Stereotactic ablative radiation therapy in the treatment of liver tumors

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Liver cancer-related death rates continue to accelerate worldwide.[1,2] Numerous local techniques are evolving to address the growing burden of disease. These techniques include surgery (partial liver resection or liver transplant), ablation (radiofrequency, microwave, ethanol, cryoablation), and intra-arterial injections (chemoembolization, radioembolization, bland embolization). Systemic treatments, such as sorafenib, regorafenib, or nivolumab, are also expanding. An additional option is stereotactic ablative radiation therapy (SABR). SABR has harnessed innovations in external-beam radiation therapy delivery and toxicity modeling to

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safely and noninvasively deliver high radiation therapy doses to liver tumors in only 1 to 5 treatments. Here we review the indications, efficacy, toxicity and methods for SABR in liver tumors. While prospective comparative data is lacking between SABR and other local techniques, we suggest that SABR offers high local control, low toxicity, and ability to treat a range of tumor volumes and locations in a precise, noninvasive manner. While choice of local liver tumor therapy is currently institution-specific, future utilization of liver SABR promises to increase with experience and recognition.

SABR in the Treatment of Primary Liver Cancer
Hepatocellular Carcinoma (HCC)

HCC is the most common primary liver cancer in the world, with a fourfold increase in incidence over the last 40 years in the United States.[3] Partial liver resection or orthotopic liver transplant (OLT) remain the accepted first-line treatments for eligible patients.[4,5]

Patients waiting for OLT are at risk for disease progression. Clinical series demonstrate that SABR can prevent HCC progression prior to transplant. Sapisochin et al compared SABR (n = 36) with transcatheter arterial chemoembolization (TACE) (n = 99) and radiofrequency ablation (RFA) (n = 244) as bridges to OLT. They found that drop-out rate, post-transplant survival and HCC recurrence were similar for all techniques, despite SABR treating a greater tumor burden than RFA: an average of 2 lesions to 1, 4.5 cm diameter to 2.5 cm, and a higher mean Model of End-stage Liver Disease (MELD) score.[6]

In the United States, 70% to 90% of all HCC cases occur with cirrhosis, and many patients are unsuitable for resection.[7] For patients unable to undergo definitive resection, **Table 1** summarizes studies demonstrating that SABR is an excellent option for tumor control with limited toxicity. No randomized data exist to prove superiority of SABR compared to other techniques. Nevertheless, a 2016 retrospective study from the University of Michigan compared SABR (n = 63 treated with 27 to 60 Gy in 3 to 5 fractions) to RFA (n = 161), showing they are equally effective for treating inoperable HCC < 2 cm, but

Table 1. SABR HCC Series Outcomes

First Author, Year	Patients/ Tumors *Liver function*	Median Diameter	Study Design	Dose/ Fractions (BED for α/β=10)	Local Control % (1y/2y/3y)	Overall Survival % (1y/2y/3y)	Toxicity % ≥ Grade 3
Sapir, 2018[9]	125/173 CTP A & B	2.4 cm	Retrospective, SABR vs TACE	42-50 Gy/3-5 (BED_{10} 100)	97/91/---	74/35/---	8
Sapisochin, 2017[6]	36/72 22 CTP A, 14 CTP B	4.5 cm	Retrospective: SABR vs TACE vs RFA, Bridge to OLT	36 Gy (30-40)/6 (median BED_{10} 58)	Drop-out rate before OLT = 16.7%	83/---/61, 61% 5-year survival	Before OLT = 0
Wahl, 2016[8]	63/83 57 CTP A, 24 CTP B, 2 CTP C	2.2 cm	Retrospective, SABR vs RFA	27-60 Gy/3-5 (median BED_{10} 100)	97/84/---	74/46/---	8
Huertas, 2015[46]	77/97 66 CTP A, 11 CTP B	2.4 cm	Retrospective	45 Gy/3 (BED_{10} 113)	99/99/---	82/57/---	5.2
Sanuki, 2014[47]	185 158 CTP A, 27 CTP B	2.5 cm	Retrospective	35-40 Gy/5 (BED_{10} 60-72)	99/93/91	95/83/70	3
Yoon, 2013[48]	93/103 69 CTP A, 2 4 CTP B	2.0 cm	Retrospective	30-60 Gy/3 (BED_{10} 60-180)	95/---/92	86/54/---	6.5
Bibault, 2013[49]	75/96 67 CTP A, 8 CTP B	3.7 cm	Retrospective	40-50 Gy/3 (BED_{10} 60-131)	90/90/---	79/50/---	8
Bujold, 2013[50]	102/164 102 CTP A	7.2 cm	Phase I/II Trial	36 Gy (30-54)/6 (median BED_{10} 58)	87/---/---	55/34/---	36
Andolino, 2011[51]	60/71 36 CTP A, 24 CTP B	3.2 cm	Retrospective	30-48 Gy/3-5 (BED_{10} 60-72)	---/90/---	---/67/---	35
O'Connor, 2012[52]	10/11 7 CTP A, 2 CTP B, 1 CTP C	3.4 cm	Retrospective: Bridge to OLT	51 Gy/3 (BED^{10} 138)	Drop-out rate before OLT= 0 %	100% 5-year survival	Before OLT = 0
Cárdenes, 2010[53]	17/25 6 CTP A, 1 1 CTP B	4 cm	Phase I Trial	40-48 Gy/3-5 (BED_{10} 72-125)	100/100/---	75/60/---	18

Key: CTP = Child-Turcotte-Pugh, SABR = stereotactic ablative radiation therapy, TACE = transarterial chemoembolization, RFA = radiofrequency ablation, BED = biologically equivalent dose

that SABR provides better local control (LC) than RFA for lesions ≥ 2 cm.[8] A second retrospective investigation compared SABR and TACE, with 2-year LC significantly better for SABR, 91.3% to 22.9%, respectively, and no significant difference in overall survival (OS).[9]

An advantage of SABR compared with other local techniques is that lesions can be treated that are difficult to access by RFA, embolization or surgery (eg, large volume tumors; disease complicated by portal thrombus;[10] and lesions near the liver capsule, major vessels or diaphragm).

First Author, Year	Patients/ Tumors	Tumor Diameter	Study Design	Dose/ Fractions (BED for $\alpha/\beta=10$)	Tumor Response % (CR/PR/SD/PD)	Local Control % (1y/2y/3y)	Overall Survival % (1y/2y/3y)	Toxicity % $\geq$ Grade 3
Meyer, 2016[54]	14/17	3.2 cm	Phase I	35-40 Gy/1 (BED_{10} 157.5)	69/31/0/0	100/100/---	85/78/---	0
Scorsetti, 2014[18]	42/52	3.5 cm	Phase II	75 Gy/3 (BED_{10} 262.5)	43/17/9/31	95/91/85	81/65/---	0
Fode, 2015[20]	225	---	Retrospective	45-68 Gy/3 (BED_{10} 112.5-228)	---	91/87/---	At 1/3/5/7.5 years: 80/39/23/12	4.8
Comito, 2014[17]	42/52	<6 cm	Phase II	75 Gy/3 (BED_{10} 262.5)	43/32/15/10	95/90/85	85/65/43	0
Stintzing, 2013[22]	30/35	3.3 cm	Retrospective: Matched study, SABR vs RFA	24-26 Gy/1 (BED_{10} 87.5)	---	85/80/---	Median OS: 34.4 months	0
Goodman, 2010[55]	19/33	4.2 cm	Phase I	18-30 Gy/1 (BED_{10} 50.4-120)	---	77/---/---	62/49/---	10.5
Lee, 2009[56]	68	5.2 cm	Phase I	41.4 (27-60) Gy/6 (BED_{10} 71.4)	6/43/30/21	71/---/---	63/---/---	10.3
Rusthoven, 2009[19]	47/63	2.7 cm	Phase I/II	36-60 Gy/3 (BED_{10} 79.2-180)	---	95/92/---	77/30/---	2.1

Key: SABR = stereotactic ablative radiation therapy, RFA = radiofrequency ablation, BED = biologically equivalent dose, CR = complete response, PR = partial response, SD = stable disease, PD = progression of disease

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver cancer worldwide, representing 10% to 20% of liver cancer diagnoses. Surgery is the only curative treatment for local disease, but up to 70% of ICC is unresectable.[11]

In 2016, physicians from MD Anderson Cancer Center and Harvard analyzed outcomes from a series of unresectable ICC patients who received chemotherapy followed by moderately hypofractionated radiation therapy and identified a survival advantage with dose escalation.[12] Patients treated to a biologically equivalent dose (BED) > 80.5 Gy had almost double the 3-year survival of those treated to lower doses (73% to 38%, respectively).

Princess Margaret Hospital conducted the first phase I trial using SABR to treat inoperable ICC. Ten patients were treated to a median dose of 36 Gy in 6 fractions, with 1-year LC of 65% and median OS of 15 months, an improvement over historic controls. There were no cases of radiation-induced liver disease (RILD), and toxicities were grade 3 or less.[13]

SABR in the Teatment of Liver Metastases

Each year, 30 000 patients with colorectal cancer (CRC) are found to have oligometastatic disease (OMD) limited to the liver either on presentation or at recurrence.[2,14,15] In 2016, the European Society for Medical Oncology recommended the use of SABR in combination with systemic agents to treat unresectable colorectal OMD.[16] In the last decade, several phase I and II studies using SABR to treat hepatic OMD from favorable primaries have reported 2-year LC rates > 90%, and median OS significantly higher than historical controls treated with systemic therapy alone (29 to 32 months vs. 24 months for chemotherapy).[17-19] In a large retrospective series studying outcomes from SABR treatment of mainly hepatic OMD, Fode et al identified 5 factors associated with favorable survival: World Health Organization (WHO) performance status 0-1, solitary metastasis, size $\leq$ 3 cm, metachronous metastases and pre-SBRT systemic therapy. BED_{10} > 100 Gy correlated with low local recurrence rates.[20]

The recent CLOCC trial (chemotherapy + local ablation vs chemotherapy) randomized 119 patients with liver-only colorectal unresectable metastatic disease to systemic therapy alone vs systemic therapy with RFA and surgical resection (when possible),

and demonstrated a median OS benefit with local therapy (45.6 months vs 40.5 months).[21] While no local ablative technique has demonstrated superiority compared to another local ablative technique in a randomized trial, Stintzing et al performed a matched comparative analysis of 60 patients with unresectable colorectal liver metastases, divided between SABR (24 to 26 Gy in 1 fraction) and RFA. One-year LC favored SABR (85%) compared to RFA (65%).[22] This suggests that SABR could further enhance survival benefits for unresectable liver metastases compared to RFA.

SABR also provides excellent control of oligometastatic liver disease from noncolorectal primaries. A 2016 series demonstrated 100% 2-year LC rates for 58 noncolorectal liver metastases.[23] Additional studies of SABR for liver metastases are summarized in **Table 2.**

SABR Technique
Dose
In practice, the authors of this manuscript generally follow the isotoxicity approach initially proposed by Dawson et al and adapted into the Radiation Therapy Oncology Group (RTOG) 1112 trial (NCT01730937) protocol.[24,25] In RTOG 1112, 5-fraction SABR is prescribed to Child-Turcotte-Pugh class (CTP) A HCC, and the mean liver dose (MLD, defined as liver minus gross tumor volume [GTV]) determines the prescription dose based on an expected 5% incidence of RILD. If the MLD in the achieved plan is less than 13 Gy, the dose is 50 Gy over 5 fractions; however, the dose is reduced as MLD increases. Caution must be employed for dose to adjacent stomach and bowel, and additional dose constraints are also provided within the RTOG 1112 protocol.

Logically, this schema can also be applied to CTP A patients with liver metastases or cholangiocarcinoma,

as $BED_{10} = 100$ Gy (50 Gy in 5 fractions) correlates with good tumor control.[12,20] For patients with limited liver metastatic disease without underlying liver dysfunction, 60 Gy in 5 fractions ($BED_{10} = 132$ Gy) can be considered. Conversely, caution must be used in CTP B patients. A phase I/II trial reported 38% grade 3 or higher toxicities for CTP B HCC patients treated with SABR.[26] The use of dose escalation in this fragile population requires careful patient selection. For CTP C patients, hospice should be considered.

Image Guidance and Respiratory Management
Since increasing MLD correlates with increasing rates of RILD and limits prescription dose and anticipated tumor control, attempts should be made to reduce the MLD.[27,28] Custom immobilization, image guidance and respiratory management allow reduction of the planning target volume (PTV) margin to about 5 mm.

Patients with limited respiratory motion assessed by fluoroscopy, 4-dimensional computed tomography (4D-CT), or cine magnetic resonance imaging (MRI) could be treated with an internal target volume (ITV) encompassing the respiratory excursion plus PTV expansion for setup uncertainty. However, craniocaudal and anterior-posterior excursions of liver tumors of 2 to 3 cm have been reported with limited motion reduction by abdominal compression.[29] Therefore, appropriate motion management techniques must be available to treat patients with large respiratory motions. Example strategies include respiratory gating, breath-hold and active tracking.[30-32] Such systems include the Cyberknife Synchrony (Accuray, Sunnyvale, California) and Varian Real-Time Position Management (Varian, Palo Alto, California) systems, which use cameras during therapy to track markers placed on the body's surface

that are correlated to the internal tumor position. A common alternative is Elekta's Active Breathing Coordinator (Elekta, Stockholm, Sweden), which tracks and assists reproducible lung filling during treatment.

These systems require internal calibration of the target position to the tracking system using fluoroscopy or breath-hold cone-beam CT at the beginning of each treatment. For these x-ray-based image guidance techniques, we strongly recommend target localization with radiopaque fiducials placed prior to simulation.[33] This has been shown to lower the maximum setup error from 12 mm (based on diaphragm position and bony landmarks) to 2 mm.[34] Residual Lipiodal (Guerbet, Villepinte, France) injected from prior TACE treatments can also be used.[35]

Definition of the target requires intravenous (IV) contrast at the time of simulation and/or careful fusion to diagnostic scans. If gating or breath-hold is employed, simulation must include images for planning in that respiratory phase.

Emerging Techniques
Recently, an MRI-guided radiation therapy system has become available for treatment of liver tumors.[36,37] MRI simplifies the SABR procedure since it enables direct tumor visualization for planning and daily setup as well as near real-time imaging during treatment. An example of MRI-guided treatment is shown in **Figure 1**. Real-time visualization of liver targets can be further enhanced by use of gadoxetate MRI contrast.[38]

In some settings, proton SABR could enhance normal liver sparing compared to conventional photon treatments given the reduced exit dose from the Bragg peak, reducing MLD and increasing the size or dose of treatment.[39,40] Nevertheless, respiratory motion offers more complications in

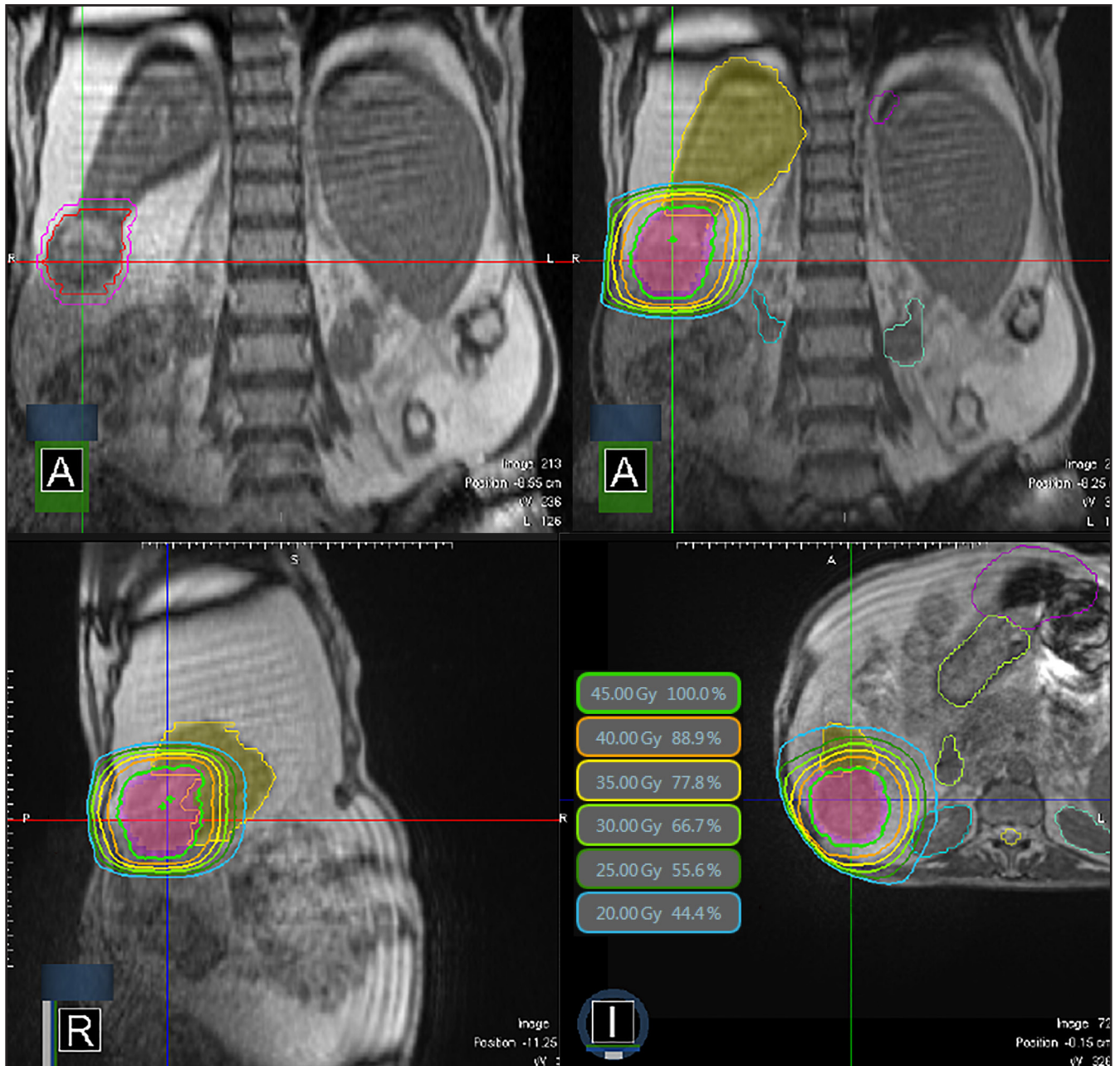SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

FIGURE 1. *Example of liver stereotactic ablative radiation therapy (SABR) treatment with MR-guided radiation therapy. A 62-year-old woman with hepatocellular carcinoma, CTP class B, underwent 45 Gy in 5 fractions of SABR to an exophytic liver mass. Top left demonstrates a coronal view of the gross tumor volume (GTV, red) expanded 5 mm to planning tumor volume (PTV, purple). The images shown were acquired in 2 minutes on the Co-60 radiation therapy device at time of simulation, and the same quality 2-minute images are obtained each day for patient setup. Tumor within the red contour is seen as hyperintense compared to the liver. The top right image demonstrates the same tumor in coronal view with PTV in color-wash purple, the liver in color-wash yellow, and the planned dose distribution extending from the center (45 Gy, green-blue line) to the outside (20 Gy, light blue line). The bottom images demonstrate the target and dose distribution for sagittal (bottom left) and axial (bottom right) views. The kidneys (light blue and light green), duodenum (dark green), spinal cord (yellow), and stomach with expansion (purple) are also contoured. During treatment, sagittal images are obtained of the GTV at a rate of 4 times per second with near real time automated target tracking and gating. If the GTV moves outside of the 5-mm tracking box, treatment is paused within milliseconds. Treatment is then resumed within milliseconds when the target returns within the tracking box.*

proton than photon treatment due to derangement of the Bragg peak location caused by target depth variability. Use of proton SABR has been limited historically because few proton therapy centers were equipped with respiratory gating; however, the number of capable centers is increasing.[41,42]

Radiation-induced Liver Disease

Recognition of the liver's parallel functional structure, reinforced by surgical experience and refined through advances in Normal Tissue Complication Probability (NTCP) modeling, provides the physiologic justification for partial-liver irradiation.[43] When one-third of the normal liver parenchyma (standardized to 700 cc of tissue) is protected from doses > 15 Gy in 3-5 fractions, the risk of RILD is < 5% for patients with baseline CTP A hepatic function.[44]

RILD is the most common dose-limiting toxicity for radiation therapy of liver tumors with time-to-onset ranging from 2 weeks to 8 months post-treatment. Classical RILD is characterized by fatigue, anicteric ascites, elevation of alkaline phosphatase out of proportion to other live enzymes, abdominal pain, and hepatomegaly. Nonclassical RILD patients present with jaundice and elevated serum transaminase. Given the overlap with liver failure of other causes, such as hepatitis, it is often difficult to directly ascribe to radiation therapy. Management is supportive, similar to management of other types of liver injury.

In practice, patients generally report transient loss of appetite and increased fatigue resolving by 3 months following SABR, with pretreatment quality of life maintained through 1 year.[45]

Conclusion

Numerous studies support SABR for the treatment of liver tumors such as unresectable hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and liver metastases. Careful consideration of image guidance and respiratory management allows for minimization of normal liver treated, improving the safety, effectiveness, and size and number of tumors that can be treated successfully. Comparative studies to other techniques, improving radiation therapy delivery technologies, and expanding indications, such as bridge to transplant in HCC or oligometastatic liver disease, may increase future utilization of liver SABR.

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