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Stereotactic radiotherapy for intrahepatic cholangiocarcinoma

Stereotactic radiotherapy - Intrahepatic cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma is an aggressive malignancy with an increasing incidence worldwide and poor prognosis, despite several advances and continuous efforts to develop effective treatments. Complete surgical resection is the mainstay of treatment and offers a potentially curative option, but is only possible in less than a third of patients, owing to advanced disease. Chemotherapy is a well-established treatment in the adjuvant and palliative setting, however, confers limited benefit. Conventional radiotherapy is challenging due to local toxicity. With recent advances in stereotactic ablative radiotherapy (SABR), it is now possible to focus ablative beams of radiotherapy precisely aimed at tumours to minimise damage to surrounding viscera. This review details the history, technical background and application of SABR to intrahepatic cholangiocarcinoma, with directions for future research suggested.

Core Tip: Intrahepatic cholangiocarcinoma maintains a dismal prognosis despite best available therapy. Complete surgical resection offers a potentially curative option but is feasible in a limited number of cases. This review explores the evolving role of Stereotactic Ablative Radiotherapy (SABR) in the management of intrahepatic cholangiocarcinoma either as an adjuvant to surgical resection, or in cases or recurrent or unresectable disease. Data on the use of SABR as a neoadjuvant/downstaging modality are scarce. Notably, published studies are limited to predominantly retrospective case series. High quality prospective trials evaluating SABR are urgently needed.

INTRODUCTION

Cholangiocarcinoma (CCA) is a rare, aggressive malignancy arising from the biliary epithelium. The overall incidence worldwide is less than 6 cases per 100,000, however, this varies significantly from country to country and is significantly more common in East Asia, [1,2] with incidences of up to 90 per 100,000 reported in Thailand.[3]

Prognosis in CCA is dismal with fewer than 10% surviving 5 years after diagnosis. Overall survival is significantly higher with extrahepatic *vs* intrahepatic tumours (15% *vs* <5% respectively).[4] The reasons for the poor survival are predominantly related to the insidious growth of the tumours, with limited clinical symptoms until the disease is disseminated, by which point surgical resection which is the sole curative option is precluded.

CLASSIFICATION OF CHOLANGIOCARCINOMA

CCA can be further subdivided by the site of origin in the biliary tract (Figure 1): intrahepatic CCAs (iCCA) arise from sites proximal to the second order branches of the right or left hepatic duct up to the canals of Hering, while perihilar CCAs (phCCA), also known as Klatskin tumours, arise between the second order branches of the right and/or left hepatic duct and the cystic duct confluence. Distal CCAs (dCCA) arise between the cystic duct confluence and the ampulla of Vater.[5-7] Perihilar and distal CCAs are collectively termed extrahepatic cholangiocarcinomas (eCCAs) and account for approximately 80% of all diagnoses of CCAs overall, while the remainder are intrahepatic.[6,8] Morphologically, depending on their pattern of growth and appearance, they are categorised in three different types. The mass-forming type, which is the most frequent, accounts for presentation with a mass, the periductal-infiltrating type is characterised by growth along the wall of the bile duct, and the intraductal-growing type by intraluminal growth.[7]

Histologically, CCAs can be broadly subdivided into papillary and mucinous carcinomas.[9] iCCAs show greater variability with further subdivision into small and large bile duct cancer. Small bile ducts are lined by cuboidal epithelium and hepatic

stem cells, which may be associated with more aggressive tumours and rarely, mixed hepatocellular cholangiocarcinomas. Large bile duct iCCAs are broadly similar to phCCA and dCCA.[10]

PRESENTATION

CCAs are typically asymptomatic in their early stages and manifest clinically only at an advanced stage. Non-specific symptoms such as abdominal pain, night sweats and weight loss may be present in the early stage.[11]

Jaundice is a hallmark feature of extrahepatic CCA as obstruction of large distal bile ducts is needed to obstruct the biliary outflow significantly. Given that iCCAs affect the smaller proximal bile ducts, jaundice is much less frequent, and presentation is more likely to be incidental finding on imaging or after work-up for deranged liver function tests.[12]

iCCAs further differ clinically from extrahepatic tumours in that they are more likely to arise on a background of diseased liver parenchyma, much like hepatocellular carcinoma. eCCAs, in contrast, are associated with chronic bile duct inflammation, such as with primary sclerosing cholangitis, choledocholithiasis or, in endemic regions, liver fluke infection.[13]

MANAGEMENT OF CHOLANGIOCARCINOMA

Complete surgical resection is the only prospect for cure in CCA, but this is only possible in <30% of patients due to advanced disease at presentation.[14,15] Surgery ranges from hepatectomy in iCCA, hepatectomy and/or hilar resection in phCCA, or pancreatoduodenectomy in extrahepatic tumours, to liver transplantation in selected cases of CCA.[7,16]

Adjuvant gemcitabine-based chemotherapy is now recommended in most international guidelines,[17-20] with evidence of increased disease-free survival (DFS);[21] overall 5-year survival can reach from 44% in dCCA to 20-40% in phCCA and iCCA.[8,16]

In the palliative setting, data is more robust in supporting chemotherapy with several randomised studies confirming the survival benefit of gemcitabine and platinum-based therapies, with a median progression free survival (PFS) of 8.0 mo.[22,23] Second line chemotherapy with FOLFOX regimens has also been shown to be of limited benefit, with an improvement in overall survival by 1 mo, although PFS was poor at 8.6% at 1 year.[24]

Locoregional Therapy

Despite institution of surgery or chemotherapy where appropriate recurrence rates remain high and, consequently, patient survival is still poor in CCA. Locally advanced disease, oligometastases and medical comorbidities may also preclude surgical intervention. Locoregional therapies such as radiofrequency ablation (RFA)[25] and trans-arterial chemo- or radio-embolization (TACE or TARE, the latter also known as selective internal radiotherapy or SIRT)[26] have been developed for locally advanced and oligometastatic disease. These therapies have also reduced cancer recurrence as adjuvant therapies along with surgery.[27]

Radiotherapy is another alternative treatment modality encompassing standard external beam, brachytherapy and stereotactic forms studied. This has several advantages to RFA and TACE/TARE, in particular being non-invasive and, not requiring the target to be near blood vessels as in TARE/TACE.

Although radiotherapy is not included in guidelines for the treatment of CCA, it has been shown to improve survival *vs* chemotherapy alone for unresectable iCCA in large propensity matched population studies, with reduced hazards of mortality [HR 0.80 (95%CI 0.71-0.91, *P* = 0.001)].[28,29]

Targeted radiotherapy is challenging due to the radiosensitivity of the liver parenchyma and surrounding gastrointestinal tract, which may result in radiation hepatitis, vomiting, diarrhoea and bowel obstruction resulting from

stricturing.[30,31]Stereotactic ablative radiotherapy (SABR) allows for high energy beams of radiation focused on target sites avoiding damage to surrounding tissues.

This review gives an overview of the technology of SABR and its application to intrahepatic cholangiocarcinoma, which possesses unique characteristics in comparison to other sites.

STEREOTACTIC ABLATIVE RADIOTHERAPY

Stereotactic ablative radiotherapy (SABR) uses multiple beams of radiation focused to a single point in three-dimensional space using a collimation system, as opposed to a single unfocused beam used in conventional radiotherapy. This allows a much larger dose of radiation in a single fraction, whilst avoiding exposure to surrounding tissues. [32] In some cases, the course may be completed in a single fraction. This concept was developed initially by Leskell and colleagues at the Karolinska Institute in Sweden in the 1960s to treat intracranial lesions. Their technology would eventually become known as the Gamma Knife (Elekta Instruments Inc., Tucker GA, USA).[33] It was not until the early 1990s until similar technology was applied outside the brain. Immobilisation of the patient or tracking of viscera is necessary when targeting the thorax and abdomen to avoid off-target viscera and mitigate against motion such as during respiration.[34]

Uematsu *et al* were one of the first to realise the clinical benefits of SABR, in 1998, in patients with locally advanced non-small cell lung cancer who were technically operable but unfit for surgery.[35] Successive studies demonstrated that SABR allowed progression-free survival in 80-90% of these patients, nearly double that of conventional radiotherapy, with significantly lower toxicity.[36]

SABR in the Liver

Following the above reports Herfarth *et al* applied this technology to the liver for unresectable, predominantly metastatic tumours of varying origin. They again showed

impressive local control rates of 81% at 18 mo.[37] Larger, contemporary series of SABR mirror Herfarth's early results in both hepatocellular carcinoma[38] and oligometastatic disease in the liver.[39,40] These series are predominantly observational, and no large-scale interventional trial has been published in this population.

Modern approaches to applying SABR in the liver involve immobilising the abdomen using body moulds or vacuum cushions. Movement from respiration is controlled by using controlled breath holding techniques or respiratory gating or tumour tracking with image guidance. Stereotactic frames and/or implanted fiducial markers may be used to provide a reference for anatomical delineation. The above methods are combined with 4D CT scanning to apply SABR, and accuracy to between 2 and 3 mm is achievable.[41,42]

Patients suitable for SABR to the liver, typically have fewer than 3 tumours at no larger than 6cm each, situated greater than 5mm from adjacent viscera so that ablative doses may be more easily achieved, although these criteria will vary depending on institutional experience.[41,42]

The side effect profile of SABR in relation to the liver most commonly consists of nausea and fever, which can be seen within a few hours of treatment. These may be prevented with prophylactic antiemetics.[43]

Late side effects include radiation induced liver disease (RILD), which may occur between 2 wk and 8 mo after completion of treatment. This includes clinical symptoms of fatigue, tender anicteric hepatomegaly and ascites. Biochemically, there is elevated alkaline phosphatase, whilst transaminases and bilirubin remain normal.[44]

Non-classical RILD (typically in patients with underlying liver disease) occurs within 3 mo of radiotherapy and consists of liver enzymes more than five times the upper limit of normal or a decline in liver function as measured by a worsening Child-Pugh score of 2 or more in the absence of classical RILD.

These occur in less than 5% of patients and are associated with cumulative doses (in conventionally fractionated radiotherapy) higher than 30-32 Gy and 28 Gy in patients with underlying liver disease.

Other specific toxicities are related to off-target effects on the gastrointestinal tract, with nausea, vomiting and diarrhoea being common. Other effects are common to all radiation therapies, and these include skin necrosis (much less common in the era of volumetric modulated arc therapy) and systemic effects such as fatigue and fever. It should be reiterated that these side effects, when they do occur, are typically milder and less frequent than with equivalent conventional radiotherapy.[45]

APPLICATION OF SABR IN INTRAHEPATIC CHOLANGIOCARCINOMA

As mentioned above, the standard of care for curative treatment of iCCA is surgical resection followed by adjuvant chemotherapy. For palliative treatment, chemotherapy with gemcitabine and platinum regimes are recommended. [17,18]We therefore focus on five scenarios where SABR may be useful in the treatment algorithm: (1) primary therapy in patients with technically resectable disease but precluded from resection due to medical comorbidities; (2) primary therapy in technically unresectable disease; this may be due to diffuse or metastatic disease; (3) recurrent disease after surgical resection; (4) following surgical resection to prevent local recurrence (adjuvant therapy), and (5) as a downstaging modality before surgery (neoadjuvant). Relevant studies are summarised in table 1.

SABR as primary therapy in medically unresectable iCCA

Shen *et al* reported data on SABR in inoperable iCCA. In this series 12/28 (42.8%) were inoperable due to medical co-morbidities or advanced age whilst the remainder were technically inoperable. Data was not stratified by the reason for inoperability, although on multivariable analysis, there was no difference in response based on this. The overall disease control rate with SABR was 89.3%, of which 42.9% had stable disease, 35.7% a partial response and 10.7% a complete response at first follow-up (median 16 mo). Predictors of successful response were median biologically effective doses (BED) of >100 Gy and having solitary lesions. Median overall survival (OS) was 15.0 mo

and median progression free survival (PFS) was 11.0 mo. OS and PFS were 32.1% and 21.4% at 2 years, respectively.[46]

A Taiwanese study included patients with solely medically inoperable tumours (14/15 iCCA). 1- and 2-year OS were 50.3 and 14.4%, while local control (LC) was achieved in only 48.5% at 1 year. The reason is likely the lower BED used at 45 Gy and the authors reported significantly higher survival with doses at >75 Gy, with 1-year OS at 58.3%.[47] A Danish study with predominantly patients with eCCA but who were also medically inoperable showed similar OS and local control rates.[48]

The largest study of SABR in iCCA (79 patients) showed 1- year OS of 87% and 3-year OS of 44%. Local control rates were 81% and 31% respectively for the same time period with a PFS of 88% and 39%. Patients in this study were excluded if treatment was directed with palliative intent, which may explain the higher survival rates, although the authors' definition of this is unclear. All patients had favourable performance status: 94% scored at 0 or 1, 6% scored 2 and no patients had performance status >2. 20% of patients had extrahepatic metastatic disease and 58% had nodal disease, implying a poor prognosis pre-treatment.[49] Nevertheless, the survival figures in this study are similar to curative resection, which according to a recent review confers an overall 3-year survival ranging from 32 to 47% and a similar 3-year recurrence free survival which is between 6 to 47%.[50] Survival also correlated with the radiation dose, with a BED greater than 80.5 Gy associated with 3-year OS of 73% *vs* 38% for patients receiving lower doses.

These results may suggest that SABR could be a suitable alternative to surgical resection in patients unfit for surgery, however comparative studies, in particular, randomized trials are needed to confirm this.

SABR as primary therapy in technically unresectable iCCA

Tse *et al* provided one of the first reports of SABR in iCCA. Their phase I study included 10 patients with iCCA who were unresectable due to metastatic disease, pre-

dominantly confined to the liver or with locoregional lymphadenopathy. The median overall survival (OS) was 15.0 mo with 58% 1-year OS.[51]

In Mahadevan and colleagues' retrospective study of locally advanced 31 iCCAs (11 further phCCAs or dCCAs), 1-year OS was 58% and 4-year OS was 19%. LC was achieved in 88% at 1 year and 79% at 4 years for the overall cohort. Median PFS was 11 mo after SABR.[52]

Barney et al performed a retrospective study consisting predominantly of patients with either primary or recurrent oligometastatic disease. OS was 73% at 1 year and LC was achieved in 100% of patients (of whom 25% had a complete response and 42% a partial response). 40% of patients had PFS.[53]

A large multicenter German and Swiss study with 64 patients (41 iCCA) showed 1-year OS of 63% and LC at 89%. After multivariable analysis, as above, improved survival and LC were achieved with higher radiation doses, without a significant increase in toxicity.[54]

Weiner et al performed a phase II study of SABR in unresectable primary liver lesions of which 14/26 (54%) were iCCA or biphenotypic with HCC. 1-year OS was 51% and PFS was 68% with only 2 of 26 (4%) patients in the study having local progression at the SABR site.[55]

Kozak et al performed a retrospective study of SABR in 40 patients with unresectable CCA (23 patients iCCA and the remainder phCCA) assessing the location of failure with respect to the radiation field. Median OS for patients with iCCA was 10 mo, 1-year OS for the entire cohort was 66%, and median follow-up was 18 mo. 12 patients (30%) had in-field local failure, whilst seventeen (42.5%) had out of field hepatic failure. Seven patients (17%) experienced regional failure predominantly in perihilar and para-aortic nodes, whilst 15 patients (37.5%) had distant failure of which the lungs were the most common site of progression (7 patients, 46.7%).[56] Given the high rates of out of field recurrence, the authors proposed elective nodal irradiation in the perihilar space to prevent regional recurrence, however there are no trials on this.

Bisello *et al* proposed a series of guidelines on clinical target volumes for biliary tract cancers, including iCCA, to incorporate sites of potential regional sites of progression. They proposed a margin of 9.8mm from the primary tumour boundary to incorporate all microscopic spread. [57] This is at the cost of potential for increased toxicity, in particular around the central biliary tree with suggested dosing limited to for example 42 Gy in 15 fractions or 35 Gy in 5 fractions.[58]

One study compared SABR to TARE and conventional chemoradiotherapy in unresectable iCCA using the US National Cancer Database. Median OS was 20 mo with SABR and significantly greater than TARE and chemoradiotherapy after adjusting for confounders with propensity weighting and multivariable regression [hazard ratio 0.44 (95%CI 0.21-0.91)].[59]

Of note, Jackson *et al* performed a propensity matched study of patients with inoperable iCCA identified from the US National Cancer Database comparing patients who received any form of radiotherapy (not specifically SABR). After propensity score matching, they showed that the addition of radiotherapy to the standard chemotherapy regimen significantly reduced the hazards of death, hazard ratio 0.83 (95%CI 0.71-0.97, $P = 0.018$). [28]

SABR for recurrent iCCA

Jung *et al* studied patients with unresectable and recurrent disease, of which 57% were iCCAs. 1- and 2-year OS in the recurrent disease group were 53% and 28%, respectively, LC rates were 91% and 81%, respectively, at the same time periods. Overall PFS for all patients were 26% and 23% at 1 and 2 years. Of note, 2 patients developed transient liver failure following SABR in this study.[60]

Franzeze *et al* performed a retrospective study of SABR in recurrent biliary tract cancer after surgical resection, of which 18/51 (35%) had iCCA. 1-year OS and PFS were 63.2% and 32.8%, respectively, whilst local control rates were 74.7% at 1 year.[61]

Ibarra *et al* performed a small multi-centre study of 11 patients undergoing SABR for iCCA, with 50% reported as undergoing this following surgical resection and recurrence (the remainder were for unresectable disease, of whom 45% had distant disease). 1-year survival was 45% and LC was estimated to be 55.5% in this study.[62]

SABR as adjuvant treatment for incomplete (R1) resection

Hammad *et al* performed a study using the US National Cancer Database of patients with iCCA who underwent surgical resection. Of the 525 out of 2897 patients who underwent postoperative conventional radiotherapy, 230 (43.8%) had positive resection margins, compared to 704 (24.3%) in the non-radiotherapy group. There was no significant OS benefit [0.99 (95%CI 0.84–1.16) P = 0.931] for patients who underwent radiotherapy, after propensity score matching and multivariable Cox regression. LC and PFS were not reported.[63]

Kim *et al* published a small case series of 18 patients with incompletely resected iCCA (R1) of whom 7 underwent adjuvant chemoradiotherapy. They found significant increases in OS, LC and PFS with chemoradiotherapy: (LC; 5.6 mo vs. not reached, P <0.001, PFS; 5.6 vs. 8.3 mo, P = 0.047, OS; 15.0 vs. 26.6 mo, P = 0.064).[64]

While there are no large studies of SABR specifically, given its advantages over conventional radiotherapy, the above studies could be regarded as showing some promise in its potential use for incomplete resection.

Studies on SABR as standard adjuvant therapy following resection of iCCA are limited, however there is a limited number of studies evaluating conventional radiotherapy following resection.

Jiang *et al* assessed adjuvant conventional radiotherapy where macroscopic regional lymph nodes were identified following surgical resection on imaging. Out of 100 patients, 24 received radiotherapy, whilst 76 did not, but it was not specified whether the latter patients received any further treatment. Median OS was significantly superior

at 68.8% in the radiotherapy group and 12.1% in the non-radiotherapy group (*P* = 0.01). After multivariable analysis, radiotherapy was independently associated with survival [hazard ratio 0.482 (95%CI 0.27-0.86)].[65] A further meta-analysis of studies assessing adjuvant radiotherapy in iCCA did not show a significantly improved patient survival.[66]

SABR and locoregional treatments as a neoadjuvant/downstaging modality

Studies assessing SABR for downstaging of iCCA (neoadjuvant therapy) have mainly focused on doing this to allow liver transplantation. Wong[67] and Sandler[68] both reported impressive OS of 80 and 75% at 1 year in the few (4 in each study) patients who underwent liver transplantation following successful SABR. However, 18/22 (82%) in Wong's study and 27/31 (87%) patients in Sandler's failed to proceed to transplant, predominantly due to tumour progression.

Conventional chemoradiotherapy has been attempted with promising results in a small case series. Of 7 patients with locally advanced, unresectable iCCA, five (71.4%) became resectable following chemoradiotherapy and one patient remained disease free after resection at 18 mo. 5-year OS was 23.6%.[69]

Rayar *et al* reported their experience of using TARE as a downstaging modality for unresectable iCCA. Of 45 patients who underwent downstaging TARE and chemotherapy, eight (17.7%) ultimately underwent surgical resection with curative intent. With a median follow-up of 15.6 mo, only two patients died perioperatively and only one died from unrelated disease. Of the remainder, two were found to have recurrence at follow-up.[70] Similarly, Edeline and colleagues reported a similar proportion of patients with iCCA downstaged to resectability (9/41, 22%) with TARE, a further two patients remained unresectable, but underwent liver transplantation. For the resected patients, 1-year OS was 88.9% and DFS was 66.8%. For both of the patients undergoing liver transplantation, solitary lung recurrence occurred at 15 and 16 mo and both were alive at 19 and 18 mo of follow-up.[71]

Side Effects and Quality of Life

Side effects were shown to be transient and mild in the majority of patients in these studies of SABR. Those studies which reported liver function tests, showed mildly deranged values of all parameters (ALP, ALT, AST and bilirubin) in most patients following SABR. Very few studies reported greater than 40% of patients having grade II symptoms. Of these, the majority are gastrointestinal side effects with nausea and diarrhoea being common.

Although bowel obstruction and perforation may be complications of radiotherapy, only one case of gastric perforation requiring surgery was found in the studies included in the review. Radiation hepatitis was rare and liver failure was reported in only 2 patients in all the studies included in this review.

One study evaluated the quality of life in patients undergoing SABR in the liver and showed a reduction in quality of life in terms of appetite and fatigue within 1 mo of treatment but returning to baseline after 3 mo. These features demonstrate overall that SABR is tolerated well, relative to other therapies.[72]

CONCLUSION

Current and future directions for research

A search of the clinicaltrials.gov registry (search terms "cholangiocarcinoma" AND "stereotactic") showed 2 actively recruiting trials evaluating stereotactic radiotherapy. Of these two, the CORRECT trial (NCT03898895) is a multicentre randomized trial evaluating a PD-1 checkpoint inhibitor (Camrelizumab) with either SABR or conventional radiotherapy *vs* standard gemcitabine chemotherapy in unresectable iCCA.[73] The second is a phase II trial of nivolumab with SABR in unresectable iCCA and dCCA.[74]

Of the remainder, 4 studies assess all types of liver tumours, 2 assess phCCA only, and the rest assess a mix of extrahepatic and intrahepatic tumours. These are all phase I and II trials.

In addition, the ABC-07 trial is actively recruiting and is a multicentre randomized controlled trial comparing chemotherapy *vs* chemotherapy and SABR in unresectable CCA (of all types) and gallbladder carcinoma.[75]

Furthermore, the ACCTICA-1 trial is primarily assessing the superiority of gemcitabine and cisplatin *vs* capecitabine in patients with resected CCA and gallbladder adenocarcinoma. However, within this trial there is a sub-study evaluating conventional radiotherapy in patients with R1 resections.[76,77]

Thus far, there have been no published randomized trials of SABR in any subgroup of iCCA, and the majority are retrospective single institution studies. Few studies have compared SABR to a control group or other locoregional therapies. There is limited literature on SABR as a downstaging modality prior to standard surgical resection of iCCA, despite evidence of excellent LC in patients who are inoperable.

High quality prospective clinical trials of SABR are urgently needed in homogeneous groups of iCCA, to explore its role as an adjuvant and neoadjuvant therapy either prior to resection or liver transplantation, and as a treatment modality in recurrent and unresectable disease.

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