Comparative Effectiveness of SBRT

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Introduction

As the use of stereotactic body radiation therapy (SBRT) across multiple disease sites increases over time, there has been a growing area of research comparing the effectiveness of SBRT to alternative treatment modalities. Comparative effectiveness studies within SBRT come from a variety of different data sources including prospective and retrospective series, large database analyses, and cost-effectiveness studies. In this chapter, we will discuss comparative effectiveness studies within SBRT. We will limit our discussion to comparative effectiveness studies evaluating stereotactic treatment to the brain, prostate, lung, and liver. For each disease site, we will include a brief overview of prospective and retrospective series, followed by a discussion of comparative effectiveness studies using large databases, and finally cost-effectiveness studies. Summaries of the selected studies for each disease site are located in the tables throughout the chapter as references.

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Brain

Prospective and Retrospective Series

Several prospective clinical trials have been conducted to compare treatment strategies for brain metastases [1, 2]. Initially, whole brain radiotherapy and radiosurgery were combined in several trails. In a phase III trial by Muacevic and colleagues, patients with a solitary brain metastasis were randomized to surgery followed by whole brain radiotherapy or Gamma Knife radiosurgery alone. Local recurrence was similar between both groups, but distant recurrence was experienced more often in the radiosurgery group. This difference was lost after adjusting for the effects of salvage radiosurgery [3]. RTOG 9508 randomized patients to whole brain radiation therapy (WBRT) versus WBRT plus a stereotactic radiosurgery (SRS) boost. On univariate analysis, there was improved median survival in the WBRT + SRS group compared to the WBRT-alone group (MS 6.5 vs. 4.9 months). Multivariate analysis showed improved survival in patients with RPA class I or favorable histology [4]. Gantery and colleagues randomized a total of 60 patients with 1–3 brain metastases to SRS and WBRT, SRS alone, or WBRT alone. Local control was improved in the group who received combined therapy compared to SRS alone or WBRT alone (median local control of 10 vs. 5 vs. 5 months, respectively) [5].

Given the increased cognitive side effects of whole brain radiotherapy, comparative trials were also conducted to eliminate WBRT from treatment of metastatic brain disease. In EORTC 22952–26,001, patients with 1–3 brain metastases who underwent surgery or SRS were randomized to WBRT or observation. The 2-year relapse rate at initial sites and new sites was decreased in the WBRT group compared to the observation group, but overall survival (OS) was similar in both groups (10.9 vs. 10.7 months) [6]. A later publication revealed that health-related quality of life scores were higher in the observation group, including cognitive function at 8 weeks and 12 months [7]. JROSG

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99–1 randomized 132 patients with 1–4 brain metastases to SRS and WBRT or SRS alone. Overall survival was similar in both groups, but 12-month brain tumor recurrence was improved in the patients who received WBRT in addition to SRS (46.8% vs. 76.4%). Local tumor control at 12 months was also improved in the patients who received combined therapy (88.7% vs. 72.5%) [8]. Chang and colleagues conducted a trial with similar randomization, but the main outcome was neurocognitive effects. In this study, 58 patients with 1–3 brain metastases were randomized to SRS and WBRT versus SRS alone. However, the trial was stopped early by the data monitoring committee because there was a high probability that patients receiving combined therapy were more likely to show a decline in learning and memory function at 4 months compared to patients who received SRS alone [9].

Sahgal and colleagues conducted an individual patient meta-analysis of phase III trials that evaluated patients with 1–4 brain metastases who were randomized to SRS alone or SRS plus WBRT. A total of 364 patients were included in the analysis from three randomized trials. SRS alone was found to improve survival in patients ≤50 years of age, but local control was improved with the addition of WBRT in all age groups [10].

Surgery and radiosurgery alone have never been directly compared in a randomized trial, as surgery is rarely used alone in the treatment of brain metastases in the modern era. Patchell and colleagues randomized patients with a single brain metastasis who underwent complete surgical resection to whole brain radiation therapy or observation. Local recurrence at the site of metastasis was 46% in the patients who received surgery alone [11]. This does not compare favorably to historical data of SRS alone (12-month local tumor recurrence rate of 27.5% in JROSG 99-1) [8].

A retrospective series by O'Neill and colleagues directly compared surgery and radiosurgery alone. In this study, 74 patients underwent surgical resection, and 23 patients underwent radiosurgery. After a median follow-up of 20 months for living patients, no SRS patients had local recurrence compared to 58% of patients in the surgical group [12].

Given the poor local control of surgery alone, surgery followed by postoperative radiosurgery has been evaluated in prospective single-arm series as well as retrospective studies. Brennan and coworkers conducted a prospective phase II trial that included 39 patients with 40 lesions who received adjuvant SRS to the surgical bed with a median dose of 1800 cGy. At 12 months, local failure was 22% and regional failure outside the treated metastasis was 44% [13]. A retrospective series by Soltys and coworkers examined 72 patients with 76 cavities who received postoperative SRS. Local control was 88% and 70% at 6 and 12 months, respectively [12, 14].

The question of radiosurgery alone versus surgery combined with radiosurgery was addressed in a retrospective series by Prabhu and coworkers that examined patients with large brain metastases ≥4 cm^3 (2 cm diameter). In this study, 213 patients with 223 brain metastases were included, and 30% were treated with SRS alone, while the remaining 70% received surgery and SRS, which was either preoperative or postoperative. The 1-year local recurrence rate was higher in the patients who received surgery alone compared to those who received surgery and SRS (36.7% vs. 20.5%) [15]. A summary of select SRS series is found in Table 1.

Large Database Studies

There are limited comparative effectiveness data from large national databases, but this may change in the near future. In 2014, the American Association of Neurological Surgeons (AANS) and the American Society for Radiation Oncology (ASTRO) launched a national registry for SRS treatments [16]. Regarding other national database publications, Kann and coworkers conducted a National Cancer Database (NCDB) study that examined patients with metastatic NSCLC, breast cancer, colorectal cancer, and melanoma who received radiation therapy to the brain. A total of 75,953 patients were included in the study, and of these,

Table 1 Select brain series: local control

Authors	Year	Comparison	Total dose	Lesions	N	Median survival (years)	Local control
Muacevic et al. [3]	2008	Surgery + WBRT vs. SRS	14–27 Gy	1	64	10.3	1 yr: 82% vs. 96.8%
Andrews et al. (RTOG 9508) [4]	2004	WBRT vs. WBRT + SRS	15–24 Gy	1–3	331	6.5	1 yr: 71% vs. 82%
El Gantery et al. [5]	2014	SRS + WBRT vs. SRS vs. WBRT	14–20 Gy	1–3	60	12	1 yr: 43% vs. 22% vs. 19%
Kocher et al. (EORTC 22952–26,001) [6]	2011	SRS + WBRT vs. SRS vs. surgery + SRS vs. surgery	20 Gy	1–3	359	10.9	2 yr: 81% vs. 69% vs. 73% vs. 41%
Aoyama et al. (JROSG 99-1) [8]	2006	SRS + WBRT vs. SRS	18–25 Gy	1–4	132	8	1 yr: 88.7% vs. 72.5%
Chang et al. [9]	2009	SRS+ WBRT vs. SRS	15–20 Gy	1–3	58	15.2	1 yr: 100% vs. 67%

Table 2 Large database and cost-effectiveness studies in SRS

Authors	Year	Analysis	Comparison	Evaluated costs	Findings
Lal et al. [19]	2012	Decision Tree	SRS + WBRT	Yes	SRS with salvage is most costly than SRS + WBRT, but also more effective
Kimmel et al. [20]	2015	Decision Tree	Surgery WBRT	Yes	SRS + WBRT and SRS alone are more cost-effective than WBRT
Lester-Coll et al. [21]	2016	Markov Analysis	WBRT SRS + WBRT	Yes	For patients with up to 10 brain metastases, SRS alone is more cost-effective than SRS + WBRT
Hall et al. [53]	2014	Retrospective	SRS + WBRT Surgery + SRS	Yes	SRS alone is more cost-effective than SRS + WBRT, but increased salvage
Savitz et al. [54]	2015	Markov Analysis	WBRT+/− Hippocampal Avoidance	Yes	SRS is cost-effective for patients with life expectancy <1 yr, otherwise HA-WBRT cost-effective
Wernicke et al. [55]	2016	Retrospective	Surgery+ CS-131 Surgery+ SRS	Yes	Surgery + Cs-131 is more cost-effective than Surgery + SRS
Kann et al. [17]	2017	NCDB	Non-SRS	No	1 yr OS favoring SRS

16.1% received SRS and the remaining 83.9% received non-SRS. The proportion of patients receiving SRS compared to non-SRS increased over time from 2004 to 2014 (9.8% to 25.6%). 1-year survival was higher in the patients who received SRS compared to those who received non-SRS (40.9% vs. 24.1%) [17].

Cost-Effectiveness Studies

Several studies have examined the cost-effectiveness of local therapies for brain metastases [18]. Lal and coworkers conducted a cost-effectiveness study using data from patients with brain metastases in a randomized trial, in which patients received either SRS and observation or SRS and WBRT. Despite SRS with salvage therapy having a higher cost compared to SRS and following WBRT, it was found to be more cost-effective [19]. Kimmel and coworkers conducted a cost-effectiveness analysis for various combinations of treatments for brain metastases. SRS and WBRT combination was cost-effective compared to WBRT alone, and SRS alone was more cost-effective than WBRT [20]. In the setting of multiple brain metastases, Lester-Coll and coworkers found SRS to be more cost-effective than SRS + WBRT in patients with up to 10 brain metastases [21]. A summary of selected large database and cost-effectiveness studies of SRS is found in Table 2.

Prostate Cancer

Prospective and Retrospective Series

Prostate cancer is one of the most commonly treated primary tumors with stereotactic body radiation therapy (SBRT) increasing in utilization across the country [22]. Although conventionally fractionated radiation therapy has shown to be quite effective in the treatment of prostate cancer, it is associated with as many as 45 treatment sessions over the course of 9 weeks. With increasing research studying the effectiveness of shortened hypofractionated dose regiments, SBRT was a natural progression in advances in treatment. Moreover, many argue that given the low alpha-beta ratio of prostate cancer, SBRT would have a radiobiological advantage to doses delivered at a larger fraction size [23].

The major limitation comparing SBRT to conventionally fractionated radiation therapy for prostate cancer is the lack of long-term SBRT follow-up and randomized data. Much of the growing evidence supporting SBRT for prostate cancer is founded upon comparisons to historical outcomes of dose-escalated conventionally fractionated radiation therapy using 3D/IMRT techniques. Among the first studies to look at prostate SBRT was from Madsen and associates in 2007 [24]. This phase I/II clinical trial evaluated the effectiveness of 33.5 Gy in 5 fractions to 40 patients with low-risk prostate cancer. With a median follow-up of 3.4 years, authors reported biochemical control of 90% by Phoenix criteria and 70% by ASTRO definition. The toxicity was acceptable with only 1 acute Grade 3 GU toxicity and no late Grade 3 or higher toxicity. In 2011, King and associates from Stanford published a prospective phase II trial of 67 patients with low to intermediate risk prostate cancer treated to a higher dose of 36.25 Gy in 5 fractions using Cyberknife SBRT [25]. With a median follow-up of 2.7 years, the authors reported a 4-year biochemical relapse-free survival was 94%. The toxicity profile remained relatively favorable with only 3.5% late grade 3 GU toxicity. More importantly, the authors found every other day treatment to be associated with a more favorable toxicity profile than daily treatment. The criticism of the initial prostate SBRT experiences was a lack of long-term follow-up data. The longest follow-up experience published to date is a retrospective series published by Katz and associates in 2016 [26]. Among 515 patients treated with organ defined low-, intermediate-, and high-risk prostate cancer treated with

35–36.25 Gy in 5 fractions, the authors found an 8-year biochemical disease-free survival of 93.6% (low risk), 84.3% (intermediate risk), and 65.0% (high risk). The authors similarly noted a late grade GU toxicity of 2% at 7 years.

Unfortunately, there is a paucity of published randomized controlled trials for which SBRT is compared to conventional radiation therapy or surgery. RTOG 0938 compared the effectiveness of 36.25 Gy in 5 fractions versus 51.6 Gy in 12 fractions for patients with favorable risk prostate cancer [27, 28] and reported initial quality of life analysis in 2016. Both fractionation schema were well tolerated [29]. The HYPO-RT-PC study compared 6.1 Gy × 7 fractions to 2 Gy × 39 fractions, enrolling 1200 patients. The study, also reported at ASTRO in 2016, reported increased urinary side effects for the more extreme fractionation arm at 1 year, but no differences at 2 years. Bowel symptoms were also greater after radiation treatment, but no differences were seen at later endpoints [30].

Ongoing trials include the UK-based phase 3 PACE trial in which low- and favorable intermediate-risk prostate cancer patients who are surgical candidates are randomized to SBRT versus surgery and those who are not surgical candidates are randomized to SBRT versus conventional radiotherapy. The NRG Oncology GU-005 study is comparing 5 fractions of 7.25 Gy to 28 fractions of 2.5 Gy and has both biochemical and quality of life endpoints.

A summary of select prostate SBRT series is found in Table 3.

Large Database Studies

Some of the most significant work comparing SBRT to alternative treatment modalities has been using large national databases. In 2014, Yu and associates published an analysis of patients from the CMS Chronic Conditions Data Warehouse who received SBRT or IMRT as a primary treatment for prostate cancer [28]. Using Medicare claims to assess for GI and GU toxicity, the authors found SBRT to be associated with worse GU toxicity at 6 months (15.6% vs. 12.6%) and 24 months (43% vs. 36%). The differences were largely driven by claims indicative of urethritis, urinary incontinence, and obstruction. Similarly, there was worse GI toxicity associated with SBRT at 6 months (5.8% vs. 4.1%). There is no large national database analysis of biochemical control for prostate SBRT versus conventionally fractionated radiation therapy; however, a recent analysis of the National Cancer Database from Ricco and associates published in 2017 found no difference in 8-year overall survival when comparing prostate cancer patients treated with SBRT versus IMRT [31].

Cost-Effectiveness Studies

There has been substantial work studying cost-effectiveness of prostate SBRT. In the previously described study by Yu and associates, the authors also examined the costs of prostate SBRT versus IMRT among Medicare beneficiaries [28]. The authors found SBRT was cheaper than IMRT ($13,645 vs. $21,023) but most expensive with respect to non-radiation-related cancer care ($2963 vs. $1978). Halpern and associates published a cost analysis in 2016 of prostate cancer patients treated with SBRT, IMRT, proton beam therapy, or brachytherapy. Brachytherapy ($17,183) was found to be the least expensive treatment modality followed by SBRT ($27,145), IMRT ($37,090), and proton therapy ($54,706) [22]. Cost-effectiveness studies by Parthan and associates which analyzed costs and toxicity using Markov modeling found prostate SBRT to be more cost-effective than proton therapy and IMRT [32]. One criticism of this study is that authors used a singular institutional source to estimate estimated rates of toxicity [18]. Sher and associates published a similar updated Markov analysis in 2014 assuming worse toxicity for SBRT and with a larger variety of sources to estimate rates of toxicity. The authors found SBRT to most likely to be cost-effective compared to IMRT [33]. A summary of select large database analysis and cost-effectiveness studies of prostate SBRT can be found in Table 4.

Table 3 Select Prostate Series: Biochemical Control and Toxicity

Authors	Year	Total dose	Fractions	N	Median follow-up	Biochemical control	Late GI toxicity	Late GU toxicity
Madsen et al. [24]	2007	33.5 Gy	5	40	3.4 years	90% (low risk)	G1–2 (37%) G3 (0%)	G1–2 (45%) G3 (3%)
Freeman et al. [56]	2011	35–36.25 Gy	5	41	5 years	93% (low risk)	G1–2 (16%) G3 (0%)	G1–2 (32%) G3 (3%)
King et al. [25]	2012	36.25 Gy	5	45	2.7 years	94% (low + int risk)	G1–2 (16%) G3 (0%)	G1–2 (28%) G3 (3%)
Katz et al. [26]	2016	35–36.25 Gy	5	515	7 years	93% (low risk) 84% (int risk) 65% (high risk)	G2 (4%) G3 (0%)	G2 (9%) G3 (3%)
Meier et al. [57]	2016	36.25 Gy	5	309	5.1 years	97% (low/int risk)	G2 (2%) G3 (0%)	G2 (12%) G3 (0%)

Table 4 Large database and cost-effectiveness studies in prostate SBRT

Authors	Year	Analysis	Comparison	Evaluated costs	Findings
Yu et al. [28]	2014	CCW Medicare	IMRT	Yes	Compared to IMRT, SBRT associated with lower costs, but higher GU toxicity.
Ricco et al. [31]	2017	NCDB	IMRT	No	No 8-year OS difference between SBRT and IMRT
Parthan et al. [32]	2012	Markov Model	3D/IMRT	Yes	SBRT is likely more cost-effective than IMRT
Sher et al. [33]	2014	Markov Model	IMRT	Yes	SBRT is likely more cost-effective than IMRT
Halpern et al. [22]	2016	SEER-Medicare	Proton, IMRT, Brachytherapy	Yes	SBRT associated with greater toxicity but lower costs compared to IMRT. Brachytherapy less costly than SBRT, but associated with greater toxicity
Hodges et al. [58]	2012	Markov Model	IMRT	Yes	SBRT cost-effective compared to IMRT, but highly sensitive to quality-of-life outcomes

Lung

Prospective and Retrospective Series

Relative to other disease sites, lung SBRT has been an area of significant comparative effectiveness research. Similar to prostate SBRT, initial trials studying the effectiveness of lung SBRT were single-arm studies compared to historical controls. Uematsu and associates published one of the first experiences of SBRT in inoperable lung cancer in 1998. With a median follow-up of 36 months, the authors found SBRT to be associated with a 2-year local control of 94% [34]. The landmark study which solidified SBRT for inoperable NSCLC was published in 2010 by Timmerman and associates. RTOG 0236 was a prospective multicenter single-arm study of 55 patients with inoperable early-stage NSCLC treated to 60 Gy in 3 fractions [35]. The authors found a promising 3-year tumor control rate of 97% with a favorable toxicity profile.

Studies comparing surgery to SBRT for lung cancer have been difficult given SBRT has often been reserved for patients who are not candidates for surgical resection. Crabtree and associates published one of the largest single institutional series of matched patients comparing surgery and SBRT [36]. The authors found no differences in 4-year local, regional, or cancer-specific survival when comparing SBRT to surgical resection. Mokhles and associates have published the comparative series with the longest follow-up [37]. With a median follow-up of 49 months, the authors studied 146 patients treated with SBRT or surgery. After propensity score matching, there was no difference in 1-year or 5-year overall survival between surgery and SBRT.

Patient accrual has halted many efforts at randomized clinical trials comparing SBRT to surgery. Both the STARS and ROSEL clinical trials which randomized SBRT to surgery for early-stage NSCLC failed to meet accrual goals. A pooled analysis of both studies was published by Chang and associates in 2016 and found SBRT to be associated with a 3-year overall survival benefit [38]. Thus, there is mounting evidence to suggesting equipoise between both surgery and SBRT for early-stage NSCLC. A summary of select lung SBRT series is found in Table 5.

Large Database Studies

Given the paucity of randomized clinical trials studying the efficacy of SBRT versus surgery for early-stage lung cancer, much of the comparative effectiveness research has risen from large database studies. Yu and colleagues, Shirvani and colleagues, and Ezer and colleagues have all conducted analysis of the SEER-Medicare database comparing surgery to SBRT for early-stage NSCLC [39–41]. Both studies from Yu and Shirvani found SBRT to be an effective treatment option compared to surgery for patients with short life expectancy and/or multiple comorbidities. Ezer and colleagues found no differences in overall survival when comparing SBRT to wedge resection, but did find segmentectomy to be associated with improved overall survival compared to SBRT. When comparing radiofrequency ablation (RFA) to SBRT for lung cancer, a meta-analysis from Bi and colleagues found SBRT to be associated with improved local control at both 1 and 5 years [42].

Cost-Effectiveness Studies

There have been a number of cost-effectiveness studies evaluating the utility of SBRT for lung cancer. Sher and colleagues published one of the first Markov analysis comparing SBRT, 3DCRT, and RFA for inoperable early-stage lung cancer [43]. SBRT was the most cost-effective under a variety of different clinical scenarios. When studying operable early-stage lung cancer, Shah and colleagues

Table 5 Select lung series

Authors	Year	Total dose	Fractions	Trial notes	N	Median follow-up	Outcome
Uematsu et al. [34]	1998	50–60 Gy	5–10	Single Arm Inoperable	50	36 months	2 yr LC: 94%, CSS: 88%
Onishi et al. [59]	2004	18–75 Gy	1–22	Single Arm Inoperable	245	24 months	2 yr LC: 85%
Timmerman et al. (RTOG 0236) [35]	2010	60 Gy	3	Single Arm Inoperable	55	34 months	3 yr tumor control: 97%
Grills et al. [60]	2010	48–60 Gy	4–5	Retrospective Compared to Wedge Resection	124	30 months	2.5 yr: No differences in local, regional, distant recurrences, or OS
Crabtree et al. [36]	2010	54 Gy	3	Propensity Matched Compared to Surgical Resection	538	31 months	4 yr: No differences in local, regional, or CSS
Onishi et al. [61]	2011	45–72.5 Gy	3–10	Single Arm Operable	87	55 months	5 yr LC: 92% (T1), 73% (T2), OS: 72% (IA), 62% (IB)
Mokhles et al. [37]	2015	54–60 Gy	3–8	Propensity Matched Compared to Surgical Resection	146	49 months	1 yr: No differences in OS, 5 yr: No differences in OS
Timmerman et al. [62]	2014 (abstract)	54 Gy	3	Single Arm Operable	26	25 months	2 yr: LC 81%, PFS 65%, OS 84%
Chang et al. [38]	2015	50–54 Gy	3–5	Pooled Trial Compared to Surgery	58	35 months	3 yr: OS Favored SBRT over Surgery

Table 6 Large database and cost-effectiveness studies in lung SBRT

Authors	Year	Analysis	Comparison	Patients	Evaluated costs	Findings
Bi et al. [42]	2016	Meta-analysis	RFA	3095 (43 studies)	No	1–5 yr.: LC Favored SBRT over RFA
Ezer et al. [41]	2015	SEER Medicare Analysis	Limited surgery	2243	No	No OS difference between SBRT and Wedge, but OS favored Segmentectomy over SBRT
Nanda et al. [63]	2015	NCDB Analysis	No Treatment	3147	No	Improved OS with SBRT despite significant comorbidity
Yu et al. [39]	2015	SEER Medicare Analysis	Surgery	1077	No	Short life expectancy: OS SBRT favored long life expectancy: Surgery favored
Smith et al. [64]	2015	SEER Medicare Analysis	Surgery	9093	Yes	SBRT less costly, but with inferior survival
Shirvani et al. [40]	2014	SEER Medicare Analysis	Surgery	9093	No	SBRT effective for patients with advanced age and multiple comorbidities
Louie et al. [65]	2011	Markov Analysis	Lobectomy	NA	No	OS favors Surgery for operable patients
Sher et al. [43]	2011	Markov Analysis	3D CRT RFA	NA	Yes	SBRT most cost-effective in inoperable stage I patients
Lanni et al. [45]	2011	Markov analysis	3D CRT	NA	Yes	SBRT more cost-effective than 3DCRT
Shah et al. [44]	2013	Markov Analysis	Surgery	NA	Yes	SBRT most cost-effective in operable stage I patients

found SBRT to be more cost-effective than surgery unless the patient was "clearly operable" and willing to undergo lobectomy [44]. The cost-effectiveness of lung SBRT is affected somewhat by the health system in which one practices. Lanni and colleagues found SBRT to be more cost-effective than 3DCRT in a US-based healthcare system in which reimbursements are based on the number of fractions [45]. However, from the Canadian payer perspective, SBRT was less cost-effective than 3DCRT because in Canada activity-related reimbursements based on the total course of treatment are used to calculate costs rather than the number of fractions received. A summary of select large database analysis and cost-effectiveness studies of lung SBRT can be found in Table 6.

Liver

Prospective and Retrospective Series

In patients with hepatic metastatic disease, options for local therapy include surgery, SBRT, Y-90 microspheres, chemo-

Table 7 Select liver series: local control

Authors	Year	Total dose	Fractions	N	Median follow-up	Outcome
Rusthoven et al. [47]	2009	36–60 Gy	3	47	16 months	2 yr LC: 92%
Milano et al. [66]	2008	50 Gy	10	121	41 months	2 yr LC: 67%
Hoyer et al. [67]	2006	45 Gy	3	44	4.3 years	2 yr LC: 79%
Mendez-Romero et al. [68]	2006	30–37.5 Gy	3	17	12.9 months	2 yr LC: 86%

embolization, and radiofrequency ablation. To our knowledge, there are no randomized trials directly comparing these modalities with SBRT. Table 1 displays the results of liver SBRT outcomes in the setting of hepatic metastases from various prospective Phase I/II trials. Actuarial local control ranges from 67% to 92% at 2 years. In terms of microsphere treatment, SIRFLOX was a phase III trial in which patients with metastatic colorectal cancer with hepatic metastases were randomized to modified FOLFOX plus or minus Y-90 microspheres. Median PFS in the liver was better in the Y-90 group (20.5 months vs. 12.6 months, $P = 0.002$) [46]. For SBRT, the median progression-free survival in the phase II trial of SBRT by Rusthoven and colleagues was 6.1 months [47].

There are also limited data regarding comparison of treatment options for hepatocellular carcinoma. RTOG 1112 is currently accruing, and it randomizes patients with unresectable HCC to sorafenib or SBRT followed by sorafenib. Su and colleagues conducted a retrospective analysis of 117 patients with hepatocellular carcinoma, 82 of which received SBRT. The remaining 35 patients underwent liver resection. After propensity score matching, overall survival and progression-free survival were similar between both groups. The 3-year OS was 91.8% in the SBRT group and 89.3% in the resection group, and the 3-year PFS was 59.2% and 62.4%, respectively [48].

Wahl and colleagues conducted a retrospective study that compared radiofrequency ablation (RFA) to SBRT of the liver for patients with hepatocellular carcinoma. A total of 224 patients with inoperable hepatocellular carcinoma were included in the study, with 161 patients undergoing RFA and 63 patients receiving SBRT. 2-year freedom from local progression was 80.2% in patients who received RFA and 83.8% in patients who received SBRT ($P = 0.016$). Overall survival at 2 years was not statistically different between groups [49]. A summary of select liver SBRT series is found in Table 7.

Large Database Studies

Given the use of SBRT to treat liver disease has only recently become more popularized, there are limited large database studies studying liver SBRT. Berber and colleagues conducted a study of 153 patients from a combined multicenter database who received SBRT for metastatic disease to the liver. A total of 363 metastatic liver lesions were included, and mean dose was 37.5 Gy. After a mean follow-up of 25 months, local control was 62% with a 1-year OS of 51% [50]. Oladeru and colleagues conducted a SEER analysis of 189 patients with unresectable HCC treated with either SBRT to selective internal radiation therapy [51]. With a median survival of 14 months, the authors found no differences in statistical significance in overall survival or disease-specific survival.

Table 8 Large database and cost-effectiveness studies in liver SBRT

Authors	Year	Analysis	Comparison	Evaluated costs	Findings
Leung et al. [69]	2016	Markov Analysis	Sorafenib	Yes	SBRT more cost-effective than Sorafenib
Kim et al. [52]	2016	Markov Analysis	RFA	Yes	SBRT less cost-effective inoperable for liver metastases
Oladeru et al. [51]	2016	SEER Analysis	SIRT	No	No differences in OS or DSS between SBRT and SIRT

Cost-Effectiveness Studies

Compared to SRS and SBRT of other body sites, relatively few cost-effectiveness studies have been conducted for SBRT of the liver. Leung and colleagues conducted a cost-effectiveness analysis of Sorafenib compared to SBRT for unresectable hepatocellular carcinoma and found SBRT to be more cost-effective in all clinical scenarios. In a study by Kim and colleagues, cost-effectiveness of SBRT was compared to radiofrequency ablation (RFA) in patients with unresectable liver metastases. The authors found that SBRT was less cost-effective than RFA for inoperable liver metastasis [52]. A summary of select large database analysis and cost-effectiveness studies of liver SBRT can be found in Table 8.

Conclusion

In this chapter, we have briefly introduced the growing comparative effectiveness research surrounding stereotactic body radiation therapy. As the use of SBRT increases, there will continue to be advances in this emerging area of research.

Moreover, as we begin to generate long-term follow-up on patients who have undergone SBRT, the utility of comparative effectiveness studies will become more important.

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