



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

**Effective:** January 1, 2025

**Next Review:** July 2025

**Last Review:** December 2024

### **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. Head and neck cancers outside of intracranial, skull base, and orbital sites, when there is documented prior radiation treatment to the planned target volume
  - B. Hemangiopericytoma outside of intracranial, skull base, or orbital sites

- C. Hepatobiliary tumor, including biliary tract cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma; excluding hepatocellular carcinoma (see Criterion D) and metastatic hepatic tumors from different primary cancers (see Criterion F).
  - D. Hepatocellular carcinoma (hepatoma) 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. Primary lung cancer: Non-small cell lung cancer (NSCLC) and Small-cell lung cancer (SCLC); tumor stage T1 or T2 and node negative.
  - F. Oligometastases when the following criteria are met:
    1. Five or fewer synchronous metastatic lesions in any one metastatic site; 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).
  - G. Pancreatic adenocarcinoma, locally advanced, borderline resectable, inoperable (See Policy Guidelines) or local recurrence after resection
  - H. Paraganglioma
  - I. Prostate cancer; very low, low, and intermediate-risk (See Policy Guidelines)
  - J. Renal cell cancer, inoperable primary, when a urological surgeon has documented inoperability
  - K. Schwannomas (see Policy Guidelines)
  - L. Spinal or paraspinal tumors (primary or metastatic) including but not limited to hemangioblastoma
- II. Stereotactic radiosurgery and stereotactic body radiation therapy (also known as Stereotactic ablative body radiotherapy) are considered **investigational** when Criterion I. is not met and for all other indications outside of intracranial, skull base, or orbital sites, including but not limited to: Primary tumors 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).”<sup>[1]</sup>

## **SCHWANNOMAS**

Schwannomas are tumors that occur along nerves. They are typically benign but may be malignant. These may also be referred to as neuromas, neurinomas "of Verocay" or neurilemmomas. A common type of schwannoma is a vestibular schwannoma, which is also known as an acoustic neuroma.

## **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 National Comprehensive Cancer Network criteria defining resectability at diagnosis of pancreatic adenocarcinoma.<sup>[2]</sup>

### **Prostate Cancer Risk Groups**

The National Comprehensive Network (NCCN) Clinical Practice Guideline for Prostate Cancer defines very low risk prostate cancer as clinical T1c stage, Grade Group 1, and PSA <10ng/ml; and low risk prostate cancer as cT1-T2a, Grade Group 1, and PSA less than 10ng/mL. Intermediate risk is defined as cT2b-cT2c, Grade Group 2 or 3, and PSA 10-20ng/ml.<sup>[3]</sup>

## **FRACTIONATION**

Fractionated stereotactic radiotherapy refers to when SRS or SBRT are performed more than once on a specific site. SRS is commonly delivered in 1 fractions and SBRT or SABR is commonly delivered in 2-5 fractions.

## DOSE CONSTRAINT REFERENCES

### Radiation Therapy Oncology Group (RTOG) Radiation Dose Constraints

Available from: [https://en.wikibooks.org/wiki/Radiation\\_Oncology/Toxicity/RTOG](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](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, Pelvis, and Extremities](#), 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. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204
7. [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 SBRT have been used for a range of malignant and non-malignant conditions. Because they are more targeted than traditional external radiation therapy, SRS and SBRT 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 2-5 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.

### Lung Cancer

#### Systematic Reviews

Viani (2022) published a meta-analysis evaluating the efficacy of SBRT versus surgery for early-stage NSCLC.<sup>[4]</sup> Thirty studies met inclusion criteria, with 29,511 patients (17,146 patients in the surgery group and 12,365 patients in the SBRT group). Of these, 26 were retrospective studies with propensity score matching, one was a randomized clinical trial, one was a retrospective study with adjustment for prognostic covariates, and two were retrospective studies without adjustment for covariates. Statistically significant publication bias for OS was identified at three years in favor of surgery ( $p=0.027$ ). A statistically significant difference between groups in favor of surgery was identified in three-year OS (HR=1.35; 95% CI 1.22 to 1.44;  $I^2=66\%$ ) and three-year cancer-specific survival (HR=1.23; 95% CI 1.09 to 1.37;  $I^2=17\%$ ). Three-year LC was not significantly different between groups (HR = 0.97; 95% CI 0.93 to 1.08;  $I^2=19\%$ ). Subgroup analyses identified no significant differences between groups in OS in the T1N0M0 subgroup or cancer-specific survival between the sublobar resection subgroup and the SBRT group.

Zhang (2022) published a systematic review of 87 studies involving SBRT ( $n=12,811$ ) and 18 studies involving RFA ( $n=1,535$ ) for patients with inoperable stage I NSCLC.<sup>[5]</sup> The local control rates with SBRT were 98%, 95%, 92%, and 92%, respectively, at one, two, three, and five years; the local control rates for RFA were significantly lower (75%, 31%, 67%, and 41%, respectively, at one, two, three, and five years;  $p<0.01$  for all comparisons). The OS rates were similar between SBRT and RFA at one year (87% vs 89%, respectively;  $p=0.07$ ) and two years (71% vs 69%, respectively;  $p=0.42$ ), whereas the OS was significantly improved with SBRT over RFA at three years (58% vs 48%;  $p<0.01$ ) and five years (39% vs 21%;  $p<0.01$ ). The most common complication of SBRT was radiation pneumonitis (9.1%), whereas pneumothorax was the most common complication of RFA (27.2%).

A systematic review by Alcibar (2021) evaluated the use of SBRT for treating inoperable stage III non-small cell lung cancer.<sup>[6]</sup> A total of six studies with 134 patients met inclusion criteria. Half of the studies were prospective and the half were retrospective. Overall median follow-up

was 18.75 months. Median local control was 76% and grade 3 or higher toxicity occurred in 12% of patients.

Ijsseldijk (2020) conducted a systematic review and meta-analysis comparing oncologic outcomes of surgery versus SBRT for patients with stage I NSCLC.<sup>[7]</sup> The analysis included a total of 100 studies. Results revealed that long-term OS and disease-free survival after lobar resection was better than SBRT in all comparisons, and for the majority of comparisons, sublobar resection was better than SBRT. Included studies were heterogeneous and of low quality; however, results remained essentially unchanged after many stratifications and sensitivity analyses.

In 2019 Li published a systematic review comparing SBRT to surgery for early-stage NSCLC. A total of 14 cohort studies (n=1,438 participants) met inclusion criteria.<sup>[8]</sup> Matching was performed for the main bias sources between the groups, including age, gender, tumor diameter, forced expiratory volume in one second, and Charlson comorbidity index. There was a statistically significant benefit for surgery over SBRT for early-stage NSCLC, with pooled OR for one-, three-, and five-year OS of 1.56 (95% CI 1.12 to 2.15), 1.86 (95% CI 1.50 to 2.31), and 2.43 (95% CI 1.8 to 3.28), respectively. The five-year distant control was 2.74 (95% CI 1.12 to 6.67). No significant differences were identified between groups for one-year or three-year disease-free survival, locoregional control, or distant control or five-year locoregional control.

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.<sup>[9]</sup> 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)<sup>[10]</sup> 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.<sup>[11]</sup> 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.<sup>[12]</sup>

### Randomized Controlled Trials

Peng (2023) performed an RCT to assess the efficacy and safety of SBRT plus targeted therapy with epidermal growth factor tyrosine kinase inhibitors (EGFR-TKIs) in patients with Stage IV NSCLC who had EGFR sensitive mutations and fewer than five metastatic lesions.<sup>[13]</sup> After three months of first line treatment with demonstrated response, 62 patients were randomized to either receive SBRT with continued EGFR-TKI therapy (31 patients) or

continued EGFR-TKI therapy alone (31 patients). After a median follow-up of 29.4 months eight (26.67%) patients in the SBRT group were living, compared to five (16.3%) in the EGFR-TKI group. Median PFS was 17.3 months in the SBRT group and 9.0 months in the control group (HR=0.52, 95% CI 0.31 to 0.89, p=0.016). Overall survival was also statistically significant (p=0.033) with median survival of 35.2 months in the SBRT+EGFR-TKI group and 23.2 months in the EGFR-TKI group. The study suggests that adding SBRT to EGFR targeted therapy prolongs survival by delaying acquired resistance to therapy, but larger randomized trials are needed.

Altorki (2021) published an RCT assessing neoadjuvant durvalumab with compared to without SBRT.<sup>[14]</sup> A total of 60 patients with potentially resectable early-stage NSCLC were randomized to receive durvalumab monotherapy (n=30) or the durvalumab plus radiotherapy (n=30). There was a statistically significant difference in major pathological response rate between the monotherapy and SBRT-treated groups (6.7% [95% CI 0.8 to 22.1] vs. 53.3% [34.3 to 71.7%]; p<0.0001). Grade 3 to 4 adverse events were reported in 17% of monotherapy- and 20% of SBRT-treated patients. The second cycle of durvalumab was withheld in three (10%) of 30 patients in the SBRT-treated group due to immune-related adverse events (grade 3 hepatitis, grade 2 pancreatitis, and grade 3 fatigue and thrombocytopenia). Two patients in each group experienced serious adverse events. There were no treatment-related deaths or any deaths within 30 days of surgery.

### Nonrandomized Comparative Studies

Numerous nonrandomized, comparative studies have compared SBRT with surgery for NSCLC. A few of them used matching and are therefore the strongest methodologically of this group. Chi (2019) reported results of a cohort study comparing surgery and SBRT for the treatment of early-stage NSCLC using data from the National Cancer Database.<sup>[15]</sup> Survival comparisons used the multivariable Cox proportional hazards model and propensity score matching incorporating preoperative risk factors significantly associated with OS. A total of 104,709 patients were included in the analysis. Of these, 91,330 were in the surgery group and 13,379 were in the SBRT group. For the propensity score–matched cohorts, 12,632 patients undergoing sublobar resection were compared with 12,632 patients undergoing SBRT and 12,632 patients undergoing lobar resection were compared with 12,632 patients undergoing SBRT. Resection, both sublobar (HR, 0.56; 95% CI 0.54 to 0.58, p<0.001) and lobar (HR, 0.47; 95% CI 0.45 to 0.49, p<0.001) were associated with reduced mortality risk compared with SBRT. Survival comparisons calculated using a stratified multivariable Cox model to adjust for confounding variables also showed an association between surgery and a reduction in mortality risk. This association was not found for less extensive surgery when 0 nodes were examined in patients aged 80 years or older with stage T2 to T3 tumors (HR for lobectomy, 0.90; 95% CI 0.65 to 1.25; p=0.53) and in selected operable patients older than 75 years with stage T1 tumors (HR for lobectomy, 1.07; 95% CI 0.57 to 2.00; p=0.84). Wu (2020) performed a similar analysis comparing sublobar resection versus SBRT or ablation for stage I NSCLC using data from the National Cancer Database. This analysis also identified shorter OS for SBRT and ablation versus sublobar resection.<sup>[16]</sup>

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.<sup>[17]</sup> 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 ( $n=398$ ).<sup>[18]</sup> 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.<sup>[19]</sup> 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),<sup>[20]</sup> 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%;  $p<0.001$ ).

Tubin (2019) compared the novel SBRT-based PARTial Tumor irradiation of HYpoxic clonogenic cells (SBRT-PATHY) to standard of care in unresectable stage IIB/IV bulky NSCLC.<sup>[21]</sup> A total of 60 patients who were considered inoperable or unsuitable for radical radio-chemotherapy were treated using SBRT-PATHY (group I,  $n = 20$  patients), recommended standard of care chemotherapy (group II,  $n = 20$  patients), and institutional conventional palliative radiotherapy (group III,  $n = 20$  patients). The median follow-up was 13 months. No statistically significant differences between groups were identified for one-year overall survival (75, 60, and 20% in groups 1, 2 and 3, respectively;  $p = 0.099$ ) or one-year cancer specific survival (90, 60, and 20% in groups 1, 2, and 3, respectively ( $p = 0.049$ )). However, multi-variate analysis for cancer specific survival was significant for treatment effect with SBRT-PATHY ( $p<0.001$ ) independent of age, sex, performance status, histology, stage, treated bulky site and tumor diameter. Bulky tumor control rate was 95, 20, and 20% in groups 1, 2, and 3, respectively. Compared to chemotherapy and conventional palliative radiotherapy, toxicity was lower and symptom control was improved in the SBRT-PATHY group.

Jeppeson (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).<sup>[22]</sup> 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<sub>1</sub>, 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).

### Noncomparative Studies

Raman (2018) reported an institutional prospective database review of 180 central and 26 ultracentral lung tumors.<sup>[23]</sup> 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 and 7.9% 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.<sup>[24]</sup> 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.<sup>[25]</sup> 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.

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.<sup>[26]</sup> 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.<sup>[27]</sup> 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 × 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.<sup>[28]</sup> 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.<sup>[29]</sup> 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.<sup>[30]</sup> 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 ( $p=0.001$ ), 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.<sup>[31]</sup>

### Section Summary

Although limited 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 and Hepatobiliary Tumors**

In order to understand the impact of SBRT in the management of hepatocellular carcinoma and other hepatic malignancies, well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved. Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs.

## Systematic Reviews

Bae (2024) conducted a systematic review and meta-analysis to determine outcomes and toxicity rates from SBRT for liver-confined HCC.<sup>[32]</sup> Seventeen studies involving 1889 patients were included with median follow-up of 24 months. An aggregated data meta-analysis found OS was 57% (95% CI, 47%-66%) at three years and 40% (95% CI, 29%-51%) at 5 years. Three and five-year local control (LC) rates were 84% (95% CI, 77%-90%) and 82% (95% CI, 74%-88%) respectively. Pooled rates of classic radiation induced liver disease (RILD) were zero percent for classic RILD (95% CI, 0%-2%) and 8% (95% CI, 5%-12%). Subgroup analysis found that tumor size was a significant prognostic factor for both LC and OS. Tumor size <3 cm was associated with improved LC and OS at three and five years (3yr LC p = 0.0162, 5yr LC p=0.0216; 3yr OS p=0.0114, 5yr OS p=0.0309). The authors concluded that SBRT is an appropriate treatment for HCC, but for tumors  $\geq 3$  cm improvement in LC is the appropriate treatment goal.

Yang (2023) performed a systematic review and meta-analysis to compare the efficacy and safety of radiofrequency ablation (RFA) to SBRT in patients with inoperable HCC.<sup>[33]</sup> Seventeen studies involving 22,180 patients were included. One and two-year OS rates were better in the RFA group (OR 0.69, 95% CI 0.50-0.96, p=0.141; OR 0.69, 95% CI 0.53-0.89, p=0.082); however, 3-5 year OS rates were similar in both groups (OR 0.94, 95% CI 0.65-1.38, p=0.001; OR 0.98, 95% CI 0.68-1.34, p=0.016) moderate to high ( $I^2=29.6-69.7\%$ ) heterogeneity. SBRT groups had higher rates of local control (freedom from local progression; FFLP) compared to RFA at one, two, and three years (OR 2.19, 95% CI 1.44-3.34, P=0.303; OR 1.57, 95% CI 1.12-2.19, P=0.268; OR 2.22, 95% CI 1.7-2.9, p=0.474). Heterogeneity was low to moderate ( $I^2=0-20.4\%$ ). No significant differences were found in the reported treatment-related complications, but the SBRT group had worse outcomes related to liver function and failure (p<0.01). The authors state baseline characteristics (e.g., liver function) likely contributed to the differences in the groups and future studies need to take into account baseline differences such as tumor size and location, prior treatment, and liver function.

Wu (2022) reported a systematic review compare external beam radiation therapy modalities for HCC with macrovascular invasion (MVI).<sup>[34]</sup> A total of 44 studies including 3,730 patients were included. Particle therapy had a pooled one-year OS (60.9%) that was significantly greater than conventional radiotherapy (45.3%; p=0.005) and SBRT (44.9%; p=0.002). Particle therapy and SBRT had significantly objective response rate compared to conventional radiotherapy, whereas only particle therapy was significantly greater than conventional radiotherapy with respect to local control rate. The most frequent types of grade  $\geq 3$  complications were hematological toxicity, hepatotoxicity, dermatological toxicity.

Bisello (2021) performed a systematic review of SBRT for the treatment of intrahepatic cholangiocarcinoma.<sup>[35]</sup> Six publications with a total of 145 patients met inclusion criteria. SBRT followed previous systemic or local treatments for 28.6 to 66.7% of patients. No meta-analysis was conducted. Median follow-up was reported in five studies and was 16 months (range 8.8 to 18.0). Median OS was reported in all studies and was 14 months (range 10 to 48 months). Reports of tumor response, local control, and toxicities were not consistently.

Shanker (2021) published a systematic review analyzing local control, survival and toxicity outcomes following SABR for HCC.<sup>[36]</sup> A total of 49 cohorts including 2,846 patients met inclusion criteria. Pooled LC rates were 91.1% (95% CI 88.3 to 93.2) at one year, 86.7% (95% CI 82.7 to 89.8) and two years, and 84.2% (95% CI 77.9 to 88.9) at three years. Pooled OS

rates were 78.4% (95% CI 73.4 to 82.6) at one year, 61.3% (95% CI 55.2 to 66.9) at two years, and 48.3% (95% CI 39.0 to 57) at three years. Grade 3 and grade 4/5 toxicity rates, calculated as population-weighted medians, were 6.5% (IQR 3.2 to 16) and 1.4% (IQR 0 to 2.1), respectively.

Long (2021) reported a systematic review of therapeutic outcome of SBRT for small liver-confined HCC ( $\leq 3$  lesions with longest diameter  $\leq 6$  cm).<sup>[37]</sup> A total of 14 observational studies including 1,238 patients met inclusion criteria. Pooled one-year OS and LC rates were 93.0% (95% CI 88.0 to 96.0%) and 96.0% (95% CI 91.0 to 98.0%), respectively. Pooled three-year OS and LC rates were 72.0% (95% CI 62.0 to 79.0%) and 91.0% (95% CI 85.0 to 95.0%), respectively. Subgroup differences were identified for Child-Pugh class one- and three-year OS rate, but not for number of lesions, pretreatment situation, age (median/mean age of 65), macrovascular invasion, tumor size, or radiation dose (median BED10 of 100 Gy). Pooled rates of grade 3 or greater hepatic complications and radiation-induced liver disease were 4.0% (95% CI 2.0 to 8.0%) and 14.7% (95% CI 7.4 to 24.7%), respectively.

Lee (2020) evaluated the efficacy of SBRT versus RFA for the treatment of liver malignancies via a meta-analysis of 11 studies involving 2,238 patients.<sup>[38]</sup> Of the 11 studies, eight involved treating patients for early HCC and three for liver metastases. Results revealed that the pooled two-year local control rate was significantly improved in the SBRT versus RFA arm (83.8% versus 71.8%;  $p=0.024$ ). The pooled two-year control rate was also significantly higher in the SBRT versus RFA arm among patients in the liver metastases studies only (83.6% versus 60%;  $p<0.001$ ) while no such significant difference was seen in HCC studies (84.5% versus 79.5%;  $p=0.431$ ). Pooled analysis of OS in HCC studies showed an odds ratio of 1.43 (95% CI 1.05 to 1.95;  $p=0.023$ ), favoring RFA. Only two liver metastases studies had comparative survival data; no significant difference was seen.

Dobrzycka (2019) published a systematic review on outcomes following SBRT for early-stage hepatocellular carcinoma.<sup>[39]</sup> A total of 16 studies met inclusion criteria, 14 of which were retrospective. The average diameter of the treated tumor was 23 mm. Weighted one-year local control was 94.1% based on 11 studies. Seven and four studies reported two- and three-year local control, respectively, and the weighted means from those studies were 92.2% and 93.7%. Weighted one-year mean OS was 90.9% based on 14 studies. Nine and four studies reported two- and three-year OS, respectively, and the weighted means from those studies were 67.4% and 73.3%. Based on all 16 included studies, 171 grade 1 to 2 toxicities (17.5%) and 53  $\geq$  grade 3 toxicities (5.3%) were reported.

Frakulli (2019) performed a systematic review SBRT for the treatment of advanced cholangiocarcinoma.<sup>[40]</sup> 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.<sup>[41]</sup> 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 cholangiocarcinomas. 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.<sup>[42]</sup> 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 × 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.<sup>[43]</sup> 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.

### Randomized Controlled Trials

Shi (2022) compared SBRT after surgical resection with hepatectomy to hepatectomy alone in 76 patients with microvascular invasion (MVI)-positive early stage HCC.<sup>[44]</sup> Seventy-six patients were randomized to either surgery or surgery with adjuvant SBRT at the surgical margin, and there were 38 subjects in each arm. In the SBRT group DFS was 92.1% in one year, 65.8% in two years, and 56.1% at three years, and DFS in the surgery control group was 76.3%, 36.8%, and 26.3% (p=0.005). OS at one, three, and 5 years was 100%, 89.5%, and 75.0% in the SBRT group and 100%, 68.4%, and 53.7% in the surgery control group (p=0.053). Nearly one third of the people in the SBRT group (12/38) experienced radiotherapy-related adverse events but none were grade 3 or higher.

### Nonrandomized Comparative Studies

Larger studies and those addressing the policy criteria (e.g. number of lesions) are addressed below.

Yang (2019) compared the outcomes of SBRT and conventionally fractionated radiotherapy in HCC patients with portal vein invasion.<sup>[45]</sup> A total of 104 patients were evaluated, 45 in the SBRT group and 59 in the conventionally fractionated radiotherapy group. The differences in rates of overall response (62.2% vs. 33.8%; p=0.003), one-year OS (34.9% vs. 15.3%; p=0.012), and in-field progression-free survival (69.6% vs. 32.2%; p=0.007) were statistically significant, with higher values in the SBRT group for all measures. After propensity score matching, the rates all remained higher in the SBRT group. No significant differences were identified in incidence of radiation-induced liver disease or increase of Child-Pugh score greater than or equal to 2 within three months of radiotherapy.

Bettinger (2019) reported on a multi-center retrospective comparative study of SBRT (n=122) or sorafenib (n=901), a tyrosine kinase inhibitor, for the treatment of advanced HCC.<sup>[46]</sup>

Unadjusted median OS was 18.1 months (95% CI, 10.3 to 25.9) for SBRT and 8.8 (95% CI, 8.2 to 9.5) for sorafenib. Adjusted median OS was 17.0 months (95% CI, 10.8 to 23.2) and 9.6 (95% CI, 8.6 to 10.7), respectively. No survival benefit was observed for patients with SBRT in patients with portal vein thrombosis. Over 80% of patients were male in each study arm. Patients in the sorafenib group had significantly worse ECOG PS scores ( $p<0.001$ ), were more frequently pre-treated with radiofrequency ablation (RFA) ( $p<0.001$ ) or transarterial chemoembolization (TACE) ( $p=0.016$ ), had a higher incidence of multifocal disease and extrahepatic metastases ( $p<0.001$ ), and had more advanced illness on the basis of the Barcelona Clinic Liver Cancer (BCLC) staging system (Grade B, intermediate and Grade C, advanced;  $p<0.001$ ). Although propensity score matching was utilized to adjust for differences in baseline characteristics, the data are limited by extensive heterogeneity in the respective treatment populations. Presently, the FDA indication for the use of sorafenib is for patients with unresectable HCC. Due to the inclusion of patients who had previously been treated by surgery and with early or intermediate stage disease on the basis of BCLC criteria, it is unclear whether some patients were candidates for re-resection, potentially limiting the relevance of this study.

Roman (2019) performed a retrospective analysis of short- and long-term outcomes of SBRT ( $n=118$ ) and surgical treatment ( $n=142$ ) for patients with liver malignancies.<sup>[47]</sup> Median OS was 27.63 months for all patients, 22.93 months in the SBRT group, and 30.65 months in the surgical group. According to a Kaplan-Meier analysis, there was no statistically significant difference in disease specific survival between groups ( $p=0.082$ ).

Nakano (2018) reported results of a retrospective analysis of 281 patients with one to three small ( $\leq 3$  cm in diameter) hepatocellular carcinoma tumors who were treated with curative intent via surgical resection or SBRT.<sup>[48]</sup> 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% ( $p=0.0149$ ) 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.<sup>[49]</sup> 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).<sup>[50]</sup> 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.<sup>[51]</sup> 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.<sup>[52]</sup> 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.

### Comparison with TACE

Comito (2022) performed a single center RCT parallel-group superiority trial comparing SBRT to a second course of TACE for the curative treatment of unresectable early or intermediate stage HCC in patients with residual disease after initial TACE treatment.<sup>[53]</sup> Forty patients were randomized to SBRT (n=21) or continued TACE (n=19). There were no significant differences in baseline patient and treatment characteristics between the study groups. Local control was better with SBRT with 84% of SBRT cases having local control at one year, vs. 23% of TACE cases. PFS was also superior with SBRT. PFS with SBRT was 37% at one year and 21% at two years, compared to PFS with TACE of 13% at one year and 6% at two years. Distant recurrence-free survival (DRFS) was longer in the TACE arm but the difference was not statistically significant (p=0.494). Median OS in both study arms was 30 months and OS was not significantly different between the two treatment groups (p=0.472).

In 2019, Shen reported results of a comparison between SBRT and TACE.<sup>[54]</sup> A total of 188 patients with medium-sized HCC (3 to 8 cm) were treated with TACE (n=142) or SBRT (n=46). For surviving patients, the median follow-up was 26.6 months and for all patients it was 17.1 months. The three-year infield control was 63.0% and 73.3% for TACE- and SBRT-treated patients, respectively. The three-year OS was 22.9% and 47.7% for the TACE- and SBRT-treated patients, respectively. Treatment modality, sex, and recurrence status were independent predictors of infield control, which number of tumors, treatment modality, albumin-bilirubin grade, tumor volume, Eastern Cooperative Oncology Group status, and recurrence status were independent predictors of OS. According to the propensity score matching analysis, the SBRT group had superior three-year infield control (p=0.007) and three-year OS (p<0.001) compared with the TACE group.

Sapir (2018) assessed 209 patients that underwent TACE (n=84) or SBRT (n=125) for HCC at a single institution.<sup>[55]</sup> 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.<sup>[56]</sup> 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.<sup>[57]</sup> 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.<sup>[58]</sup> 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.<sup>[59]</sup> 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.

### 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.

Wong (2021) reported outcomes in patients bridged to liver transplantation for HCC. A prospective cohort of SBRT-treated patients was compared with a retrospective cohort of TACE- or HIFU-treated patients.<sup>[34]</sup> A total of 40 SBRT patients, 59 TACE patients, and 51 HIFU patients were evaluated. The primary endpoint of tumor control rate at one year post-bridging therapy was 92.3%, 43.5%, and 33.3% after SBRT, TACE, and HIFU, respectively ( $p=0.02$ ). Time-to-progression at one and three years was significantly different between groups (10.8%, 18.5% in SBRT, 45%, 54.9% in TACE, and 47.6%, 62.8% in HIFU;  $p<0.001$ ). There were no statistically significant differences between groups in perioperative complications and patient and recurrence-free survival rates after transplant.

Sapisochin (2017) performed an intention-to-treat analysis to examine the safety and efficacy of SBRT as a bridge to liver transplantation for HCC.<sup>[60]</sup> 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 ( $\geq$  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

Foerster (2021) published a systematic review of SBRT for high-risk prostate cancer. A total of 21 studies met inclusion criteria.<sup>[61]</sup> The majority evaluated SBRT of the prostate alone, while three reported on prostate and pelvic node SBRT. Acute and chronic GU toxicity grade  $\geq 2$  was 12 to 46.7% and 7 to 60%, respectively, in studies that included pelvic nodal irradiation and 0 to 89% and 2 to 56.7%, respectively in the prostate-only studies. Acute and chronic grade  $\geq 2$  GI toxicity was 0% to 4% and 4 to 50.1%, respectively, in studies that included pelvic nodal irradiation, and 0 to 18% and 0 to 40%, respectively, for studies without pelvic nodes irradiation. The range of biochemical control rates was 82 to 100% after two years and 56 to 100% after three years.

A systematic review and meta-analysis by Valle (2021) evaluated local salvage therapies after radiotherapy for prostate cancer.<sup>[62]</sup> A total of 150 studies met inclusion criteria. The within modality between study heterogeneity was significant and therefore adjustment was required. Adjusted five-year recurrence-free survival was not significantly different between any modality and radical prostatectomy, but severe GU toxicity was significantly higher with radical prostatectomy than with any form of radiotherapeutic salvage. Severe GI toxicity was significantly lower in patients with high-dose-rate brachytherapy salvage than with radical prostatectomy (adjusted rates 1.8 vs. 0.0%, p<0.01). No other significant differences were identified between groups for severe GI toxicity.

Achard (2020) performed a systematic review of SBRT vs. elective nodal radiotherapy for nodal oligorecurrent prostate cancer.<sup>[63]</sup> A total of 22 articles were included, four of which were prospective phase II trials. PFS rates were better in the elective nodal radiotherapy-treated patients (52 to 80%) than in those treated with SBRT (16 to 58%). The toxicity rate was slightly

lower in the SBRT group.

Jackson (2019) performed a systematic review and meta-analysis on SBRT for localized prostate cancer.<sup>[64]</sup> Thirty-eight prospective studies between 1990 and 2018 were retrieved featuring low- (45%), intermediate- (47%), and high-risk (8%) patients (n=6116). Most common dose received was 7.25 Gy/fraction (range 5 to 10) in a median of 5 fractions (range 4 to 9). Five-and seven-year biochemical relapse-free survival (bRFS) rates were 95.3% (95% CI 91.3 to 97.5; I<sup>2</sup> 87.96; Q value 74.9, p<0.001) and 93.7% (95% CI 91.4 to 95.5), respectively. Late grade 3 or higher genitourinary (GU) or gastrointestinal (GI) toxicity rates were 2.0% (95% CI, 1.4 to 2.8) and 1.1 (95% CI, 0.6 to 2.0), respectively. In 33 studies that reported on the use of androgen-deprivation therapy (ADT), 15% of patients received ADT alongside SBRT. The impact of ADT on pooled outcomes is unknown. Furthermore, studies did not stratify bRFS rates by patient risk level, contributing to high heterogeneity in the results.

Kishan (2019) pooled long-term outcomes from 10 single-center and two multi-center prospective trials evaluating SBRT for the treatment of low-to-intermediate risk prostate cancer (n=2142).<sup>[65]</sup> Doses of SBRT ranged from 33.5 to 40.0 Gy in 4 to 5 fractions. Overall, 115 patients (5.4%) received concurrent ADT. Mean overall follow-up duration was 6.9 years (interquartile range [IQR], 4.9 to 8.1). For patients with low, intermediate-favorable, and intermediate-unfavorable, and any intermediate risk level, biochemical recurrence rates were 4.5% (95% CI 3.2 to 5.8), 8.6% (95% CI 6.2 to 11.0), 14.9% (95% CI 9.5 to 20.2), and 10.2% (95% CI 8.0 to 12.5), respectively. Corresponding overall survival rates were 91.4% (95% CI, 89.4 to 93.0), 93.7% (95% CI, 91.0 to 95.6), 86.5% (95% CI, 80.6 to 90.7), and 91.7% (95% CI, 89.2 to 93.6), respectively. There were 13 (0.6%) and 2 (0.09%) reported cases of acute grade 3 or higher genitourinary (GU) or gastrointestinal (GI) toxicities. The incidence of late grade 3 or higher GU and GI toxicities was 2.4% (95% CI, 1.8 to 3.2) and 0.4% (95% CI, 0.2 to 0.8), respectively. The analysis was limited by heterogeneity in toxicity reporting and scoring criteria and lack of comparative studies.

Loi (2019) published a systematic review assessing sexual function in prostate cancer patients who had been treated with SBRT.<sup>[66]</sup> A total of 12 studies representing 1221 patients who had not received androgen-deprivation therapy (ADT) and were available at final follow-up were analyzed. Studies used varying definitions for erectile dysfunction (ED); some were based on the Sexual Health Inventory for Men (SHIM) scale whereas others were based on the Expanded Prostate Cancer Index Composite (EPIC)-26. At 60 months, ED was reported by 26 to 55% of previously sexually functioning patients in 5 of 12 studies.

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.

### Randomized Controlled Trials

Poon (2021) reported results of a randomized trial comparing SBRT (36.25 Gy delivered in five fractions over two weeks) and conventionally fractionated radiotherapy (76 Gy delivered in 38 fractions over 7.5 weeks) for the treatment of low- and intermediate-risk localized prostate cancer.<sup>[67]</sup> A total of 64 men were randomized to receive SBRT (n=31) or conventional

fractionation (n=33). Median follow-up was 2.3 years. There were no significant differences between groups in the primary endpoint, variation in patient-reported quality of life (PRQL) at one year assessed by changes in the Expanded Prostate Cancer Index Composite (EPIC) questionnaire scores, at 3, 6, 9 and 12 months. There were statistically significant differences between groups in grade  $\geq 1$  acute and one-year late gastrointestinal toxicities, with 35% vs. 87% acute toxicities for conventional fractionation versus SBRT, respectively ( $p < 0.0001$ ), and 64% vs. 84% toxicities at one year for conventional fractionation versus SBRT, respectively ( $p = 0.03$ ).

Brand (2019) reported acute toxicity findings from a randomized trial comparing SBRT with conventionally fractionated and moderately hypofractionated radiotherapy (PACE-B study).<sup>[68]</sup> A total of 874 men with WHO performance status 0-2, low-risk or intermediate-risk prostate adenocarcinoma (Gleason 4 + 3 excluded) were enrolled in this international, phase 3, open-label, randomized, non-inferiority trial. Patients were randomly assigned to receive conventionally fractionated or moderately hypofractionated radiotherapy (n=4,41; 78 Gy in 39 fractions over seven to eight weeks or 62 Gy in 20 fractions over four weeks, respectively), or stereotactic body radiotherapy (n=433; 36.25 Gy in five fractions over one to two weeks). The primary endpoint of the trial was freedom from biochemical or clinical failure, and the coprimary outcomes for this acute toxicity substudy were worst grade 2 or more severe Radiation Therapy Oncology Group (RTOG) gastrointestinal or genitourinary toxic effects score up to 12 weeks after radiotherapy. No statistically significant differences in toxicity were reported. Grade 2 or more severe toxic gastrointestinal events were reported in 12 and 10% of patients in the conventionally fractionated or moderately hypofractionated group and stereotactic body radiotherapy groups, respectively ( $p = 0.38$ ). Grade 2 or worse genitourinary toxicity were reported in 27 and 23% of the conventionally fractionated or moderately hypofractionated group and stereotactic body radiotherapy groups, respectively ( $p = 0.16$ ).

Tree (2022) published a follow-up toxicity analysis of the PACE-B study after two years.<sup>[69]</sup> Outcomes of interest were the cumulative incidence of grade 2 or worse genitourinary or gastrointestinal toxicity, grade 2 or worse erectile dysfunction, and other symptoms, including hot flashes, other pain, fatigue, anorexia, weight loss, and radiation dermatitis. Data was available for 796 of 844 patients (91%) at 24 months. Nine patients died between radiotherapy treatment and the 24-month follow-up; and no deaths were treatment-related. Cumulative grade 2 or worse genitourinary (GU) toxicity rates were higher in the SBRT group, using both radiation therapy oncology group (RTOG) grades ( $p = 0.0015$ ) and Common Terminology Criteria for Adverse Events (CTCAE) grades ( $p = 0.0001$ ). The most frequent GU toxicity was urinary frequency, but grade 3 urinary frequency was rare; less than 1% in both groups. Cumulative gastrointestinal toxicity at grade 2 or worse nearly the same in both treatment groups using both RTOG and CTCAE measures ( $p = 0.92$ ;  $p = 0.91$ ), and incidence of gastrointestinal toxicity was low overall. Erectile dysfunction and other symptoms were not significantly different.

### Nonrandomized Comparative Studies

Gogineni (2021) compared low-dose-rate (LDR) brachytherapy and SBRT for the treatment of low- and intermediate-risk prostate cancer.<sup>[70]</sup> Sequential low- and intermediate-risk prostate cancer patients treated definitively with SBRT (n=118) and low-dose-rate brachytherapy (n=219). Five-year biochemical control was 91.6% and 97.6% for low-dose-brachytherapy and SBRT, respectively ( $p = 0.108$ ). The difference between groups in pre- to post-treatment increase in American Urologic Association (AUA) scores was statistically significant, with the

LDR and SBRT groups reporting 17.2 and 10.3, respectively at one month ( $p < 0.001$ ) and 14.0 and 9.7, respectively, at three months ( $p < 0.001$ ). The LDR and SBRT groups reported 0.8% and 2.5% late grade 3 GU toxicity ( $p = 0.238$ ) and 0.0% and 2.5% late grade 3 GI toxicity ( $p = 0.018$ ).

Patel (2020) reported a comparison of SBRT and EBRT using data from the National Cancer database on men > 40 years old with localized prostate cancer treated with radiation therapy and concomitant ADT with curative intent.<sup>[71]</sup> Median follow-up was 74 months. Regardless of risk group, there was no difference in estimated six-year OS between radiation therapy modality. The multivariate analysis did not identify any difference in risk of death following SBRT versus EBRT (unfavorable intermediate: adjusted HR 1.09, 95% CI 0.68 to 1.74,  $p = 0.72$ ; high risk: adjusted HR 0.93, 95% CI 0.76 to 1.14,  $p = 0.51$ ).

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.<sup>[72]</sup> 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 (odds 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.<sup>[73]</sup> 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.<sup>[74-97]</sup> Other noncomparative studies have reported on reirradiation using SBRT for recurrence<sup>[98]</sup> and on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence,<sup>[99]</sup> rectal tolerance,<sup>[100]</sup> and health-related QOL outcomes.<sup>[101]</sup>

### 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.

### Systematic Reviews

Liu (2021) reported a meta-analysis of survival outcomes following SBRT for locally advanced and borderline resectable pancreatic cancer.<sup>[102]</sup> A total of 19 studies met inclusion criteria. Overall study quality was rated as good using the Newcastle-Ottawa scale. For patients with locally advanced pancreatic cancer, the pooled median OS rates were 57% at one year, 19% at two years, and 10% at three years. The median PFS was 10 months. Pooled PFS rates at one, two, and three years were 36%, 12%, and 4%, respectively. Pooled incidence rates of acute gastrointestinal (GI), acute hematologic and late GI toxicity (grade $\geq$ 3) were 2%, 4% and 8%, respectively. For patients with borderline resectable pancreatic cancer, pooled one- and two-year OS rates were 75% and 29%, respectively, while pooled one- and two-year PFS rates were 48% and 18%, respectively. The median PFS was 12.2 months and incidence rates of toxicity (grade  $\geq$  3) were 0%.

Zaorsky (2019) reported a systematic review of SBRT with varying doses for nonmetastatic pancreatic cancer.<sup>[103]</sup> 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  $\alpha/\beta$  of 10) <70 Gy versus  $\geq$ 70 Gy.

Buwenge (2018) published a systematic review that evaluated the impact of SBRT on pain reduction.<sup>[104]</sup> 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  $\geq$ 3) rates were 3.3% to 18.0% and 6.0% to 8.2%, respectively. A 2022 update included 19 studies and continued to report high heterogeneity.<sup>[105]</sup> The pooled rate of complete response, reported in three studies, was 51.9% (95% CI 39.3 to 64.3%), and the rate of partial plus complete pain response, reported in nine studies, ranged between 44.4 and 100% (median: 78.6%).

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.<sup>[106]</sup> 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.

Groot (2016) published a systematic review comparing outcomes from re-resection, chemoradiotherapy, and SBRT in patients with isolated local recurrence (ILR) after initial curative-intent resection of primary pancreatic cancer.<sup>[107]</sup> A total of 18 studies reporting on 313 patients was included for analysis, which included four retrospective case series (n=60) on SBRT. Morbidity and mortality were reported for re-resection (29% and 1%), chemoradiotherapy (54% and 0%), and SBRT (3% and 1%). Morbidity for re-resection was defined as the sum of surgical complications and non-surgical 30-day complications. For chemoradiotherapy and SBRT, it was defined as toxicities of grade 3 or higher as defined by the Common Terminology Criteria for Adverse Events v4.0 guidelines. Mortality was defined as death within 30 days post-intervention. Median survival post-treatment was 32 months (range, 16 to 32), 19 months (range, 16 to 19), and 16 months (range, 9 to 16) for re-resection, chemoradiotherapy, and SBRT, respectively. The disease-free interval for the re-resection group tended to be longer than for chemoradiotherapy or SBRT, a finding that is known to correlate with improved outcomes for patients with ILR. Acute and late toxicity rates were reported for chemoradiotherapy (52% and 2%) and SBRT (3% and 2%), respectively. The analysis was limited by heterogeneity in treatments, including inconsistent use of combination systemic therapies.

### Comparative Studies

Ma (2022) conducted a RCT focused on adjuvant therapy for stage II pancreatic adenocarcinoma.<sup>[108]</sup> After surgical resection 38 patients were randomized to receive SBRT followed by gemcitabine chemotherapy, or gemcitabine therapy alone. Most patients in both groups (34/38) experienced tumor recurrence prior to the last follow-up. Median OS was 28 months in the gemcitabine-only arm and 15 months in the SBRT arm. The HR for death was 0.56 (95% CI 0.23-1.36, p=0.20). There were no significant differences in adverse events between the two groups.

Arcelli (2020) reported a multicenter case-control study comparing SBRT plus chemotherapy and conventionally fractionated chemoradiation for locally advanced pancreatic cancer.<sup>[109]</sup> A total of 80 patients were matched according to age (over versus equal to or younger than 65 years), tumor diameter (two cut-offs:  $\leq 3.0$  and  $\leq 3.9$  cm), clinical tumor stage and clinical nodal stage, neoadjuvant CHT, and adjuvant CHT. There were no statistically significant differences in acute or late toxicity, DMFS, PFS, or OS between the two cohorts. Median one-year and two-year LC was 53.1% and 40.5% in the chemoradiation cohort and 80.4% and 49.8% in the SBRT cohort, respectively. There was no significant difference in OS between groups (p=0.031).

Wu (2019) reported the effects of SBRT and conventionally fractionated radiation therapy, both with concurrent chemotherapy, on total lymphocyte counts in patients with pancreatic adenocarcinoma.<sup>[110]</sup> Included patients were treated with conventionally fractionated radiation therapy with concurrent Nelfinavir (n=28), SBRT with concurrent Nelfinavir (n=27), or SBRT with concurrent chemotherapy (n=45). The conventionally fractionated group had significantly lower median lowest total lymphocyte counts (p<0.0001) and median total lymphocyte count over time (p<0.0001). There was no significant difference in median OS between SBRT and conventional fractionation.

Park (2017) published a retrospective review of patients treated with SBRT (n=44) or IMRT (n=226) for unresectable stage I-III pancreatic adenocarcinoma.<sup>[111]</sup> 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.<sup>[112]</sup> 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;  $p<0.001$ ). 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 ( $p=0.001$ ).

### 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**

Stereotactic radiotherapy (SRT) is being considered in the setting of oligoprogression to delay the need to change systemic therapy. Cheung (2021) conducted a prospective multicenter study to evaluate the use of SRT in oligoprogressive mRCC patients to determine the local control (LC), progression-free survival (PFS), cumulative incidence of changing systemic therapy, and overall survival (OS) after SRT to oligoprogressive metastatic renal cell carcinoma (mRCC) lesions in patients who are on tyrosine kinase inhibitor (TKI) therapy.<sup>[113]</sup> Patients with mRCC who had previous stability or response after  $\geq 3$  months of TKI therapy were eligible if they developed progression of five or fewer metastases. Thirty-seven patients with 57 oligoprogressive tumors were enrolled. Oligoprogressive tumors were treated with SRT, and the same TKI therapy was continued afterward. Competing risk analyses and the Kaplan-Meier methodology were used to report the outcomes of interest. The median duration of TKI therapy prior to study entry was 18.6 months; one year of LC of the irradiated tumors was 93% (95% confidence interval [CI] 71-98%). The median PFS after SRT was 9.3 mo (95% CI 7.5-15.7 months). The cumulative incidence of changing systemic therapy was 47% (95% CI 32-68%) at 1 yr, with a median time to change in systemic therapy of 12.6 months (95% CI



9.6-17.4 months). One-year OS was 92% (95% CI 82-100%). There were no grade 3-5 SRT-related toxicities. LC of irradiated oligoprogressive mRCC tumors was high, and the need to change systemic therapy was delayed for a median of >1 year. The use of stereotactic radiotherapy in metastatic kidney cancer patients, who develop growth of a few tumors while on oral targeted therapy, can significantly delay the need to change to the next line of drug therapy.

Correa (2019) published a PRISMA-based systematic review and meta-analysis of SBRT for primary RCC.<sup>[114]</sup> The primary outcome was LC (defined as tumor-size reduction and/or absence of local progression). The secondary outcomes were toxicity and renal function. A total of 26 studies met inclusion criteria. Of the 372 patients included, 78.5% had confirmed RCC histology upon pre-treatment biopsy and 80% had localized disease (stage I-II) while 20% had stage III to IV disease. The random-effect estimate of local control, based on 25 studies, was 97.2% (95% CI 93.9 to 99.5%). For toxicity (grade 3 to 4) and renal function (post-SBRT change in estimated glomerular filtration rate), random effect estimates, based on 23 and 8 studies, respectively, were, 1.5% (95% CI 0.0 to 4.3%), and -7.7 ml/min (95% CI -12.5 to -2.8). Heterogeneity was minimal ( $I^2$  0 to 20%).

Siva (2018) retrospectively evaluated 223 patients who received single- or multi-fraction SBRT for primary RCC.<sup>[115]</sup> 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.<sup>[116]</sup> 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.

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.<sup>[117]</sup> 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 to 21.8 months). No patient experienced worsening of hypertension or required hemodialysis.

Ranck (2013) reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT.<sup>[118]</sup> 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.

## **Paraganglioma**

Glomus jugulare tumors (GJTs) are benign paragangliomas of the jugular foramen. Traditional management of these tumors involves surgical resection; however, considering the proximity of these tumors to important neurovasculature, stereotactic radiosurgery (SRS) may be an appropriate noninvasive treatment to consider. Campbell (2023) published a systematic review and meta-analysis focused on tumor control and treatment complications from surgery vs. stereotactic radiosurgery (SRS) for jugular paraganglioma.<sup>[119]</sup> Data from 107 studies involving 3498 patients (2215 surgical patients and 1283 patients who were treated with SBRT). All studies were retrospective. The quality of the evidence was deemed “good” for 85 studies using the Newcastle-Ottawa Scale. The SRS group was older than the surgery group. The SRS group had larger tumor volume and were more likely to have had prior surgery. The SRS group was also more likely to present with dysphagia, tongue weakness, and headache, while the surgery group was more likely to have tinnitus and deafness. Recurrence rates were low for both groups but were lower for SRS (7% long-term recurrence vs. 15% with surgery). Surgery was associated with more complications, specifically cranial nerve (CN) VII, IX, X, XI, and XII palsies, cerebral spinal fluid leaks and postoperative dysphagia. A major limitation of the study was the authors were unable to analyze the available data for statistical significance. However, the study shows that both treatments are effective in the treatment of jugular paraganglioma.

Ong (2022) published a systematic review and meta-analysis to evaluate SRS as a treatment option for GJTs.<sup>[120]</sup> An online search using PubMed, Web of Science, Scopus, and Cochrane databases was performed in March 2019 for articles on radiosurgery treatment of GJTs. The screening process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The final analysis comprised 23 studies including 460 patients. Average rates of tinnitus, hearing loss, and lower cranial nerve deficit as presenting symptoms were 56% (95% confidence interval [CI], 46%-66%), 56% (95% CI, 44%-68%), and 42% (95% CI, 31%-54%), respectively. Overall clinical status improvement rate after treatment was 47% (95% CI, 37%-57%). Rates of tinnitus, hearing loss, and lower cranial nerve improvement after treatment were 54% (95% CI, 44%-63%), 28% (95% CI, 19%-40%), and 22% (95% CI, 11%-39%), respectively. The mean follow-up time across studies was 47 months (range, 4-268 months). The aggregate tumor control rate at the time of follow-up was 95% (95% CI, 93%-97%). The tumor control rate of 95% and 47% symptomatic improvement suggest that SRS may be a suitable treatment modality for these hypervascular skull base tumors.

## **Primary Spinal Tumors**

Conti (2022) published a systematic review and meta-analysis of radiosurgery for benign spinal hemangiomas.<sup>[121]</sup> Three series of cases involving 24 patients were assessed. The review found that the complete response rate from radiosurgery was 45.7% and the overall response rate was 94.1%. The review found that radiosurgery was effective for spinal hemangioma but did not include studies that compare radiosurgery to other treatments for spinal hemangioma.

## **Oligometastases**

In order to understand the impact of SBRT on metastatic cancer outcomes well-designed randomized controlled trials (RCTs) are preferred. However, these are often difficult to perform given the populations involved. Therefore, this evidence section includes meta-analyses of nonrandomized studies and larger nonrandomized studies in addition to RCTs.

### Systematic Reviews

Deodato (2021) reported a systematic review of outcomes following SBRT for nodal metastases.<sup>[125]</sup> A total of 29 studies including 969 patients met inclusion criteria. There was statistically significant heterogeneity in patient and treatment characteristics. Pooled two-year LC was 79.3% (95% CI 72.8% to 85.7%) based on 11 reporting studies and pooled two-year PFS was 35.9% (95% CI 22.1% to 49.7%) based on eight reporting studies. Grade  $\geq$  3 and grade 5 toxicity rates were 2.0% and 0.2%, respectively.

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.<sup>[131]</sup> 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.

### *Bone oligometastases*

The role of SBRT is being investigated as a way to improve local control and survival, as well as provide palliative pain relief for people with metastasis to the bones. Singh (2024) published a systematic review and meta-analysis to determine local control, overall survival (OS), pain response, and toxicity after SBRT for non-spinal bone metastases.<sup>[122]</sup> Nine studies involving 528 patients were included. One study was prospective. After SBRT the local control rate was 94.6% (95% CI, 87.0-99.0%), the combined partial and complete pain response rate was 87.7% (95% CI, 55.1-100.0%), and the combined acute and late grade 3-5 toxicity rate was 0.5% (95% CI, 0%-5.0%). The pathologic fracture rate was 3.1% (95% CI, 0.2%-9.1%) and the one-year OS rate was 71.0% (95% CI, 51.7%-87%). The authors concluded that local control and pain response rates were superior to historical outcomes with minimal toxicity but further study is needed.

Guninski (2024) published a systematic review and meta-analysis of SBRT for spine metastases.<sup>[123]</sup> The study involved 69 studies, of which 14 were prospective, that involved 5736 participants with 7236 spinal lesions. The primary outcome was efficacy, defined as the pooled pain response and one-year local control. Secondary outcomes related to safety included pooled pain flare rate, vertebral fracture rate, and radiation induced myelopathy rate. The pooled overall response rate for pain was 83% and the complete response rate was 36%. The pain flare rate after SBRT was 6%. The authors note the response rates are higher than observed with conventional radiation therapy in previous studies. The pooled one-year rate of local control was 94%. Vertebral fracture occurred in 8.8% of participants and 1.7% required surgery related to vertebral fracture. Radiation-induced myopathy was rare and reported in only four studies. The review was limited by incomplete reporting of data, heterogeneous study populations involving different histologies and metastases burden, as well as evolving radiation therapy techniques over the course of the study. The authors concluded that SBRT is effective

for both pain relief and local control with low rates of toxicity in the treatment of spinal metastases.

Ito (2022) published a systematic review and meta-analysis of RCTs comparing SBRT to conventional radiotherapy (cEBRT) for painful bone metastases.<sup>[124]</sup> Seven studies involving 964 patients were assessed. Two studies were phase III and five were phase II trials. Four studies were of spinal metastasis, one was of bone metastases, and three studies involved both spine and bone metastases. In the studies 522 patients were treated with SBRT and 442 were treated with conventional radiotherapy. Overall pain response rates at three months were 45% in the SBRT arm and 36% in the cEBRT group, which was not significant (RR=1.19; 95% CI 0.93-1.53; p=0.14). A focused analysis of studies involving spine metastases also was not statistically significant with response rates of 40% in the SBRT arm and 35% in the cEBRT arm (RR=0.14; 95% CI 0.71-1.84; p=0.44). No significant differences were seen in adverse events, quality of life, or survival. The authors state that the results of the meta-analysis may be inconsistent with retrospective research in particular that favors SBRT because SBRT tends to be offered to patients in better condition than those who are treated with cEBRT.

Spencer (2019) reported a systematic review of outcomes following SBRT for bone metastases.<sup>[125]</sup> A total of 57 studies met inclusion criteria. No meta-analysis was conducted due to clinical and methodological diversity and risk of bias present in the included studies. The majority of studies addressed spinal metastases, while eight included other sites of disease. A wide range of median OS was reported in the included studies, from 8 to 34 months. The authors concluded that this suggested a high risk of selection bias in the included observational studies. The measurement and definitions of pain response varied across studies, and only 10.5% of studies used the international consensus endpoint definitions of pain response. For the studies that addressed tumors in a location other than the spine, the total treated population pain response rates were 60 to 88% and local control rates were 70 to 96%.

### *Lung oligometastases*

Mayinger (2023) published a systematic review of SBRT for pulmonary oligometastases that reported outcomes and treatment-related toxicities.<sup>[126]</sup> The review of 35 studies included five randomized studies, but the majority (27) were retrospective. The primary outcome measures were safety, defined as  $\geq$  grade 3 toxicities and efficacy, defined as local control at 1-5 years. The analysis also included the influence of treatment techniques. The most commonly reported primary tumors were non-small cell lung cancer (NSCLC), colorectal cancer and sarcoma. The median local control rate was 90% (range 57%-100%) at one-year and 79% (70%-96%) at five years. The most frequent grade  $\geq 3$  toxicities were grade 3 pneumonitis (n=14) and late lung fibrosis (n=14). Other grade 3 toxicities included bronchial stenosis (n=3), dyspnea (n=4), rib fracture (n=2) and other toxicities that occurred in one participant. Ten participants had grade 4 or 5 toxicities and 12 studies reported zero grade  $\geq 3$  toxicities. The authors concluded that SBRT is effective for pulmonary oligometastasis with low rates of toxicity. Based on the review recommendations for staging, patient selection, treatment and follow-up were developed.

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%,<sup>[127]</sup> ranging from higher rates in a study by Norisha (2008) of 84%<sup>[128]</sup> to lower rates, such as 39%, reported from a multi-institutional trial.<sup>[129]</sup>

### *Metastatic Breast Cancer*

Viani (2021) reported a systematic review evaluating the efficacy of SBRT for the treatment of breast cancer metastases.<sup>[130]</sup> The ten studies that met inclusion criteria included 467 patients. Local control rates were 97% (95% CI 95 to 99%) and 90% (95% CI 84 to 94%) and OS was 93% (95% CI 89 to 96%) and 81% (95% CI 72 to 88%) at one and two years, respectively. The rate of any grade 2 was 4.1 % (95% CI 0.1 to 5%) and any grade 3 toxicity was 0.7% (0 to 1%), respectively.

### *Metastatic Prostate Cancer*

Yan (2020) performed a systematic review of SBRT for oligometastatic prostate cancer involving 10 studies (six observational cohorts; one phase I single arm prospective trial; one phase II single arm prospective trial; two phase II RCTs) with 653 patients and 1,111 lesions.<sup>[131]</sup> Results revealed an overall local control rate of 97% (95% CI 94 to 100), median ADT-free survival of 24.7 months (95% CI 20.1 to 29.2 months), two-year biochemical free survival of 33% (95% CI 11 to 55), two-year PFS of 39% (95% CI 24 to 54), and two-year ADT-free survival of 52% (95% CI 41 to 62). Patients treated with SBRT were half as likely to experience PSA progression than those on observation when evaluating RCT data alone.

Vilela (2018) performed a systematic review of the safety and effectiveness of SBRT for oligometastatic recurrent prostate cancer.<sup>[132]</sup> 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. Using the GRADE system, the quality of evidence was assessed as low. 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 2020, Viani published a systematic review on the same topic as the above Vilela systematic review, SBRT for oligometastatic recurrent prostate cancer.<sup>[133]</sup> The 2020 systematic review included six studies not included in the Vilela publication. Two were identified during the Vilela search and excluded and five were published after the Vilela search dates. Overall, Viani identified 23 observational studies that met the inclusion criteria. According to the meta-analysis, the proportional rates of local control and progression-free survival were 0.976 (95% CI 0.96 to 0.98) and 0.413 (95% CI 0.378 to 0.477), respectively. The androgen deprivation-free survival was 20.1 months. There was a linear relationship between biologically effective dose and local control ( $p=0.017$ ). Acute and late grade 2 or higher toxicity were reported in 1.3 and 1.2%, respectively.

### *Metastatic gynecologic cancer*

Yegya-Raman (2020) assessed the efficacy and safety of SBRT for oligometastatic gynecologic malignancies. A total of 16 unique studies with 667 patients met inclusion criteria.<sup>[134]</sup> Metastases were located in the abdomen (44.2%), pelvis (18.8%), thorax (15.5%), neck (4.6%), central nervous system (4.3%), bone (1.6%), and other/unspecified (11%). Response rate ranged from 49 to 97%, with seven of the eight studies reporting over 75% response rate. Local control ranged from 71% to 100% and median PFS ranged from 3.3 to 21.7 months. No grade  $\geq 3$  toxicities were observed in 9/16 (56%) studies.

### *Metastatic Lung Cancer*

Virbel (2021) performed a systematic review of the evidence regarding the use of SBRT for the treatment of oligometastatic lung disease.<sup>[135]</sup> The search dates were limited to January 1, 2015 to December 31, 2020. A total of 18 studies met inclusion criteria. No meta-analysis was completed. Oligometastatic disease was defined differently between articles, with eight studies defining it as one to five, one article as one to four, three articles as one to three, and six articles with no definition. The median number of treated metastases was between one and two in the included studies. Of the four included studies that evaluated the relationship between tumor size and LC, three reported that size impacted LC, with larger size associated with worse outcomes, and one reported no relationship. Overall, the authors concluded that SBRT is safe and effective in patients with oligometastases limited to one to three organs.

Tsao (2019) completed a systematic review of SBRT for extracranial oligometastatic NSCLC involving four prospective phase II randomized trials (n=188), four prospective nonrandomized studies (n=140), and 11 retrospective studies (n=1,288). Results revealed a median OS ranging from 13.5 to 55 months and a PFS ranging from 4.4 to 14.7 months.<sup>[136]</sup> The authors noted that results from mature phase III RCTs are needed to fully determine the benefits and risks of SBRT for oligometastatic NSCLC.

### *Metastatic Renal Cancer*

Zaorsky (2019) conducted a systematic review and meta-analysis of SBRT for oligometastatic renal cell carcinoma.<sup>[137]</sup> A total of 28 studies with 1602 unique patients were included. For extracranial disease, the summary effect size for one-year local control and the one-year survival rates were 89.1% (95% CI 83.6 to 93.7%,  $I^2=71%$ ) and 86.8% (95% CI 62 to 99.8%,  $I^2=95%$ ), respectively, and for intracranial disease were 90.1% (95% CI 83.5 to 95.3%,  $I^2=74%$ ) and 49.7% (95% CI 41.1 to 58.3%,  $I^2=74%$ ), respectively. For extracranial and intracranial disease, incidence of grade 3 to 4 toxicity was 0.7% (95% CI 0 to 2.1%,  $I^2=0%$ ) and 1.1% (95% CI 0 to 7.4%,  $I^2=53%$ ), respectively.

### *Metastatic Colorectal Cancer*

Choi (2020) published a systematic review and meta-analysis of tumor control and OS following SBRT for pulmonary oligometastases from colorectal cancer.<sup>[138]</sup> Fourteen studies including a total of 495 colorectal cancer patients with pulmonary oligometastases met inclusion criteria. The pooled estimate LC rate at one, two, three, four, and five years after SBRT was 81.0%, 71.5%, 56.0%, and 61.8%. The OS rate was 86.9%, 70.1%, 57.9%, and 43.0%, respectively, at the same time points. Two studies reported rates of grade 3 or higher pulmonary toxicity, and those rates were 2.2% and 10.8%.

In a 2018 systematic review, Petrelli analyzed the efficacy of SBRT to treat colorectal cancer liver oligometastases.<sup>[139]</sup> 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 to 92.2) and 56.5% (95% CI 36.7 to 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 to 90.2) and 59.3% (95% CI 37.2 to 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.<sup>[140]</sup> 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.

### Comparative Studies

Palma (2019) compared SBRT versus standard of care palliative treatment in patients with oligometastatic cancers in the randomized, phase 2, open-label Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial.<sup>[141]</sup> This multicenter study enrolled 99 adults with a controlled primary tumor and one to five metastatic lesions. After stratification by the number of metastases, patients were randomly assigned in a 1:2 ratio to either palliative standard of care or standard of care plus SBRT to all metastatic lesions. Results revealed a median OS of 28 months (95% CI, 19 to 33) in the control group versus 41 months (95% CI, 26 to not reached) in the SBRT group (HR, 0.57; 95% CI 0.30 to 1.10;  $p=0.09$ ). Grade 2 or worse adverse events occurred more frequently in the SBRT group (29% versus 9%;  $p=0.026$ ) and treatment-related deaths were reported in 3 patients in the SBRT group versus 0 in the control group. In a subsequent publication of long-term results of the SABR-COMET trial, the five-year OS rate was 17.7% in the standard of care arm versus 42.3% in the SBRT arm ( $p=0.006$ ).<sup>[142]</sup> The five-year PFS was not reached in the standard of care group but was 17.3% in the SBRT group ( $p=0.001$ ). No new grade 2 to 5 adverse events were reported and there were no differences in QOL between the groups.

Harrow (2022) published a follow-up study of outcomes beyond five years from the SABR-COMET trial.<sup>[143]</sup> OS after eight years was 27.2% in the SABR arm and 13.6% in the control arm ( $p=0.008$ ). Patients in the SABR arm experienced more grade  $\geq 2$  toxic effects (30.3% vs. 9.1%;  $p=0.019$ ; however there were no new grade 3 to 5 toxic effects. Differences in quality of life and overall use of systemic therapy were not significant, but people in the SABR arm were less likely to be treated with chemotherapy (33.3% vs. 54.6%,  $p=0.043$ ).

A number of studies were published in 2018 that evaluated the safety and efficacy of SBRT of oligometastases. Most addressed lung<sup>[144-148]</sup> or liver<sup>[149-151]</sup> metastases, although some addressed both<sup>[152]</sup> and others addressed adrenal<sup>[153, 154]</sup>, bone<sup>[155-157]</sup>, and other sites<sup>[158, 159]</sup>. The largest and those that are prospective or comparative are discussed below.

A 2018 retrospective study published by Franzese compared SBRT with microwave ablation.<sup>[160]</sup> Data from 135 patients with liver metastases were extracted and analyzed. Median follow-up time was 24.5 months (2.4 to 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 to 95; versus the microwave ablation group 84%; 95% CI 0.72 to 0.91). The likelihood of local relapse was lower in the SBRT-treated group (adjusted hazard ratio 0.31; 95% CI 0.13 to 0.70,  $p=0.005$ ).

### *Bone oligometastases*

Ryu (2023) performed an RCT comparing SRS to cEBRT for localized vertebral metastases of the spine.<sup>[161]</sup> The study involved 339 adult patients with treatment naïve vertebral metastases and a baseline pain score of at least 5/10. The primary end point was pain response at three months. Patients were randomized to receive SRS or cEBRT. Complete response was defined as pain score of 0, no increase in narcotic pain medication, and no progressive pain at the other treated spine. Partial response was an improvement of at least three points from baseline pain score and no increase in narcotic medication. There was not a significant difference in pain response at three months ( $p=0.99$ ). At 12 months, 46.6% of the patients

were alive and pain response differences were still not significant ( $p=0.49$ ). There were no significant differences in adverse events at three months ( $p=0.99$ ) or at one year ( $p=0.38$ ).

Ito (2022) published a single-center, single-arm, phase 2 study aimed to prospectively evaluate the outcomes of separation surgery and SBRT for metastatic epidural spinal cord compression (MESCC).<sup>[162]</sup> Patients with symptomatic MESCC due to a solid carcinoma were enrolled. The protocol for treatments comprised preoperative embolization, separation surgery, and spine SBRT. Surgical procedures were performed via the posterior approach, with decompression and a fixation procedure. The prescribed dose for spine SBRT was 24 Gy in 2 fractions. The primary endpoint was the 12-month local failure rate. The secondary endpoints were ambulatory functions and adverse effects. A total of 33 patients were registered between November 2017 and October 2019. All patients met the inclusion criteria, and all but one completed the protocol treatment. Of the included patients, 23 (70%) had radioresistant lesions. The Bilsky grade at registration was 1c in 3 patients, 2 in 8 patients, and 3 in 21 patients. The median follow-up duration after registration was 15 months (range, 3-35 months). Three months after the administration of treatments according to the protocol, 90% of patients (26 of 29) had disease of Bilsky grade  $\leq 1$ . The 12-month local failure rate was 13%. Twenty patients could walk normally or with a cane 12 months after registration. Radiation-induced myelopathy, radiculopathy, and vertebral compression fracture were observed in 0, 1, and 6 patients, respectively. Separation surgery with SBRT for MESCC was effective in decompression and long-term local control.

Pielkenrood (2022) reported results of a randomized controlled trial comparing conventional radiotherapy versus SBRT (the VERTICAL trial).<sup>[163]</sup> A total of 110 patients with painful bone metastases were randomized 1:1 to receive conventional radiotherapy or SBRT. Intention-to-treat (ITT) and per-protocol (PP) linear mixed model analysis adjusting for baseline scores were used to assess changes in quality of life (QoL) over time. According to both analyses, QL scores improved over time comparably between groups with the exception of functional interference and psychological aspects in the ITT. At 12 weeks, the improvement in functional interference was significantly greater in the conventional radiotherapy group than that in the SBRT group (25.5 vs 14.1 points, respectively;  $p=0.04$ ). At eight weeks, the improvement in psychosocial aspects scores was significantly greater in the conventional radiotherapy group than that in the SBRT group (12.2 vs 7.3;  $p=0.04$ ).

Mazzola (2022) reported outcomes of a multiinstitutional study of SBRT for the treatment of bone oligometastatic prostate cancer.<sup>[164]</sup> Patients undergoing androgen deprivation therapy were excluded. A total of 40 patients were included, of whom 70% had a single oligometastatic lesion, 22.5% had two lesions, 5% had three lesions, and 2.5% had four lesions. SBRT was delivered in three to five fractions for a total of 24 to 40 Gy (median 30 Gy). The median follow-up was 22 months. One- and two-year rates of local control (LC) rates were 96.3% and 93.9%, and distant progression-free survival (DPFS) rates were 45.3% and 27%. A second SBRT course was proposed with concurrent ADT in seven patients and ADT alone was delivered in 11 patients due to polymetastatic spread. One- and two-year ADT-free survival rates were 67.5% and 61.8%.

Ito (2021) published a multicenter prospective noncomparative study on palliative SBRT for painful non-spine bone metastases.<sup>[165]</sup> A total of 38 patients with 41 osseous lesions from primarily lung (22%), prostate (15%), uterine (15%), and renal (12%) cancers. Median follow-up after registration was eight months. The three- and six-month pain responses for evaluable



lesions was 78% and 75%, respectively. The six-month LC was 92%. Post-radiation bone fracture occurred in 17% of patients and grade 2 limb edema in 7%.

Sahgal (2021) published an RCT of SBRT versus conventional EBRT for painful spinal metastases.<sup>[166]</sup> Eligibility criteria were age 18 years and older, painful (defined as  $\geq 2$  points with the Brief Pain Inventory) MRI-confirmed spinal metastasis, no more than three consecutive vertebral segments to be included in the treatment volume, Eastern Cooperative Oncology Group performance status of 0 to 2, a Spinal Instability Neoplasia Score of less than 12, and no neurologically symptomatic spinal cord or cauda equina compression. A total of 229 patients were randomized to receive conventional EBRT (n=115) or SBRT (n=114). An intention-to-treat analysis was performed including all patients. Median follow-up was 6.7 months. Complete response for pain was achieved at three months in 35% of the SBRT group and 14% of the EBRT group (p=0.0002; multivariable adjusted analysis: OR=3.47, 95% CI 1.77 to 6.80, p=0.0003). Grade 3 pain occurred in five [4%] of 115 patients in the conventional EBRT group and five (5%) of 110 patients in the SBRT group. No treatment-related deaths were reported.

Napieralska (2014) reported a series 48 cases of prostate cancer bone metastases (in 32 patients) treated with SBRT primarily for pain control.<sup>[167]</sup> 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.

#### *Metastatic head and neck cancer*

McBride reported a randomized, phase II trial assessing nivolumab with vs. without SBRT.<sup>[168]</sup> A total of 62 patients with metastatic or recurrent head and neck squamous cell carcinoma were randomly assigned to receive nivolumab (n=30) or nivolumab plus SBRT (n=32). No statistically significant differences between groups were identified for ORR (34.5% [95% CI, 19.9% to 52.7%] v 29.0% [95% CI, 16.1% to 46.6%]; p=0.86), overall survival (p=0.75), progression-free survival (p=0.79), response duration (p= .26), or grade 3 to 5 toxicities (13.3% v 9.7%; p=0.70).

#### *Metastatic prostate cancer*

Francolini (2023) published a phase II RCT comparing abiraterone acetate and prednisone (AAP) to AAP with SBRT to all sites of oligometastasis from prostate cancer in 157 participants.<sup>[169]</sup> Oligometastasis involved three or fewer bone or nodal lesions. The primary endpoint was the rate of biochemical response (prostate-specific antigen [PSA] decrease  $\geq 50\%$  in six months). Secondary endpoints were complete biochemical response, defined as PSA  $< 0.2$  ng/ml at six months; and progression-free survival (PFS). Six months after treatment initiation 92% of the treatment arm with SBRT had a biochemical response compared to 68.3% of the control arm (95% CI, 2.05 to 13.88; p=0.001). On multivariate analysis, only treatment, not baseline PSA, number of metastatic sites, initial stage, presence of bone or de novo metastatic disease, was predictive of biochemical response (odds ratio (OR) 4.5; 95% CI, 1.7-11.95; p=0.003). Complete biochemical response and PFS were also significantly higher in the SBRT arm (p<0.001). A limitation of the study was that there were fewer participants with >1 metastatic lesion in the SBRT arm (p = 0.05). The authors concluded that SBRT with AAP as first-line treatment for oligometastatic prostate cancer is associated with improved biochemical response and PFS but phase III trials are needed to confirm the study findings.

Phillips (2020) conducted the phase 2, randomized Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) study, which enrolled 54 men with recurrent hormone-sensitive prostate cancer and one to three metastases detectable by conventional imaging who had not received ADT within six months of enrollment or three or more years total.<sup>[170]</sup> These men were randomly assigned to stereotactic ablative radiotherapy or observation in a 2:1 ratio; 36 to treatment and 18 to observation. Results revealed that progression at six months was observed significantly more frequently in patients in the observation group versus active treatment (61% versus 19%;  $p=0.005$ ). Stereotactic ablative radiotherapy was also associated with significant improvement in median PFS (not reached versus 5.8 months; HR, 0.30; 95% CI 0.11 to 0.81;  $p=0.002$ ). No adverse effects of grade 3 or greater were reported.

### *Lung Oligometastases*

Londero (2020) compared surgery versus SBRT for the treatment of pulmonary metastases in a systematic review of 79 studies (61 on surgical treatment and 18 on SBRT).<sup>[171]</sup> Results revealed no difference in short-term survival when comparing pulmonary metastasectomy and SBRT; however, survival rates were improved in the long-term among patients who underwent surgery. Mortality and morbidity after treatment were 0 to 4.7% and 0 to 23% for surgery and 0 to 2% and 4% to 31% for SBRT. The authors concluded that surgical metastasectomy remains the treatment of choice for pulmonary oligometastases.

### *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%.<sup>[172]</sup>

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.<sup>[172]</sup> Prospective studies have reported one-year OS rates ranging from 61% to 85% and two-year OS rates ranging from 30% to 62%.<sup>[172]</sup> Another systematic review by Tree concluded similar findings evaluating similar studies.<sup>[173]</sup> 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, Méndez Romero (2021) reported outcomes of 515 patients based on a web-based registry.<sup>[174]</sup> A total of 668 liver metastases were registered, with 80.3% coming from colorectal cancer, 8.9% from lung cancer, and 4% from breast cancer. Actuarial one-year local control and OS were 87% and 84%, respectively. The rate of grade 3 or higher toxicity was 3.9%.

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.<sup>[175]</sup> 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.<sup>[176]</sup> 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.<sup>[177]</sup> 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.<sup>[33]</sup> 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. A recent multicenter analysis reported one- and two-year OS of 72.3% and 53.5% one- and two-year LC of 85.4% and 79.2% following treatment of adrenal metastases of lung primary tumor with SBRT.<sup>[178]</sup>

### Section Summary

The evidence for the use of SBRT to treat oligometastases primarily consists of relatively small, noncomparative studies that confirm clinically important rates of local control. However, the evidence consistently reports a high rate of tumor control for isolated or few metastases ( $\leq 3$  or  $\leq 5$ ). 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% to 84%) among the studies. Although some adverse events were reported, the overall rates for adverse events were low.

### **Other Indications**

SBRT has been investigated for the treatment of additional conditions, including cardiac arrhythmias<sup>[179]</sup> and ventricular tachycardia<sup>[180]</sup>. The evidence for these other indications is limited in volume and in quality.

## 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.<sup>[181]</sup>

Cancer Site	Tumor Type	Recommendation	Version
Bone	Osteosarcoma	Consider use of SRS/SBRT, especially for oligometastases.	2.2024
Bone	Ewing sarcoma	Consider use of SRS/SBRT, especially for oligometastases.	2.2024
Bone	Chondroma/ chondrosarcoma	Consider specialized techniques, which include SRS for resectable and unresectable chondromas and chondrosarcomas.	2.2024
CNS	Recurrent spinal ependymoma	In some instances focal SRS/SBRT to spinal tumors may be appropriate, with care to respect normal tissue constraints of spinal cord and surrounding structures.	2.2024
CNS	Primary spinal cord tumors	In some instances focal SRS/SBRT to spinal tumors like hemangioblastoma may be appropriate, with care to respect normal tissue constraints of spinal cord and surrounding structures Meningioma: Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures.	2.2024
CNS	Metastatic spine tumors	Stereotactic radiation approaches (SRS/stereotactic body radiotherapy [SBRT]) for spinal cases may be preferred for patients with life expectancy $\geq 3$ months where tumor ablation is a goal of treatment, in tumors considered radioresistant (eg, renal cell, melanoma, sarcoma, hepatocellular, some colorectal and NSCLC cases), and in select patients for optimal pain relief. Stereotactic radiation approaches may also be preferred in the setting of tumor recurrence after prior radiation as a strategy to limit radiation dose to the spinal cord or other critical structures.	2.2024
CNS	Leptomeningeal metastases	SRS or RT to bulky disease and neurologically symptomatic or painful sites.	2.2024
Colorectal	Metastatic to liver or lung	Colon and Rectal: In patients with a limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of	4.2024 3.3024

surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or SBRT. Consider SBRT for patients with oligometastatic disease.

<b>Head and Neck</b>	Palliative radiation for advanced cancer, or reirradiation	<p><b>Palliative radiation</b> using CD-CRT, IMRT, and SBRT should be considered in the advanced cancer setting when curative intent is not appropriate.</p> <p><b>Reirradiation</b> with 3D-CRT, SBRT, PBT, or IMRT</p> <p>If the area in consideration overlaps with the previously radiated volume, the prior radiotherapy should have been more than 6 months from the appearance of new disease. When using SBRT techniques for reirradiation, careful selection of patients is advised. The best outcomes are seen in patients with smaller tumors and no skin involvement. Caution should be exercised in cases of circumferential carotid artery involvement. Before reirradiation, the patient should have a reasonable ECOG performance status of 0–1. Patients who are more than 2 years from prior radiation, who have surgery to remove gross disease prior to reirradiation, and who are free of organ dysfunction (eg, laryngectomy, feeding tube) have better outcomes.</p>	<b>4.2024</b>
<b>Hepatobiliary Cancer</b>	Hepatocellular carcinoma	<ul style="list-style-type: none"> <li>• All tumors irrespective of the location may be amenable to RT (3D conformal RT, intensity-modulated RT [IMRT], or stereotactic body RT [SBRT]). Image-guided RT is strongly recommended when using RT, IMRT, and SBRT to improve treatment accuracy and reduce treatment related toxicity.</li> <li>• There is growing evidence for the usefulness of SBRT in the management of HCC. SBRT can be considered as an alternative to ablation/ embolization techniques or when these therapies have failed or are contraindicated.</li> <li>• SBRT (typically 3–5 fractions) is often used for patients with 1 to 3 tumors.</li> </ul>	<b>2.2024</b>

<b>Hepatobiliary Cancer</b>	Biliary Tract Cancers	All tumors irrespective of the location may be amenable to RT (3D-CRT, IMRT, or SBRT).Image-guided RT (IGRT) is strongly recommended when using RT, intensity-modulated RT (IMRT), and stereotactic body RT (SBRT) to improve treatment accuracy and reduce treatment-related toxicity.	<b>3.2024</b>
<b>Kidney</b>	Non-clear cell and clear cell renal cell carcinoma	SBRT should be considered as the primary radiation modality in all situations unless precluded by anatomic site, proximity to organs at risk, or past treatments. Primary disease: Definitive radiation using SBRT may be considered as a treatment option for non-optimal surgical candidates. SBRT can be considered for patients with T1 tumors that are not abutting the bowel. SBRT should be considered for patients with oligometastasis unless metastasectomy is planned or SBRT cannot be delivered due to anatomic site, proximity to OAR, or past treatments.	<b>1.2025</b>
<b>Lung</b>	Non-small-cell lung cancer; Initial treatment	Medically inoperable, no nodal disease Stage I -Stage IIIA: Definitive radiation therapy, preferably SABR. SABR is most commonly used for tumors up to 5cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.	<b>7.2024</b>
<b>Lung</b>	Non-small-cell lung cancer – Stage IV; brain metastasis	Surgical resection or SABR	<b>7.2024</b>
<b>Lung</b>	NSCLC: Resectable recurrence	Reresection (preferred) and/or external-beam RT or SABR.	<b>7.2024</b>
<b>Lung</b>	Small cell lung cancer (SCLC)	SABR/SBRT is effective for patients with clinical limited stage I to IIA (T1-2, N0) SCLC, especially if medically inoperable or patient refuses surgery. Principles of SABR for SCLC are similar to those for NSCLC.	<b>3.2024</b>
<b>Lung</b>	NSCLC:Progression on biomarker directed therapy	Asymptomatic or symptomatic with limited progression (3-5 sites, excluding brain): Consider definitive local therapy (e.g., SABR or surgery) for limited lesions.	<b>7.2024</b>
<b>Pancreas</b>	Pancreatic adenocarcinoma – Locally advanced	If good or intermediate performance status, in selected patients, locally advanced without systemic metastases, induction chemotherapy followed by chemoradiation or SBRT; or chemoradiation or SBRT in patients who are not candidates for	<b>3.2024</b>

induction chemotherapy. As second-line therapy following disease progression, SBRT is an option if not previously given and if primary site is the sole site of progression.

<b>Pancreas</b>	Pancreatic adenocarcinoma - Local recurrence after resection in Pancreatic operative bed	<ul style="list-style-type: none"> <li>• Clinical trial (preferred) or Systemic therapy +/- chemoradiation or SBRT (if not previously done) or SBRT or Palliative and best supportive care (category 2A)</li> </ul>	<b>3.2024</b>
<b>Prostate</b>	Prostate cancer	<ul style="list-style-type: none"> <li>• SBRT is acceptable for treatment of primary prostate cancer across all risk groups and for locoregional and/or distant metastases.</li> <li>• SBRT is recommended for metastasis-directed therapy: <ul style="list-style-type: none"> <li>○ For limited metastatic disease (oligometastatic) when ablation is the goal.</li> <li>○ For limited progression (e.g., oligoprogression) or limited residual disease on otherwise effective systemic therapy when progression-free survival is the goal.</li> <li>○ For symptomatic patients with a lesion occurring in or immediately adjacent to a previously irradiated treatment field.</li> <li>○ At physician discretion for more durable control of pain than achieved with typical palliative regimens</li> </ul> </li> </ul>	<b>4.2024</b>
<b>Skin</b>	Melanoma – metastatic	Ablative treatment for intact extracranial metastases – higher doses utilizing conformal techniques such as stereotactic body radiation therapy (SBRT) may offer more durable local control. SBRT may be considered for selected patients with oligometastasis.	<b>2.2024</b>
<b>Soft tissue sarcoma – extremity, superficial trunk, head/neck</b>	Sarcoma – synchronous or recurrent stage IV disease	<ul style="list-style-type: none"> <li>• If single organ and limited tumor bulk amenable to local therapy, consider SBRT .</li> <li>• If disseminated metastases, SBRT is a palliative option.</li> </ul>	<b>2.2024</b>
<b>Thyroid</b>	Metastatic disease	Surgical excision, EBRT, SBRT, or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are asymptomatic in weight-bearing sites. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery is preferred over whole brain radiation.	<b>3.2024</b>

**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)<sup>[182]</sup>
- In patients with stage I NSCLC who cannot tolerate lobectomy or segmentectomy:<sup>[182]</sup>
  - 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.<sup>[183]</sup>
- For tumors within 2 cm of the proximal bronchial tree, a modified SBRT treatment schedule is suggested to decrease treatment-related toxicity.<sup>[183]</sup>
- For second primary lung cancer, SRS is an emerging technology, particularly when there is limited pulmonary reserve.<sup>[182]</sup>

### Lung Cancer

- In lung cancer patients with 1-3 brain metastases, stereotactic radiosurgery (SRS) alone is the recommended initial therapy (Grade 1A).<sup>[184]</sup>

## 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:<sup>[185]</sup>

- “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 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.”



For patients with [extracranial] oligometastatic NSCLC, a risk adapted approach using stereotactic RT (preferred), hypofractionated RT, or alternatively definitive chemoradiation based on the location and burden of disease is recommended.<sup>[186]</sup>

### **Small Cell Lung Cancer**

For patients with stage I or II node negative limited stage small cell lung cancer (SCLC) who are medically inoperable, ASTRO recommends either SBRT or conventional fractionation (Strength of recommendation: Strong; Quality of evidence: Moderate).<sup>[187]</sup>

### **Pancreatic Cancer**

For patients with pancreatic cancer, ASTRO makes the following recommendations related to the use of SBRT:<sup>[188]</sup>

- Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry. (Strength of recommendation: Strong; Quality of evidence: Very Low)
- For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended. (Strength of recommendation: Conditional; Quality of evidence: Low)
- For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended. (Strength of recommendation: Conditional; Quality of evidence: Low)

### **Prostate Cancer**

In 2022, the American Urological Association and ASTRO published a joint guideline on the management of clinically localized prostate cancer.<sup>[189]</sup> Regarding SBRT (referred to as ultra-hypofractionated radiation therapy), the recommendations are:

- Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT (Conditional recommendation; Evidence Level: Grade B)
- In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (Strong Recommendation; Evidence Level: Grade B)

The guideline notes, “Ultra hypofractionation in high-risk patients receiving EBRT with elective nodal coverage is not currently recommended outside a clinical trial or multi-institutional registry due to insufficient comparative evidence.”

## **AMERICAN SOCIETY OF CLINICAL ONCOLOGY**

### **Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer Brain Metastases**

The American Society of Clinical Oncology (ASCO) makes the following recommendations for patients with brain metastases from HER2-positive advanced breast cancer:<sup>[190]</sup>

- 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.

### **Locally Advanced, Unresectable Pancreatic Cancer**

ASCO makes the following recommendations for patients with locally advanced, unresectable pancreatic cancer:<sup>[191]</sup>

- “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)

### **Localized Prostate Cancer**

In 2018, ASCO produced a guideline in collaboration with ASTRO and the American Urological Association addressing the use of hypofractionated radiation therapy for localized prostate cancer.<sup>[192]</sup> The guideline defines hypofractionation as EBRT delivered with a fraction size greater than or equal to 500 cGy. The guideline makes the following evidence-based recommendations:

- “In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultra hypofractionation may be offered as an alternative to conventional fractionation.” (Conditional recommendation, moderate quality of evidence)

- “In men with intermediate-risk prostate cancer receiving EBRT, ultra hypofractionation may be offered as an alternative to conventional fractionation. The task force strongly encourages that these patients be treated as part of a clinical trial or multi-institutional registry.” (Conditional recommendation, low quality of evidence)
- “In men with high-risk prostate cancer receiving EBRT, the task force does not suggest offering ultra hypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence.” (Conditional recommendation, low quality of evidence)

## Salivary Gland Malignancy

In 2021, ASCO published a guideline on the management of salivary gland malignancy. The only reference to SRS or SBRT is a recommendation stating that surgery (metastectomy) or SBRT may be offered for adenoid cystic carcinoma and/or low-grade tumors with indolent biology with limited metastases (i.e.,  $\leq 5$  metastases).

## 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 including biliary tract cancer and cholangiocarcinoma. 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 and Hepatobiliary Carcinoma

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) and hepatobiliary cancer 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) or hepatobiliary cancer 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

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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.

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## **Primary Lung Cancer**

Non-comparative studies have consistently shown that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for patients with lung cancer, 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 primary lung cancer. Therefore, SRS and SBRT may be considered medically necessary for patients with primary lung cancer, when policy criteria are met.

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 primary lung cancer. Therefore, SRS and SBRT for primary lung cancer 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.

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## 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.

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## 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 Planning Services:

Treatment delivered with LINAC based MLC may involve planning with the following codes.

Codes	Number	Description
CPT	77301	Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

**NOTE:** 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:

<b>Codes</b>	<b>Number</b>	<b>Description</b>
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	<del>C9795</del>
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
G0563		Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance and real-time positron emissions-based delivery adjustments to 1 or more lesions, entire course not to exceed 5 fractions

**Date of Origin:** July 2019