



# External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline—A Surgical Perspective

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The management of primary liver cancer, comprised of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC), has evolved over time and entails a multidisciplinary approach. While surgical resection, orthotopic liver transplantation (OLT), and ablation remain the mainstay of curative therapy for carefully selected individuals, additional treatments include the use of systemic chemotherapy, immunotherapy, and liver-directed therapies, including ablation, embolization, and radiation. Determining when each of these modalities should be utilized involves a collaborative approach among several disciplines to ensure optimal patient outcomes. Recently, advances in external beam radiation technology has led to renewed interest in its utilization for primary liver cancers.

The Society of Surgical Oncology (SSO) joined the American Society of Clinical Oncology (ASCO), and the American Society of Transplant Surgeons (ASTS) in the provision of a process led by the American Society of Radiation Oncology (ASTRO) to collaborate with ASTRO, to create a guideline on the utilization of external beam radiation therapy (EBRT) for primary liver cancers. Recommendations

were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.<sup>1</sup> One SSO member, specializing in surgical oncology and hepato-pancreato-biliary tumors, was appointed as SSO's official representative to the panel developing the guideline. The resultant recommendations using the evidence-based guideline were developed, reviewed, and voted upon by a 17-member panel. The guidelines were also sent to two officially invited SSO peer reviewers for additional review and comment as well as being available for public comment. The ASTRO Board approved the guideline first and then it was sent to all the collaborating organizations for endorsement.

The evidence-based guidelines were endorsed by the SSO in November 2021. The SSO also shared comments with its endorsement for future iterations or if opportunities for edits arose. The guidelines were also endorsed by the ASTS, Canadian Association of Radiation Oncology, and European Society for Radiotherapy and Oncology.

In this editorial, we summarize and comment on the ASTRO guideline, published in *Practical Radiation Oncology*.<sup>1</sup> The expert panel's recommendations focus on the use of EBRT in the neoadjuvant setting prior to surgery, in the adjuvant setting after surgery, and as definitive or palliative treatment for those not felt to be surgical candidates.

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## TREATMENT PRINCIPLES OF PRIMARY LIVER CANCER

All primary liver cancers should undergo a diagnostic and staging work-up based on National

Comprehensive Cancer Network (NCCN) guidelines and be managed by a multidisciplinary team.<sup>2</sup> Hepatic resection or OLT (for patients with HCC and cirrhosis) remain the primary treatment modality for resectable or localized tumors and these options should be considered first.<sup>2-4</sup> In those with localized disease who are not felt to be appropriate surgical or transplant candidates, local ablative therapies should then be considered. Studies demonstrate superior survival utilizing these modalities in applicable patients when compared with radiation or systemic therapy alone. For patients who are not candidates for these modalities, other local liver-directed options, including transarterial chemoembolization (TACE), Yttrium-90 radioembolization, and radiation, should be considered.<sup>5</sup>

An individual may not be a candidate for resection or transplant if they have metastatic disease, if there is extensive liver tumor burden precluding safe intervention, or if patient comorbidities including liver disease preclude a safe procedure. In recent decades, advances in radiation technology and delivery have led to increasing use of EBRT as an alternative for the treatment of localized primary liver cancers. As such, EBRT may be considered as a potential first-line single therapy option for those patients with liver-confined HCC or IHC who are not candidates for a curative-intent surgical intervention but for whom liver-directed therapies are being considered as alternatives. Furthermore, specific situations exist in which EBRT may be considered in the neoadjuvant or adjuvant setting surrounding surgery.

### NEOADJUVANT EXTERNAL BEAM RADIATION THERAPY (EBRT)

The ASTRO guidelines propose that EBRT may be considered prior to surgery in carefully selected circumstances. EBRT can be considered to downstage or stabilize disease in HCC patients awaiting liver transplantation. Retrospective studies have demonstrated that EBRT, predominantly stereotactic body radiation therapy (SBRT), is a safe and effective bridge to transplantation, with upwards of 63% of patients successfully receiving an OLT after neoadjuvant radiation.<sup>6,7</sup> Studies evaluating pathologic complete response (CR) after EBRT in patients undergoing OLT have demonstrated a CR rate of anywhere from 8.6% to 63%, the wide range potentially related to the time to transplant from EBRT completion.<sup>6,8</sup> Outcomes are favorable, with overall survival (OS) ranging from 61% to 73%, and do not seem to differ compared with other bridging techniques such as TACE or radiofrequency ablation (RFA).<sup>6,9</sup> However, no definitive conclusions can be made with regard to EBRT compared with other liver-directed techniques when it comes to bridging to OLT.

EBRT can also be used for potentially resectable, liver-confined HCC with portal venous (PV) tumor thrombus to

reduce tumor burden prior to undergoing hepatectomy.<sup>10</sup> This is typically used in patients with Cheng type II (involving the right/left PV) or type III tumor thrombus (involving the main PV).<sup>10</sup> However, this treatment strategy is largely limited to Asian countries and has not been routinely practiced in Western countries. As such, the use of EBRT in these patients should be discussed in a multidisciplinary setting in specialized centers.

EBRT must be carefully administered so as not to preclude surgical intervention in the future. Great care is required to protect the uninvolved liver from increasing doses of radiation to reduce the risk of fibrosis, especially in patients with underlying cirrhosis where additional fibrosis from radiation may increase the risk of post-hepatectomy liver failure. Another critical consideration is that neoadjuvant radiation therapy can increase the complexity of liver transplantation or hepatectomy by making the case technically more challenging, increasing the risk of perioperative morbidity, or possibly even preventing a successful operative intervention. Some complications attributable to radiation include biliary anastomotic strictures, hepatic arterial stenosis, and/or portal vein friability and thrombosis.<sup>11</sup> Thus, factors such as underlying liver function, concomitant use of chemotherapy, and tumor burden should be considered when contemplating radiation therapy as part of the treatment algorithm and planning the radiation dose and fractionation. Multidisciplinary discussions should include a hepato-biliary surgeon and/or transplant surgeon and should occur as the introduction of EBRT prior to surgical intervention can drastically impact the operative intervention and increase the risk of perioperative morbidity and mortality.

### ADJUVANT EBRT AND FOR RECURRENT DISEASE

The ASTRO guidelines advise certain situations when EBRT can be used after surgery or local therapy as well as for recurrent disease. For example, adjuvant EBRT can be considered after curative resection of IHC for certain high-risk features, including a positive surgical margin and the involvement of regional lymph nodes. Retrospective studies have demonstrated improved 3-year intra- and extrahepatic control with EBRT and resection compared with surgery alone.<sup>12</sup> Furthermore, retrospective studies demonstrate the addition of adjuvant EBRT to concurrent chemotherapy for resected IHC improves local control and OS.<sup>13</sup> However, with a lack of prospective data, the use of adjuvant EBRT should only be considered in selected cases in the setting of multidisciplinary discussion to determine optimal sequencing and timing of radiation therapy relative to systemic chemotherapy.

For HCC, EBRT can be considered to treat local recurrence after hepatic resection or other ablative therapies.<sup>14</sup>

Two- and 5-year OS rates are upwards of 82% and 64%, respectively, when EBRT is used in this setting.<sup>14</sup> EBRT can also be performed when repeat ablation or other liver-directed therapies cannot be attempted or would be sub-optimal based on location.<sup>15</sup> In addition, EBRT can be administered after an incomplete response to ablation for HCC. Two-year rates of local control have been reported in up to 89% of patients undergoing consolidative SBRT after TACE.<sup>15,16</sup>

## DEFINITIVE OR PALLIATIVE EBRT

The ASTRO guidelines propose the use of EBRT as definitive therapy for individuals with unresectable, liver-confined tumors with well-compensated underlying liver function. EBRT can be used alone or in combination with ablation for liver-confined tumors that are too extensive (multifocal and/or unresectable) for surgery. It may be a preferable therapy over ablative techniques in patients with large tumors (>3 cm) or tumors near other organs such as the gallbladder, diaphragm, or vasculature where a heat sink effect is likely.<sup>17</sup> Small, retrospective phase I and II studies have demonstrated similar outcomes after EBRT when compared with liver-directed therapies such as RFA for early-stage, liver-limited disease.<sup>18</sup> However, these studies are highly selected and involve patients with small-sized HCC with a limited number of lesions (generally less than five) who were not candidates for surgical or ablative procedures, making their applicability limited. As such, the decision for EBRT or other liver-directed therapies should be evaluated in a multidisciplinary setting for patients not considered a surgical candidate. In addition, EBRT can be used in conjunction with TACE in unresectable HCC, with several meta-analyses demonstrating an improvement in response rates and OS with this combination compared with TACE alone.<sup>13</sup>

Systemic therapy is the mainstay of metastatic or unresectable liver tumors, especially considering recent promising data utilizing targeted and immune-based therapies.<sup>19</sup> In the palliative setting, EBRT can be considered in patients with progression of liver disease on systemic therapy without distant metastases. The goal in this situation is to improve local control and intrahepatic progression-free survival rates.<sup>20</sup> For IHC, for example, the addition of EBRT in these patients can lead to an improved 1-year OS from 39% to 70% while providing adequate local control.<sup>21,22</sup> Furthermore, EBRT can be used in the palliative setting to alleviate pain in patients with symptomatic liver lesions. Palliative liver EBRT has been demonstrated to improve pain symptoms at 1 month in those with extensive HCC.<sup>23</sup>

## CONCLUSION

The ASTRO guidelines provide important information on the use of EBRT for primary liver cancers. These guidelines consider the various situations in which EBRT can be utilized, including the neoadjuvant and adjuvant settings or as definitive or palliative therapy. This is an emerging tool in the multidisciplinary management of these malignancies, although further randomized controlled trials will be needed to better assess the precise indications for EBRT for liver-confined tumors. The SSO agrees with the guidelines put forth by ASTRO while recommending caution in the use of EBRT in patients who may be a candidate for surgical intervention. In all situations, it is important to discuss patients in a multidisciplinary setting that includes a hepatobiliary surgeon prior to administering perioperative or definitive EBRT.

**DISCLOSURE** The authors declare that they no conflict of interest.

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