Alongi, F, Filippi, AR, et al. Long-term local control achieved after hypofractionated stereotactic body radiotherapy for adrenal gland metastases: a retrospective analysis of 34 patients. *Acta oncologica (Stockholm, Sweden)*. 2012 May;51(5):618-23. PMID: 22263925
129. Holy, R, Piroth, M, Pinkawa, M, Eble, MJ. Stereotactic body radiation therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]*. 2011 Apr;187(4):245-51. PMID: 21424513
130. Casamassima, F, Livi, L, Masciullo, S, et al. Stereotactic radiotherapy for adrenal gland metastases: university of Florence experience. *International journal of radiation oncology, biology, physics*. 2012 Feb 1;82(2):919-23. PMID: 21300473
131. Chawla, S, Chen, Y, Katz, AW, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *International journal of radiation oncology, biology, physics*. 2009 Sep 1;75(1):71-5. PMID: 19250766
132. Ahmed, KA, Barney, BM, Macdonald, OK, et al. Stereotactic body radiotherapy in the treatment of adrenal metastases. *American journal of clinical oncology*. 2013 Oct;36(5):509-13. PMID: 22781389
133. Napieralska, A, Miszczyk, L, Tukiendorf, A, Stapor-Fudzinska, M. The results of treatment of prostate cancer bone metastases after CyberKnife radiosurgery. *Ortopedia, traumatologia, rehabilitacja*. 2014 Jul 3;16(3):339-49. PMID: 25058109
134. Myrehaug, S, Sahgal, A, Hayashi, M, et al. Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review. *Journal of neurosurgery Spine*. 2017 Oct;27(4):428-35. PMID: 28708043

135. Bernard, V, Bishop, AJ, Allen, PK, et al. Heterogeneity in Treatment Response of Spine Metastases to Spine Stereotactic Radiosurgery Within "Radiosensitive" Subtypes. *International journal of radiation oncology, biology, physics*. 2017 Dec 1;99(5):1207-15. PMID: 29029886
136. Chang, JH, Gandhidasan, S, Finnigan, R, et al. Stereotactic Ablative Body Radiotherapy for the Treatment of Spinal Oligometastases. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2017 Jul;29(7):e119-e25. PMID: 28237218
137. NCCN Guidelines for Treatment of Cancer by Site. [cited 6/18/2019]; Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
138. Howington, JA, Blum, MG, Chang, AC, Balekian, AA, Murthy, SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013 May;143(5 Suppl):e278S-313S. PMID: 23649443
139. Donington, J, Ferguson, M, Mazzone, P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest*. 2012;142:1620-35. PMID: 23208335
140. Simoff, MJ, Lally, B, Slade, MG, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e455S-97S. PMID: 23649452
141. Derdeyn, CP, Zipfel, GJ, Albuquerque, FC, et al. Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(8):e200-e24. PMID: 28642352
142. Videtic, GMM, Donington, J, Giuliani, M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Practical radiation oncology*. 2017 Jun 05. PMID: 28596092
143. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. [cited 19]; Available from:
144. Balaban, EP, Mangu, PB, Khorana, AA, et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016 Aug 01;34(22):2654-68. PMID: 27247216
145. BlueCross BlueShield Association Medical Policy Reference Manual "Stereotactic Radiosurgery and Stereotactic Body Radiotherapy." Policy No. 6.01.10

CODES

NOTE: Coding for stereotactic radiosurgery typically consists of a series of CPT codes describing the individual steps required; medical radiation physics, clinical treatment planning, attachment of stereotactic head frame, treatment delivery and clinical treatment management.

The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the

treatment planning.

Treatment delivery:

The codes used for treatment delivery will depend on the energy source used, typically either photons or protons.

Codes	Number	Description
CPT	32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
	77371	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
	77372	Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial 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 fraction
	77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

NOTE: Codes for treatment delivery primarily reflects the cost related to the energy source used, and not physician work.

Clinical treatment management:

CPT	77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.)
	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)
HCPCS	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

Date of Origin: *July 2019*