Received:
20 January 2017

Revised:
6 April 2017

Accepted:
25 April 2017

<https://doi.org/10.1259/bjr.20170061>

Cite this article as:

Sahai P, Kumar S, . External radiotherapy and brachytherapy in the management of extrahepatic and intrahepatic cholangiocarcinoma: available evidence. *Br J Radiol* 2017; **90**: 20170061.

REVIEW ARTICLE

External radiotherapy and brachytherapy in the management of extrahepatic and intrahepatic cholangiocarcinoma: available evidence

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ABSTRACT

This review aims to summarize the currently available evidence for the role of external radiotherapy and brachytherapy in the management of cholangiocarcinoma. High locoregional disease recurrence rates after surgical resection alone for both the extrahepatic cholangiocarcinoma (EHCC) and intrahepatic cholangiocarcinoma (IHCC) provide a rationale for using adjuvant radiotherapy with chemotherapy. We performed a literature search related to radiotherapy in cholangiocarcinoma published between 2000 and 2016. The role of radiation is discussed in the adjuvant, neoadjuvant, definitive and the palliative setting. Evidence from Phase II trials have demonstrated efficacy of adjuvant chemoradiation in combination with chemotherapy in EHCC. Locally advanced cholangiocarcinoma may be treated with neoadjuvant chemoradiotherapy. In the case of downsizing, assessment for resection may be considered. Brachytherapy offers dose escalation after external radiotherapy. Selected unresectable cases of cholangiocarcinoma may be considered for stereotactic body radiation therapy with neoadjuvant and/or concurrent chemotherapy. Liver transplantation is a treatment option in selected patients with EHCC and IHCC after neoadjuvant chemoradiation. Stenting in combination with palliative external radiotherapy and/or brachytherapy provides improved stent patency and survival. Newer advanced radiation techniques provide a scope for achieving better disease control with reduced morbidity. Effective multimodality treatment incorporating radiotherapy is the way forward for improving survival in patients with cholangiocarcinoma.

INTRODUCTION

Cholangiocarcinoma is classified into extrahepatic and intrahepatic types. Extrahepatic cholangiocarcinoma (EHCC) is further divided into hilar and distal cholangiocarcinoma. The lesions within 2 cm of the confluence of the right and the left hepatic ducts are called perihilar or Klatskin's tumours. Surgical resection is the primary modality of treatment for cholangiocarcinoma. However, only a limited number of patients are considered resectable at presentation. Furthermore, the long-term survival remains dismal with surgery alone. Therefore, there is a need to assess additional modalities of treatment to decrease the mortality related to these tumours. We performed a PubMed search using the MeSH terms: Biliary Tract Neoplasms/radiotherapy OR Cholangiocarcinoma/radiotherapy as of December 2016. We reviewed the literature related to radiotherapy in cholangiocarcinoma published between 2000 and 2016. This review aims to summarize the currently available evidence for the role of external radiotherapy and

brachytherapy in the management of cholangiocarcinoma. The role of radiation is discussed in the adjuvant, neoadjuvant, definitive and the palliative setting.

EXTRAHEPATIC CHOLANGIOCARCINOMA

Patterns of disease recurrence and survival after surgical resection

A series from the Memorial Sloan Kettering Cancer Center¹ reported on recurrence rates of 76 patients of resected hilar cholangiocarcinoma (HCCA). All the patients had undergone bile duct resection and reconstruction with supraduodenal lymphadenectomy. The surgical resection was combined with a major hepatectomy in 58 of the 76 patients. Adjuvant radiotherapy or chemotherapy was delivered in 7 out of the 76 patients. Recurrence was seen at a median time of 20.3 months (range, 4–111 months), with 49% patients (37 of 76) manifesting locoregional recurrence, 11 of whom had distant relapse as well. The independent predictors of recurrence were lymph node

Table 1. Summary of studies on adjuvant radiotherapy in extrahepatic cholangiocarcinoma

Author, year	Type of study	Number of patients	Disease characteristics	Adjuvant treatment modality	Radiotherapy	Chemotherapy	Follow-up (months) Median (range) (months)	Overall survival	Failure
Oh et al, ⁹ 2007	Retrospective	60	EHCC ≥pT2 or LN+ or R1	RT ± CT	45/1.8 Gy per fr Boost 9–10 Gy for R1/R2 3DCRT	Concurrent: 5-FU or gemcitabine (<i>n</i> = 12)	17 (4–81)	2-year 36.6% 5-year 12.3%	LR = 30% LR + D = 18.3%
Ben-David et al, ¹⁰ 2006	Retrospective	81	EBBTC (EHCC and GB) LN+ or R1 or ≥ T2	CCRT	Median 53.1, 54.9 and 60.2 Gy for R0, R1 and R2; 1.8/2.0 Gy day ⁻¹ or 1.5/1.65 Gy twice daily 3DCRT	Concurrent (54%): systemic 5-FU or intrahepatic floxuridine or bromodeoxyuridine	14.4 (1.2–117.6)	Median 15.7 and 12 months for distal and hilar CC, respectively	All pts: LR = 13.5% D = 8.6%
Beltran et al, ¹¹ 2011	Retrospective	23	EBBTC Stages II–IVA	CCRT	Median 50.4 Gy (45–60 Gy) 3DCRT	Concurrent: 5-FU based	30 (3–98)	5-year 61.4% vs 16.7% for R0 vs R1	LR + D = 39%
Kim et al, ¹² 2002	Retrospective	84	EHCC Stages I–IVA	CCRT followed by ACT	40–45 Gy in 1.8–2.0 Gy per fr (2 weeks rest after 20 Gy) 2D	Concurrent: 5-FU ACT: 5-FU based for 1 year	23 (2–75)	2-year 52% 5-year 31%	LR = 47% Abdominal = 10%
Lim et al, ¹³ 2009	Retrospective	120	EHCC Stages I–III	CCRT (<i>n</i> = 30) CCRT followed by ACT (<i>n</i> = 90)	40–54/ 1.8–2.4 Gy per fr (2 weeks split course)	Concurrent: 5-FU 500 mg m ⁻² i.v. D1 to D3 and D28–D30 ACT: 5-FU or capecitabine for 6–12 months	21.4	3-year 30.8% vs 62.6% for CCRT vs CCRT + ACT	LR = 18.3% L + D = 19.2% D = 19.2%
Hughes et al, ¹⁴ 2007	Retrospective	34	Distal CC Stage II/III	CCRT followed by ACT	Median 50.4 Gy (40–54 Gy) in 1.8–2.5 Gy per fr 3DCRT	Concurrent: 5-FU based ACT: 5-FU based	41	Median 36.9 months 5-year 100% vs 24% for LN– vs LN+	L = 11.8% D = 53% L + D = 5.8%

(Continued)

Table 1. (Continued)

Author, year	Type of study	Number of patients	Disease characteristics	Adjuvant treatment modality	Radiotherapy	Chemotherapy	Follow-up (months) Median (range) (months)	Overall survival	Failure
Schoppmeyer et al, ¹⁵ 2006	Phase I/II	18	EHCC R0 LN+ R1/R2 unresectable	CCRT followed by ACT	49.6 Gy/31 frs of 1.6 Gy/6 frs per week 3DCRT	Concurrent: gemcitabine 1000 mg m ⁻² i.v. weekly ACT: 6 cycles gemcitabine 1000 mg m ⁻² D1 and D8; capecitabine 750 mg m ⁻² D1 to D14 q21 d	19.5 (6.8–25.5)	Median 11.1 months (not reached for resected pts)	Recurrence 28.6% (in resected pts)
Cho et al, ¹⁷ 2015	Phase II	48	Pancreaticobiliary EHBTC or ampulla (<i>n</i> = 21)	ACT before and after CCRT	45 Gy/25 frs/5 weeks plus boost 3DCRT	ACT: 2 cycles before and after RT gemcitabine 1000 mg m ⁻² D1 and D8; docetaxel 35 mg m ⁻² D1 and D8 q21 d Concurrent: 5-FU 225 mg m ⁻² per day infusion	24 (3.2–97)	For EHBTC or ampulla: Median 23.8 months 1-year 75% 2-year 49.1%	All pts: D = 83%
Ben-Josef et al, ¹⁶ 2015	Phase II	79	EHBTC (EHCC = 68.4%) pT2–4 or LN+ or R1	ACT followed by CCRT	52.5–59.4 Gy/25–33 frs/5 frs per week IMRT/3DCRT	ACT: 4 cycles gemcitabine 1000 mg m ⁻² D1 and D8; capecitabine 1500 mg m ⁻² PO D1 to D14 q21 d Concurrent: capecitabine 1330 mg m ⁻²	35	2-year 68% for EHCC	For EHCC: L = 7.8% L + D = 13.7% D = 23.5%

2D, two-dimensional; 3DCRT, three-dimensional conformal radiation therapy; 5-FU, 5-fluorouracil; $\geq$ T2, Advanced T; ACT, adjuvant chemotherapy; CC, cholangiocarcinoma; CCRT, concurrent chemoradiation; CT, chemotherapy; D, distant; EHBTC, extrahepatic biliary tract cancers; EHCC, extrahepatic cholangiocarcinoma; fr, fraction; GB, gall bladder; i.v., intravenous; IMRT, intensity modulated radiation therapy; L, local; LN, lymph node; LR, locoregional; pts, patients; R0, no residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour; RT, radiotherapy.

positivity, R1 resection and moderate or poor tumour differentiation. The rates of recurrence were similar in patients with or without pre-operative biliary interventions or stenting. Local recurrences were observed at the hilum, bilioenteric anastomosis or the liver resection margin. Regional recurrences were observed in the retroperitoneal lymph nodes. The sites for the distant recurrences were peritoneum, liver, lung, mediastinum, skin or brain.

A major hepatectomy is required for complete tumour clearance of HCCA as it often extends to the second-order biliary radicals and/or involves major portal vascular structures.¹ Locoregional recurrence likely arises from microscopic residual disease or disease in the lymphatics. As the locoregional area gets included in a radiation field, a reduction in the risk of recurrence could be achieved with radiotherapy. Intrahepatic and distant recurrences result from haematogenous spread, the risk of which could be reduced with chemotherapy.¹ Murakami *et al*² reported the risk of recurrence in patients with hilar, distal or ampullary carcinoma as per the Union for International Cancer Control (sixth edition) TNM stage group. After resection, the recurrence rate for Stage II or III *vs* I was 82% *vs* 13%, respectively. Stage IB disease resulted in a higher risk of recurrence at 20% than 9% with Stage IA. The 5-year survival differed between Stage II/III and I at 21% *vs* 82%. The survival in patients with middle or lower EHCC has been shown to be better than those with upper locations.³

Extrahepatic cholangiocarcinoma—adjuvant radiotherapy

There have been reports of improved survival with adjuvant radiotherapy after resection.⁴ Gerhards *et al*⁵ reported median survival of 24 months with adjuvant radiotherapy as compared with 8 months with surgery alone for HCCA. Given the lack of randomized trials, 10 retrospective cohort studies were included

in a systematic review and meta-analysis on adjuvant radiotherapy in EHCC.⁶ The results demonstrated an improvement in overall survival (OS) with adjuvant three-dimensional conformal radiation therapy (3DCRT); hazards ratio 0.62, 95% confidence interval: 0.48–0.78, $p < 0.001$. Late radiation toxicity was observed in 2–9% of the patients, which mainly comprised late obstruction or gastrointestinal bleeding. A population-based analysis of EHCC from the Surveillance, Epidemiology and End Results database ($n = 1569$) from 1973 to 2005 showed that the majority of the survival benefit with adjuvant radiotherapy was seen within the initial 1 or 2 years.⁷ A survival benefit with adjuvant chemoradiation (CRT) in biliary tract cancers (BTCs), *i.e.* cholangiocarcinoma and gall bladder cancer, has been revealed in a systematic review and meta-analysis.⁸

The optimal timing of adjuvant radiotherapy in EHCC is yet to be defined. Selected studies using various adjuvant radiotherapy regimens in EHCC are summarized in Table 1.^{9–16} Adjuvant concurrent CRT (CCRT) was initiated at 4.4–14.9 weeks after surgery in the study by Lim *et al*.¹³ The high local failure rate noted in this study could be explained by the use of split course radiotherapy schedule that is no longer recommended as it compromises disease control. The factors associated with OS were elevated carbohydrate antigen 19-9, histologic grade and the pattern of adjuvant treatment. An improvement in survival has been observed with adjuvant CCRT in combination with chemotherapy.^{14,15} Most of the studies used gemcitabine- or 5-fluorouracil (5-FU)- or capecitabine-based adjuvant regimens (Table 1). A combination of taxane with gemcitabine for adjuvant chemotherapy with CCRT has been evaluated in a Phase II study in pancreatic cancers and BTCs.¹⁷ The treatment was discontinued by 15% of the patients owing to adverse events. Grade 3 or greater non-haematological toxicities were observed in 15% of patients. The adjuvant regimen and the results of the recently published Phase II S0809 trial provide a benchmark for

Table 2. Established neoadjuvant treatment protocols before liver transplantation for hilar cholangiocarcinoma

Protocol	EBRT	Brachytherapy	Chemotherapy	Reference
Nebraska	None	60 Gy over 55–60 h ¹⁹² Ir	Concurrent 5-FU 300 mg m ⁻² per day i.v. infusion; continued until transplantation	Sudan <i>et al</i> , ²⁵ 2002
Mayo	45 Gy/30 frs/3 weeks/2 frs per day of 1.5 Gy each	After 2–3 weeks of EBRT, 20–30 Gy ¹⁹² Ir	Concurrent 5-FU 500 mg m ⁻² day ⁻¹ i.v. bolus D1 to D3 of EBRT and 5-FU 225 mg m ⁻² day ⁻¹ i.v. infusion with brachytherapy 5-FU 225 mg m ⁻² day ⁻¹ i.v. infusion, 7 days week ⁻¹ for 5 weeks then 1 week off or capecitabine 2000 mg m ⁻² day ⁻¹ PO, 2 out of every 3 weeks until transplantation	De Vreede <i>et al</i> , ²⁶ 2000 and Heimbach <i>et al</i> , ²⁷ 2004
Michigan	SBRT 50–60 Gy in 3–5 frs over 2 weeks	None	After 1 week of SBRT, capecitabine 1330 mg m ⁻² day ⁻¹ PO, 1 week rest every 6 weeks	Welling <i>et al</i> , ²⁸ 2014
Iowa	44 Gy in 22 frs, 5 days per week	After 14–21 days of EBRT-30 Gy ¹⁹² Ir	None	Wu <i>et al</i> , ²⁹ 2008

¹⁹²Ir, Iridium-192; 5-FU, 5-fluorouracil; EBRT, external beam radiation therapy; fr, fraction; i.v., intravenous; PO, per oral; SBRT, stereotactic body radiation therapy.

the planning of future Phase III studies.¹⁶ The adverse effects reported in the S0809 trial were mainly haematologic, hand-foot syndrome or diarrhoea.

Extrahepatic cholangiocarcinoma—neoadjuvant radiotherapy

Neoadjuvant therapy in HCCA has been used in two surgical settings, namely before resection and prior to liver transplantation (LT). In a systematic review of neoadjuvant therapy before resection, Grendar et al¹⁸ reported 10 studies which

included a total of 98 patients. Although there was heterogeneity in the chosen regimens which included radiotherapy, chemotherapy or photodynamic therapy, these studies provide Level IV evidence for improved R0 resection rates and survival benefit in primarily unresectable tumours. Radiotherapy as a neoadjuvant regimen was used in four of these studies recruiting a total of 52 patients.^{19–22} Two studies on pre-operative 5-FU-based CRT (45–50.4 Gy in conventional fractionation) demonstrated achievement of R0 resection in unresectable tumours.^{19,21} A Phase I trial estimated the maximum tolerated dose of

Table 3. Summary of studies on stereotactic body radiation therapy for cholangiocarcinoma

Author, year	No. of patients	Site	Tumour size/volume Median (range)	Dose	Chemotherapy	Overall survival	Toxicity
Tao et al, ⁴⁹ 2016	79	IHCC	7.9 cm (2.2–17 cm)	35–100 Gy in 3–30 frs Median 58.05 Gy	Before RT (<i>n</i> = 70): gemcitabine based Concurrent (<i>n</i> = 50): capecitabine After RT (<i>n</i> = 37): irinotecan or gemcitabine based	Median 30 months 3-year 44%	No RILD
Mahadevan et al, 2015 ³⁴	34	IHCC (31 lesions) HCCA (11 lesions)	63.8 cm ³ (5.8–500.6 cm ³)	Median 30 Gy in 3 daily frs	Gemcitabine based (<i>n</i> = 18)	Median 17 months 1-year 58% 2-year 31%	Duodenal ulcer (<i>n</i> = 2) Cholangitis (<i>n</i> = 1) Liver abscess (<i>n</i> = 1)
Barney et al, 2012 ³⁵	10	IHCC (<i>n</i> = 6) EHCC (<i>n</i> = 4)	PTV 79.1 cm ³ (16–412.4 cm ³)	45–60 Gy in 3–5 daily frs Median 55 Gy in 5 frs	Before RT (<i>n</i> = 4)	1-year 73%	Grade 3 biliary stenosis (<i>n</i> = 1) Grade 5 liver failure (<i>n</i> = 1)
Polistina et al, 2011 ³⁶	10	HCCA	<6 cm	30 Gy in 3 daily frs	Gemcitabine 1000 mg m ⁻² i.v. weekly	Median 35.5 months 2-year 80% 4-year 30%	Duodenal ulcer (<i>n</i> = 1) Duodenal stenosis (<i>n</i> = 2)
Momm et al, 2010 ³⁷	13	EHCC (Klatskin's tumour)	PTV 190.2 cm ³ (47–393 cm ³)	32–56 Gy in 3–4 Gy per fr, 3 times a week	Pre- and post-RT (<i>n</i> = 2) Post-RT (<i>n</i> = 4) Gemcitabine or 5-FU based	Median 33.5 months	Infectious cholangitis (<i>n</i> = 5)
Kopek et al, 2010 ³⁸	27	Klatskin's tumour (<i>n</i> = 26) IHCC (<i>n</i> = 1)	CTV 32 cm ³ (9–205 cm ³)	45 Gy in 3 frs over 5–8 days	None	Median 10.6 months	Duodenal/pyloric ulceration (<i>n</i> = 6) Duodenal stenosis (<i>n</i> = 3)
Tse et al, 2008 ⁵⁰	10	IHCC	172 cm ³ (10–465 cm ³)	28.2–48 Gy in 6 frs, 3 frs per week Median 32.5 Gy	None	Median 15 months 1-year 58%	Transient biliary obstruction (<i>n</i> = 2) No RILD

CTV, clinical target volume; EHCC, extrahepatic cholangiocarcinoma; fr, fraction; HCCA, hilar cholangiocarcinoma; IHCC, intrahepatic cholangiocarcinoma; PTV, planning target volume; RILD, radiation-induced liver disease; RT, radiotherapy.

gemcitabine at 600 mg m^{-2} with 45 Gy in 1.8-Gy daily fraction for neoadjuvant CRT.²² The surgical morbidity was found similar in patients treated with or without neoadjuvant CRT in the study by Nelson *et al*.²¹ Furthermore, neoadjuvant radiotherapy was shown to result in a reduced risk of implantation metastases after endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography.²⁰

LT is a viable therapeutic option for patients with unresectable peri-HCCA. However, results with LT alone have been disappointing with high rates of tumour recurrence ranging from 51²³–80%.²⁴ Following the encouraging outcomes with radiotherapy in advanced tumours, its role in a neoadjuvant regimen was explored. This resulted in the evolution of the Nebraska, Mayo, Michigan and Iowa protocols which used various combinations of radiotherapy and chemotherapy, as summarized in Table 2.^{25–29}

The Mayo clinic protocol for neoadjuvant CRT prior to LT is the most widely followed and consists of a combination of external beam radiotherapy (EBRT) and brachytherapy with 5-FU or capecitabine-based chemotherapy.^{26,27} In the protocol, EBRT was given as 45 Gy in 30 fractions over 3 weeks with 2 fractions per day. Brachytherapy was given as a dose of 20–30 Gy with Iridium-192 (¹⁹²Ir) seeds through an endoscopically placed stent or a transhepatic catheter to encompass 1.5- to 2.0-cm margins above and below the tumour. Staging laparotomy was performed at least 2 weeks after the completion of brachytherapy. The patients with negative staging laparotomy were taken up for LT. The actuarial 5-year survival was estimated to be 82% after the neoadjuvant therapy followed by LT. The morbidity with the Mayo protocol is significant but not prohibitive.

In the largest collective review to date of neoadjuvant CRT in LT for unresectable peri-HCCA, Murad *et al*³⁰ reported outcomes in 287 patients from 12 US centres. The diagnosis was established by a malignant-appearing stricture on cholangiography with malignant endoluminal brushing or biopsy, carbohydrate antigen 19-9 >100 U/ml, mass on imaging and/or polysomy on fluorescence *in situ* hybridization. The neoadjuvant protocols varied in the included individual elements and combinations used. External radiotherapy (40–60Gy) was given in 99% of all patients, while 75% received brachytherapy; radiosensitizing chemotherapy was given in 98%, while maintenance chemotherapy was used in 65% of patients. A drop-out before LT was observed in 71 patients with the rate of 11.5% in 3 months. At a median follow-up of 2.5 years (0.1–17.8 years), the intent-to-treat survival at 2 and 5 years was 68% and 53%, respectively. The recurrence-free survival (RFS) was superior in patients with mass <3 cm as compared with >3 cm (69% *vs* 32%). The morbidity included fatigue (41%), gastroduodenal ulcers (34%), gastrointestinal dysmotility (18%), and stenosis and/or thrombosis of the portal vein (23%) or hepatic artery (12%). Long-term biliary complications included anastomotic strictures at the choledochojejunostomy or duct-to-duct site in 17% and ischaemic cholangiopathy related to arterial compromise in 7%.

In summary, neoadjuvant radiotherapy before liver resection improves resectability rates, reduces recurrence and may prolong

survival. However, this is not a standard practice and the evidence is from small case series only. On the other hand, in the LT setting, neoadjuvant radiotherapy with chemotherapy is the standard of care and has significantly improved OS and disease-free survival.

Extrahepatic cholangiocarcinoma—definitive radiotherapy

It has been reported that 20–50% of patients with EHCC are amenable to radical surgical resections.³¹ Amongst the operated patients, nearly 50–60% undergo resection with free margins. The remaining unresectable patients are evaluated for treatment with definitive radiotherapy.

Conventional fractionated 3DCRT was used in a study³² on 30 patients with locally advanced EHCC. A dose ranging from 30 to 78 Gy in 1.8–2.0 Gy per fraction (median = 48.25 Gy) was used. Concurrent chemotherapy was given in 60% of the patients with cisplatin and/or 5-FU. The 1- and 3-year progression-free survival was 38% and 16%, respectively. Disease relapse was observed in 20 of 30 patients, 75% of which was metastatic. Autorino *et al*³³ reported 2-year OS of 27% in patients with unresectable EHCC treated with CCRT (50.4 Gy) with weekly gemcitabine 100 mg m^{-2} as a 24-h infusion. The median OS was better in patients treated with intraluminal brachytherapy (ILBT) boost also after 3DCRT (21 *vs* 14 months).

Stereotactic body radiation therapy (SBRT) has been used to treat EHCC (Table 3).^{34–38} Polistina *et al*³⁶ evaluated CRT for locally advanced HCCA. Unresectability was defined by bilateral parenchymal or vascular involvement. Of 10 patients, 6 had hilar lymphadenopathy. All patients underwent an initial bilateral biliary drainage with plastic stents, which was percutaneous in nine and endoscopic in one. This was later converted to metal stents for better and reliable drainage before radiotherapy. Cyberknife SBRT with three fractions of 10 Gy was given with weekly gemcitabine. Radiological response was observed in 80% of the patients (complete response in two; partial response in four; and stable disease in two patients). Median time to progression was 30 months. Acute toxicity was vomiting, gastritis, leukopenia or duodenal bleeding, which was mainly grade 1 ($n = 3$) or 2 ($n = 2$). Duodenal ulcer or stenosis was the main late toxicity. Distant metastasis was the pattern of failure on follow-up in six patients.

A lesser dose per fraction of 3–4 Gy for SBRT was given in the study by Momm *et al*.³⁷ Of 13 patients, 6 had also received chemotherapy before or after radiotherapy. The median time with freedom from tumour progression was 32.5 months (6.1–60.4 months). The first site of tumour progression was the primary tumour region (liver and/or local peritoneum). On follow-up, liver metastases were detected in two patients. No late effects were observed.

Extrahepatic cholangiocarcinoma—palliative radiotherapy

There is limited evidence that stenting in combination with radiotherapy may offer better palliation and marginally improve survival.³⁹ A percutaneous uncovered metallic stent (UMS)

combined with EBRT 37–40.7 Gy in 10–11 fractions, 3.7 Gy per fraction was compared with UMS alone in unresectable HCCA in a study.³⁹ Successful drainage by stenting was defined by a decrease in serum bilirubin >75% in 2 weeks. The following were criteria for defining stent occlusion: increase in bilirubin, enzymes and total leukocyte count with biliary dilatation on imaging. A longer median stent patency was noted with UMS + radiotherapy compared with UMS alone (326 vs 196 days, $p = 0.022$). Similarly, the median survival was also longer with the addition of radiotherapy (367 vs 267 days, $p = 0.025$).

INTRAHEPATIC CHOLANGIOCARCINOMA

Patterns of disease recurrence and survival after surgical resection

A multi-institutional database of 301 patients with intrahepatic cholangiocarcinoma (IHCC) from 1990 to 2011 was evaluated by Hyder et al.⁴⁰ Surgical resections were R0 in 81.1% of the patients. A little more than one-third of the patients had received adjuvant chemotherapy with or without radiotherapy. Recurrence was observed in 53.5%, out of which 60.9% was intrahepatic; 18.6% was simultaneous intra- and extrahepatic; and 21% was extrahepatic only. The 5-year actuarial risk of any recurrence was estimated to be >60%. The risk of recurrence appeared to be the highest over the first 24–36 months after surgery. Stagewise median RFS was 36.5, 11.4 and 17 months for Stages I, II and III, respectively. The factors associated with the risk of recurrence were macrovascular invasion, tumour size ≥ 5 cm, nodal metastasis and unknown nodal metastasis. Other factors such as microvascular invasion, multiple tumours and perineural invasion were not independently associated with RFS. After recurrence, the patients treated with chemotherapy or best supportive care had a median survival of 9.2 months (95% confidence interval 7.4–14.2 months). In another study from the Memorial Sloan Kettering Cancer Center on IHCC,⁴¹ recurrences were seen in 62.2% of the patients after resection. The majority of the recurrences were observed in the liver remnant.

After a potentially curative resection for IHCC, a 5-year survival ranging from 24.5%⁴² to 43%⁴³ has been reported. An intra-ductal papillary component in IHCC has been shown to result in a long-term survival.⁴² Survival in patients with IHCC has been reported to be lower than in those with extrahepatic middle or lower locations of the bile duct.³

Intrahepatic cholangiocarcinoma—adjuvant radiotherapy

A Surveillance, Epidemiology and End Results analysis⁴⁴ of 3839 patients with IHCC revealed a better median OS of 11 months with surgery and adjuvant radiotherapy than 6 months with surgery alone, $p = 0.014$. Surgery followed by adjuvant radiotherapy offered the greatest benefit in OS (hazards ratio 0.40). The systematic review and meta-analysis by Horgan et al⁸ on BTCs included only one study with patients with IHCC. The results revealed a non-significant improvement in OS with any adjuvant therapy compared with surgery alone (pooled odds ratio 0.74; $p = 0.06$). With chemotherapy or CRT, a statistically greater benefit was observed than radiotherapy alone with odds ratio 0.39, 0.61 and 0.98, respectively. The greatest benefit of adjuvant therapy was observed in patients with lymph node

positive or R1 status. In a multicentre retrospective study from 31 Japanese institutions on BTCs,⁴⁵ the number of patients with IHCC were 14. The results demonstrated that a post-operative radiotherapy dose of 54 Gy was safe and effective for patients with R0 and R1 resection. Given the high locoregional recurrence rates after surgery alone for IHCC, adjuvant CRT protocols may be used as studied in the case of EHCC.

Intrahepatic cholangiocarcinoma—neoadjuvant radiotherapy

Orthotopic LT with neoadjuvant and adjuvant therapies provides a better RFS than radical bile duct resection and partial hepatectomy with adjuvant therapy in locally advanced IHCC.⁴⁶ LT with neoadjuvant and adjuvant therapies have been associated with a better survival than LT alone or with adjuvant treatment alone.⁴⁶ Perineural invasion and multifocal tumours have been shown to predict lower survival after resection or LT.⁴⁶

A protocol from the University of California Los Angeles⁴⁷ was devised for the treatment of locally advanced IHCC as well as HCCA. It involved a tumour biopsy followed by neoadjuvant therapy. The neoadjuvant protocol used locoregional therapy followed by chemotherapy. The tumours ≤ 6 cm were treated with SBRT with a dose of 40 Gy in five fractions over 7–12 days, whereas the ones with a size >6 cm were treated with trans-arterial chemoembolization. Subsequently, 5-FU or capecitabine in combination with oxaliplatin-, leucovorin- or gemcitabine-based chemotherapy was given. The response assessment was performed by imaging and tumour markers. The subsequent risk stratification for LT was based on surgical staging laparoscopy. Low- and intermediate-risk group of patients underwent LT. A repeat biopsy was performed for the high-risk group, and LT was considered in the presence of a favourable response to neoadjuvant therapy. Adjuvant chemotherapy was given based on the tumour biology determined in pre-treatment biopsy and the explanted specimen. Adjuvant chemotherapy was administered with the aim to decrease the risk of recurrence because of the immunosuppressive therapy given after LT. The 5-year RFS was significantly higher in the low-risk groups than the intermediate- and high-risk groups (78% vs 19% vs 0%; $p < 0.001$).

Intrahepatic cholangiocarcinoma—definitive radiotherapy

The combination of radiation with chemotherapy offers a significantly higher survival than chemotherapy alone in unresectable IHCC.⁴⁸ A mean dose of 44.7 Gy (25–60 Gy) in fractions of 2.0–3.0 Gy, five times a week with concurrent capecitabine and cisplatin was used in the institutional series reported by Kim et al.⁴⁸

SBRT has been used as a treatment modality for unresectable IHCC. The results of selected series are summarized in Table 3.^{34,35,38,49,50} Tao et al⁴⁹ described survival results with ablative doses of definitive radiotherapy in inoperable IHCC, which compared favourably with resection. The majority of the patients had received systemic chemotherapy before radiotherapy, and concurrent chemotherapy was given in more than half of the patients. The 3-year OS was 73% in patients treated with a biological equivalent dose of >80.5 Gy. A temporary

worsening of appetite and fatigue with SBRT for cholangiocarcinoma has been observed with quality-of-life assessments.⁵¹ The quality of life improved or remained stable in the majority of patients in the study by Klein *et al*⁵¹ at 1 year following SBRT.

Proton beam therapy (PBT) is a promising area in the treatment of unresectable cholangiocarcinoma.^{52,53} Twenty patients with unresectable IHCC were treated with PBT in an institution from Japan.⁵³ Patients with tumour size ranging from 1.5 to 14 cm (median = 5 cm) with Child–Pugh Class A or B were included. A median dose of 72.6 Gy equivalent in 22 fractions was delivered. Concurrent TS-1 (combination of tegafur, gimericil and oteracil) was given to four patients. Amongst the group of patients treated with curative intent, 1- and 3-year local control and OS rates were 88%, 60% and 82%, 38%, respectively. The patients without jaundice had a better survival than the ones with jaundice. Acute morbidities were dermatitis, anorexia, nausea, gastric ulcer, bone marrow suppression and elevated transaminase. Late effects were gastric ulcer and biliary tract infection. A recent report by Hong *et al*⁵² estimated a 2-year local control rate of 94.1% with PBT in unresectable IHCC.

Cholangiocarcinoma—external radiotherapy target volumes

Adjuvant radiotherapy covers the pre-operative tumour bed and regional lymph nodal regions, *i.e.* portal, coeliac and retropancreaticoduodenal. Some institutes have reported inclusion of the para-aortic nodal region also for distal cholangiocarcinoma.^{9,11,14} Conventional radiotherapy for unresectable cases covers the gross tumour volume (GTV) with a 1.0-cm margin for generating the clinical target volume (CTV). Niska *et al*⁵⁴ assessed if the GTV varies between various phases of multiphasic CT imaging in the case of IHCC. The results showed that the IHCC lesions were best identified on the portal venous phase in 64% and the arterial phase in 29% of the cases. The authors concluded that the assessment of all available intravenous contrast phases is essential to accurately define GTV. A study assessed the microscopic invasion of IHCC on the tumour specimens.⁵⁵ The results demonstrated that a GTV-to-CTV expansion of 9.8 mm was required to encompass all the microscopic disease with 100% accuracy. The planning target volume margin is given based on the respiratory motion as assessed on fluoroscopy or four-dimensional CT (4DCT). Nodal volumes depending on the primary location are included. Contouring atlases from the Radiation Therapy Oncology Group and the University of Michigan provide a guide for delineating the nodal target volumes.

Positron emission tomography CT-based radiotherapy for unresectable cases offers a potential for an accuracy of target delineation with a reduction in geographic misses.⁵⁶ Image-guided intensity-modulated radiation therapy may provide an improvement in dosimetric coverage of the target volume with a reduction of toxicity.⁵⁷ The dose constraints for adjuvant 3DCRT were given as follows in the Phase I/II trial by Schoppmeyer *et al*:¹⁵ spinal cord, maximum dose 40 Gy; right kidney, 50% of volume $\leq$ 20 Gy; left kidney, 30% of volume $\leq$ 30 Gy; and uninvolved liver, 50% of volume $\leq$ 30 Gy.

The SBRT technique for cholangiocarcinoma has been described by Barney *et al*³⁵ from the Mayo clinic. After immobilization,

axial 4DCT images were acquired. The patient's respiratory pattern and the CT data were linked at the time of simulation. The CTV was considered identical to the GTV. The internal target volume was generated accounting for the movement of the tumour using the 4DCT images. The planning target volume was generated by a uniform 5-mm expansion. With the median dose prescription of 55 Gy (45–60 Gy) in 3 or 5 daily fractions, constraints to the organs at risk were as follows: bowel structures (stomach, duodenum and intestine), maximum point dose of 32 Gy and a 10-cm³ constraint of 20 Gy; liver, at least 700 cm³ of normal liver to receive $<$ 21 Gy; kidney, at least 200 cm³ of each kidney to receive $<$ 17.5 Gy; and spinal cord, maximum dose of 20 Gy. Image guidance was performed prior to each radiation fraction with a precision of $\pm$ 3 mm.

CHOLANGIOCARCINOMA—BRACHYTHERAPY

With the addition of ILBT to external radiotherapy in the adjuvant setting, no significant benefit has been reported in HCCA.⁵ However, in the case of R1 resection, a combination adjuvant therapy with EBRT plus ILBT has been shown to provide a comparable survival as in patients with R0 resection in HCCA.⁵⁸ As brachytherapy allows a rapid dose fall-off, a localized coverage of the gross tumour area can be achieved with the sparing of surrounding tissues. Hence, a higher dose to the tumour can be attained without an increase in morbidity. A study from the Japanese Radiation Oncology Study Group⁵⁹ assessed unresectable BTCs treated with EBRT + ILBT *vs* EBRT alone. The combination treatment was given as EBRT 50 Gy in 1.8–2.0 Gy per fraction with percutaneous transhepatic cholangiography-guided ¹⁹²Ir high-dose rate (HDR)-ILBT dose of 18 Gy (6 Gy per fraction). The ILBT dose was prescribed at 1.0 cm from the centre of the source in the majority of patients. A 2-year local control with EBRT + ILBT *vs* EBRT alone was 65% *vs* 35%, respectively. However, there was no difference in 2-year disease-specific survival (42% *vs* 41%). Similar results of improved local control with the addition of ILBT boost have been reported from other institutions.⁴ With the addition of brachytherapy in neoadjuvant CRT protocol prior to LT, no differences in the recurrence rates have been observed.³⁰

Mattiucci *et al*⁶⁰ conducted a Phase I study for determining the dose of ¹⁹²Ir HDR-ILBT as a palliative treatment for EHCC. The patients underwent endoscopic retrograde cholangiopancreatography-guided metallic stenting followed by ILBT. One or two catheters were inserted, and a daily dose fraction of 5 Gy was delivered. A maximum tolerated dose of 25 Gy in five fractions was reached. Stenting in combination with ILBT has been shown to provide a longer stent patency and survival in patients with malignant biliary obstruction.^{61,62}

Chen *et al*⁶² treated patients with malignant obstruction with percutaneous transhepatic biliary drainage followed by stenting ($n = 20$) or combined with HDR-ILBT through an external–internal drainage catheter within 1–3 weeks of stenting ($n = 14$). The schedule for HDR-ILBT was 3–4 sessions of 4–7 Gy each at an interval of 3–6 days covering the stricture with a margin of 1.0 cm proximally and distally. The dose was prescribed at 0.5–1.0 cm from the source axis. ILBT resulted in a longer stent patency. A prospective pilot study on ILBT from India⁶³ treated

18 inoperable patients with malignant biliary obstruction. Percutaneous transhepatic biliary drainage was performed followed by internal–external drainage. After an interval of 1 week, two sessions of HDR-ILBT with a dose of 8 Gy, each 1 week apart were delivered. The patients had good symptom relief in pruritus and icterus with a significant improvement in the quality of life. Another ILBT technique with an endoscopically inserted catheter *via* a nasobiliary tube has been reported by Mukewar et al.⁶⁴ A CT-guided percutaneous brachytherapy has been used as a treatment option for unresectable IHCC.⁶⁵ Anti-tumour activity with ¹²⁵I seeds interstitial brachytherapy has been demonstrated in EHCC cell lines in a study by Lin et al.⁶⁶

Cholangiocarcinoma—radiosensitization with oncolytic viral therapy

Oncolytic herpes simplex virus strains are replication competent which are modified by deletion of certain growth genes to attenuate virulence. An upregulation of gene products whose function is similar to the deleted ones is achieved by radiation, thereby promoting viral replication.⁶⁷ In the study by Jarnagin et al.,⁶⁷ NV1023 virus strain was used and GADD34 protein was upregulated under deoxyribonucleic acid damage caused by low-dose EBRT. As a result, there was synergistic tumouricidal effect in the cholangiocarcinoma cell lines limited to the radiation field. Oncolytic viral therapy offers a potential for enhancement of therapeutic ratio with radiotherapy.

Future directions

The attainment of good locoregional control is crucial in the case of both EHCC and IHCC. There is a need to test sequencing of adjuvant CCRT and chemotherapy in Phase III trials for EHCC and IHCC. Some of the ongoing trials will further elaborate on the role of radiotherapy in cholangiocarcinoma.⁶⁸ A Phase III trial aims to compare adjuvant CRT vs chemotherapy in EHCC and gall bladder cancer (NCT02798510). A prospective study is evaluating induction gemcitabine followed by 5-FU-based CCRT and maintenance capecitabine prior to LT in unresectable

cholangiocarcinoma (NCT00301379). A randomized prospective multicentric study is ongoing with an aim to compare 5-year OS and 3-year RFS between resection vs CCRT followed by LT in HCCA (NCT02232932). A Phase III trial from India is ongoing comparing intensity-modulated radiation therapy with weekly gemcitabine and systemic chemotherapy vs systemic chemotherapy alone in unresectable cholangiocarcinoma (NCT02773485). The 3-year OS, locoregional progression-free survival, toxicity, quality of life, resectability and cause-specific survival will be assessed between the two arms.

CONCLUSIONS

High locoregional disease recurrence rates after surgical resection alone for both EHCC and IHCC provide a rationale for using adjuvant radiotherapy with chemotherapy. Evidence from Phase II trials have demonstrated efficacy of adjuvant CRT in combination with chemotherapy in EHCC. Locally advanced cholangiocarcinoma may be treated with neo-adjuvant chemoradiotherapy. In the case of downsizing, assessment for resection may be considered. Brachytherapy offers dose escalation after external radiotherapy. Selected unresectable cases of cholangiocarcinoma may be considered for ablative radiotherapy with neoadjuvant and/or concurrent chemotherapy. LT is a treatment option in selected patients with EHCC and IHCC after neoadjuvant CRT. Stenting in combination with palliative external radiotherapy and/or brachytherapy provides improved stent patency and survival. Newer advanced radiation techniques provide a scope for achieving better disease control with reduced morbidity. Effective multimodality treatment incorporating radiotherapy is the way forward for improving survival in patients with cholangiocarcinoma.

ACKNOWLEDGMENTS

The authors thank Dr TK Chattopadhyay, Senior Professor, HPB Surgery, Institute of Liver and Biliary Sciences, India, for providing inputs in writing this article.

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