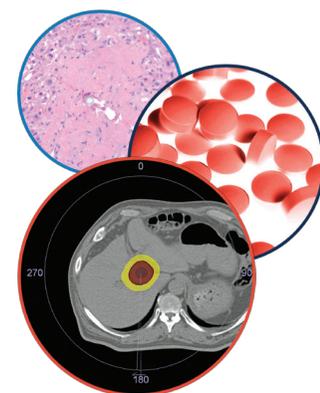


## REVIEW

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# Locoregional therapies in cholangiocarcinoma



## Hepatic Oncology

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### Practice points

- Palliative endoscopic biliary stenting for malignant biliary obstruction improves survival, but routine biliary drainage prior to curative-intent surgery increases the rate of complications.
- Radiofrequency ablation is a thermal ablative technique that can improve biliary drainage in malignant biliary obstruction, either as a primary treatment or to treat tumor ingrowth in uncovered metal stents. However, prospective data supporting its efficacy are lacking.
- Microwave ablation and irreversible electroporation are alternative ablative techniques that may allow for treatment of unresectable intrahepatic cholangiocarcinomas that lie near to essential biliary or vascular structures, although prospective data are needed to assess their efficacy.
- Photodynamic therapy can maintain biliary patency in the palliation of cholangiocarcinoma and may improve progression-free survival, although there is a paucity of high-quality data to support its use.
- There is evidence that hepatic artery-based therapies (selective internal radiotherapy, hepatic artery infusion and transarterial chemoembolization) can provide local tumor control. Although current guidelines do not recommend their routine use, they acknowledge that radiotherapy and selective internal radiotherapy may be considered after first line chemotherapy.
- Evidence for the use of external beam radiotherapy with conventional fractionation, with or without concomitant chemotherapy, is conflicting and largely limited to retrospective analyses. Brachytherapy has been used in multimodal neoadjuvant chemoradiotherapy regimens prior to liver transplantation for unresectable perihilar cholangiocarcinoma, with encouraging long term survival rates. There is no established role for palliative brachytherapy.
- Stereotactic body radiotherapy and proton beam therapy allow for higher doses of radiation to be given while limiting radiation damage to surrounding normal tissue; early phase trials have shown promising results.
- Patients should be encouraged to participate in clinical trials investigating the efficacy of locoregional therapies in cholangiocarcinoma to provide evidence for their use.

Cholangiocarcinoma is a rare and aggressive malignancy of the biliary tract. Complete surgical resection can be curative, but the majority of patients are diagnosed with advanced disease and usually die within a year of diagnosis. Most deaths are attributable to local disease progression rather than distant metastases, supporting the use of locoregional therapies. There is evidence that locoregional therapies can provide local tumor control resulting in increased survival while avoiding some of the side effects of systemic treatments, increasing potential treatment options for patients who may be unsuitable for systemic palliative treatments. This review considers the evidence for locoregional therapies in cholangiocarcinoma, which can be classified into endoscopic, vascular, percutaneous and radiation oncological therapies. Current guidelines do not recommend the routine use of locoregional therapies due to a lack of prospective data, but the results of ongoing trials are likely to increase the evidence base and impact on clinical practice.

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- therapeutic

Cholangiocarcinomas are bile duct tumors arising from biliary tree epithelia [1]. They are classified as intrahepatic, perihilar or distal extrahepatic based on their position along the biliary tract. Worldwide, the incidence of intrahepatic cholangiocarcinoma is increasing whereas perihilar and distal extrahepatic cholangiocarcinomas are decreasing [2]. It is usually diagnosed at an advanced stage due to late development of symptoms and aggressive tumor biology [3]. Patients with unresectable disease often die within a year of diagnosis, most commonly from biliary obstruction leading to liver failure or biliary sepsis [4]. Notably, these causes of death are attributable to local disease progression rather than distant metastases and several therapies attempt to improve survival by controlling locoregional progression. This review considers the evidence supporting locoregional therapies for cholangiocarcinoma, which can be classified into endoscopic, vascular, percutaneous and radiation oncological therapies (Figure 1).

**Endoscopic therapies**

- **Biliary stenting**

**Preoperative stenting**

Preoperative stenting involves the insertion of one or more stents into the bile duct to improve biliary drainage prior to surgery. Although animal experiments suggested that preoperative biliary stenting reduced mortality by improving endotoxaemia and nutritional status [5], a randomized controlled trial (RCT) comparing surgery with or without preoperative endoscopic biliary stenting (EBS) in malignant distal biliary obstruction found no mortality reduction, higher rates of serious complications (74 vs 39%) and more frequent hospital readmissions with preoperative EBS [6]. A subsequent cochrane review did not recommend their routine use [7]. Although there are no RCTs assessing preoperative EBS in hilar strictures, a systematic review and meta-analysis (SRMA; 11 nonrandomized studies, n = 711) found no survival benefit from preoperative EBS with an increased risk of postoperative complications [8]. However, preoperative EBS is necessary in certain circumstances, including acute cholangitis (most commonly secondary to contrast injection during Endoscopic Retrograde Cholangiopancreatography (ERCP)), severe jaundice and before starting neoadjuvant treatment [5,9,10]. In these circumstances, covered self-expanding metal stents (SEMS) are superior to plastic stents. An SRMA (five studies,

n = 704) found reduced re-intervention rates (3.4 vs 14.8%) and pancreatic fistulae (5.1 vs 11.8%) with SEMS for distal biliary obstruction, although none of the cohort had cholangiocarcinoma [11]. A small retrospective analysis (n = 27) found a reduced failure rate from SEMS for preoperative stenting of the future liver remnant in perihilar cholangiocarcinoma (0/10 SEMS vs 7/17 plastic stents), although the authors acknowledged limitations of the study design for assessing superiority [12].

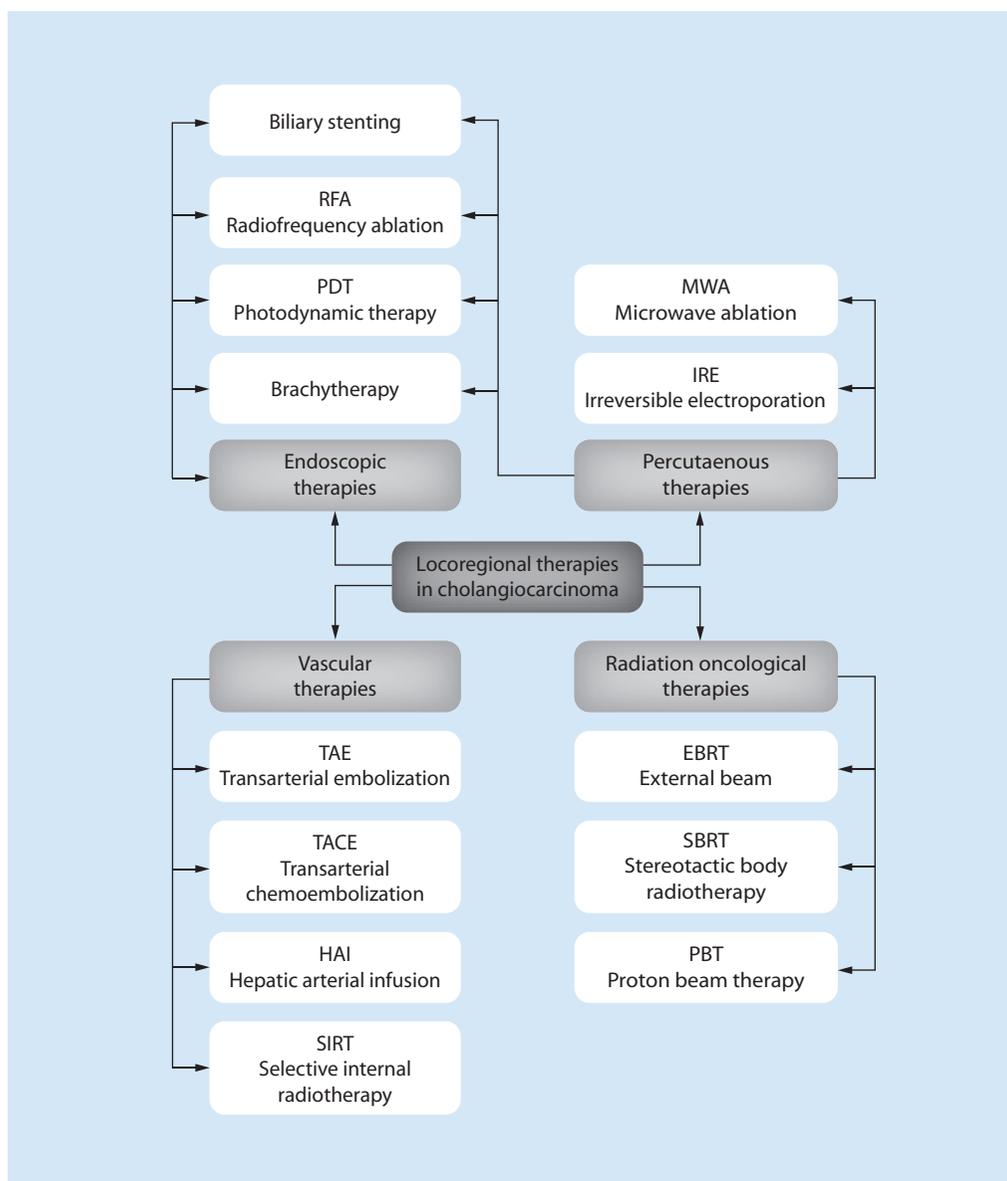
**Palliative stenting**

The technique for palliative stenting is the same as preoperative stenting and is used to improve biliary drainage and prevent death from liver failure or biliary sepsis. In patients with a life expectancy of more than 4 months, SEMS are superior to plastic stents [13]. Two recent SRMAs comparing SEMS and plastic stents (11 retrospective and prospective studies, n = 947 and 20 RCTs, n = 1713, respectively) found SEMS to be associated with longer stent patency, lower re-intervention rates and lower rates of cholangitis [14,15].

Tumor ingrowth in uncovered SEMS can lead to recurrent biliary obstruction. An SRMA (14 RCTs, n = 1417) comparing covered versus uncovered SEMS found no significant difference in time to stent blockage/dysfunction or overall survival (OS), although the cause of stent blockage (tumor ingrowth in uncovered SEMS vs tumor overgrowth in covered SEMS) was significantly different [16]. Covered SEMS were also more likely to migrate. However, subgroup analysis in another SRMA found uncovered SEMS to be associated with a higher OS [15].

There is conflicting evidence for the use of bilateral stents in unresectable hilar cholangiocarcinoma. A review in 2013 identified two RCTs and four retrospective studies comparing unilateral versus bilateral stents [17]. Although three studies advocated unilateral stenting and three advocated bilateral stenting, both RCTs recommended unilateral stenting. As draining 25–30% of liver volume is considered adequate for the resolution of obstructive jaundice in most patients, bilateral stenting is unlikely to provide a significant benefit in most patients [17]. However, bilateral stenting is required if jaundice does not improve with unilateral drainage or there is sepsis within the contralateral lobe.

Endoscopic ultrasound-guided biliary drainage is an alternative endoscopic technique for patients who have failed or have



**Figure 1. Locoregional therapies in cholangiocarcinoma.**

contraindications to EBS and percutaneous drainage. A stent can be placed transduodenally or by forming a hepaticogastrostomy [18]. An SRMA (42 studies,  $n = 1192$ ) found this technique to have a 94.7% technical success rate and 91.7% functional success rate but a complication rate of 23.3% [19]. Complications include bleeding (4%), bile leak (4%), pneumoperitoneum (3%) and stent migration (<3%).

#### • Radiofrequency ablation

Radiofrequency ablation (RFA) involves the passage of an electrical probe into the biliary tree to the site of the tumor, creating a therapeutic

heating zone causing coagulative necrosis [20]. Endoscopic RFA can be used palliatively either as a primary treatment to resolve obstructive jaundice or to treat tumor ingrowth in uncovered SEMs, although there are no published RCTs on its use. A recent SMRA (nine studies,  $n = 263$ , 173 with cholangiocarcinoma) reported a technical success rate of 96.8%, a mean bile duct diameter increase of 3.5 mm and a median stent patency duration of 7.6 months [21]. The pooled adverse event rate was 17%, the most common complications being pain (11%), cholangitis (8%) and cholecystitis (4%). Three patients had late-onset biliary bleeding, two of whom

died [22]. Pooled 30-day, 90-day and 2-year mortality was 1.5, 20.9 and 48.1%, respectively. A retrospective matched cohort study (n = 66, 36 with cholangiocarcinoma) comparing stenting with or without RFA found age, chemotherapy and RFA to be predictors of survival on multivariable Cox proportional hazard analysis (p = 0.012) [23]. RCTs are required to provide higher quality evidence of the efficacy of RFA in cholangiocarcinoma.

• **Photodynamic therapy**

Photodynamic therapy (PDT) is an ablative technique involving intravenous administration of a photosensitizing agent followed by intraluminal laser irradiation [24]. An SRMA (10 studies, n = 402) comparing PDT (percutaneous or endoscopic) versus stenting alone in unresectable cholangiocarcinoma found a significant increase in OS with PDT (413 vs 183 days) with no significant difference in rates of cholangitis, although 10.5% of PDT patients had photosensitivity reactions [25]. This SRMA did not include an RCT comparing EBS versus EBS with PDT that was stopped due to worse OS in the PDT group (5.6 vs 8.5 months) [26]. A recent RCT (n = 20) comparing chemotherapy with EBS versus chemotherapy with EBS and PDT found longer median progression-free survival (PFS) in the group having PDT [27].

• **Brachytherapy**

Intraluminal brachytherapy involves the insertion of Iridium-192 wires percutaneously or endoscopically. It has been used as part of neoadjuvant chemoradiotherapy regimes prior to orthotopic liver transplantation (OLT) for unresectable perihilar cholangiocarcinoma, but is more commonly used in the palliative setting [28,29]. A recent retrospective analysis using the US surveillance, epidemiology and end results (SEER) database compared external beam radiotherapy (EBRT; n = 1188) versus EBRT with brachytherapy (n = 91) [30]. After excluding patients with metastatic disease, there was only a trend toward improved survival with the addition of brachytherapy to EBRT (10 vs 13 months, p = 0.08). The most recent prospective study (2007, n = 42) comparing percutaneous SEMS versus percutaneous SEMS with intraluminal brachytherapy found survival to be higher with the addition of brachytherapy (298 vs 388 days, p < 0.05) [31]. Based on these promising results, further prospective trials are warranted.

**Vascular therapies**

A number of therapies are delivered to the tumor via the hepatic artery to provide local tumor control: hepatic artery embolization, selective internal radiotherapy, hepatic artery infusion and transarterial chemoembolization (TACE).

• **Hepatic artery embolization**

Hepatic artery embolization (HAE), also known as transarterial embolization, causes tissue hypoxia by infusing the hepatic arterial supply of the tumor with an embolic agent. Although HAE is infrequently used compared with TACE, there is little evidence to support the superiority of TACE over HAE in cholangiocarcinoma. In a multi-institutional retrospective analysis (n = 198), only 13 patients (6.6%) underwent HAE compared with TACE (70.2%) or selective internal radiotherapy (SIRT) (23.2%) [32]. There was no significant difference in survival based on the treatment type (median OS of 13.4, 14.3 and 11.3 months for TACE, HAE and SIRT respectively), although no subgroup analysis on complication rates or tumor responses between the different treatments was reported.

• **Selective internal radiotherapy**

SIRT, also known as transarterial radio-embolization, is arterially delivered brachytherapy involving infusion of <sup>90</sup>yttrium resin or glass microspheres into the tumor's blood supply resulting in mechanical embolization of the tumor vasculature and local delivery of radiation. A recent review identified eight studies (2008–2016) with data on outcomes following SIRT for intrahepatic cholangiocarcinoma [33]. Median survival ranged from 4.4 to 52 months, although many patients had also undergone prior chemotherapy making interpretation of survival data difficult [34–39]. A recent systematic review and pooled analysis (12 studies, n = 298) found SIRT to provide partial tumor responses in 28% and stable disease in 54% of patients 3 months post-treatment, although heterogeneity in study designs precluded a meta-analysis [40]. Factors predictive of a better response include Eastern Cooperative Oncology Group performance status 0, no portal vein thrombosis, peripheral rather than infiltrative tumors and a tumor burden <25% of total liver volume [34–36]. Although post-radioembolization syndrome is usually mild and self-limiting, reported grade III/IV side effects include hepatic enzyme dysfunction and rarely gut ischemia or

peptic ulceration secondary to inadvertent delivery of microspheres into vessels supplying the gastrointestinal tract [33].

#### • Hepatic artery infusion

Hepatic artery infusion (HAI), also known as transarterial chemoinfusion, involves the radiological or surgical placement of an arterial catheter attached to an infusion pump allowing for the delivery of chemotherapeutic agents directly to the tumor [41]. A recent review identified 11 studies (2002–2015) investigating the use of HAI (n = 299, 232 with cholangiocarcinoma) [42]. Complete or partial responses were seen in 7.5–66.6%, stable disease in 18.2–64% and conversion to resectability in 3.8–27.3%. Median OS ranged from 4.2 to 31.1 months with reported minor and major complications of 0–100% and 0–13%, respectively [43–53]. A Phase II trial investigating the use of HAI in 37 patients with perihilar cholangiocarcinoma found complete and partial tumor responses in six patients (16.2%) and 19 patients (51.4%), respectively [54]. Median PFS was 12.2 months and median OS was 20.5 months. Patients were more likely to respond to treatment if they had periductal-infiltrating rather than mass-forming tumors (complete or partial response in 82.6 vs 42.9%, 1 year OS 82.4 vs 21.4%).

#### • TACE

Conventional TACE (cTACE) involves injection of chemotherapeutic agents followed by embolization of the tumor microcirculation with foam or microspheres. Drug-eluting bead TACE (DEB-TACE) uses embolizing beads loaded with chemotherapeutic agents, and degradable starch microsphere TACE (DSM-TACE) is similar to DEB-TACE but with rapid degradation (25–40 min) of the microspheres after administration [55]. A recent systematic review (nine studies, n = 421) reported on the utility of cTACE in the treatment of inoperable intrahepatic cholangiocarcinoma [56]. Median OS from diagnosis and from procedure ranged from 12 to 25.2 months and 9.1 to 16.3 months, respectively. Three studies showed a significant survival benefit compared with patients receiving best supportive care alone [56]. Major complications included myocardial infarction, pulmonary edema/infarction, hematological and liver toxicities, hepatic artery dissection, anaphylaxis and one reported death. The same review also identified five studies (n = 83) reporting on

the use of DEB-TACE in cholangiocarcinoma. Median OS from procedure ranged from 11.7 to 17.5 months respectively, similar to the OS reported for cTACE.

A meta-analysis in 2013 (16 studies, n = 542) reported on the imaging responses, complications and OS following hepatic artery-based therapies (cTACE, DEB-TACE, DSM-TACE and HAI) for unresectable intrahepatic cholangiocarcinoma [57]. Weighted median OS from diagnosis and from procedure was 15.7 and 13.4 months, respectively. Tumor responses (based on RECIST criteria) were complete in 1.6%, partial in 21.2%, stable in 53.9% and progressive in 23.2%. Grade III/IV complications occurred in 18.9% of patients, with a 30-day mortality of 0.7%. However, the meta-analysis did not directly compare the different therapies and there was no comment on conversion to resectability.

There are no RCTs directly comparing the vascular therapies TACE, SIRT and HAI. An SRMA in 2015 (20 studies, n = 657) found median OS to be greatest for HAI (22.8 months) followed by SIRT (13.9 months) and cTACE/DEB-TACE (12.4 and 12.3 months, respectively) [58]. Response to therapy (complete or partial) was also highest with HAI (HAI 56.9%, SIRT 27.4% and TACE 17.3%). However, the rate of grade III/IV complications was also highest following HAI (0.35, 0.32 and 0.26 events per patient for HAI, DEB-TACE and cTACE, respectively). This may be due to an altered risk profile leading to selection bias (HAI requires surgical or radiological implantation of a pump or port, whereas the other modalities do not).

### Percutaneous therapies

#### • Biliary stenting, radiofrequency ablation, photodynamic therapy & brachytherapy

Stenting, RFA, PDT and brachytherapy can all be performed percutaneously as well as endoscopically. Two retrospective studies (n = 169) reported fewer infectious complications from preoperative percutaneous biliary drainage for perihilar cholangiocarcinoma (65 vs 10.4% and 48 vs 9%) [59,60] which has led to the DRAINAGE RCT comparing percutaneous stenting with EBS (currently recruiting) [61]. There is no evidence for the superiority of percutaneous versus endoscopic RFA in cholangiocarcinoma, although no RCTs have been performed to date [62]. A recent retrospective study (n = 37) found that although there was no difference

in OS, patients having percutaneous PDT for unresectable perihilar cholangiocarcinoma had longer hospital admissions than those having endoscopic PDT (37 vs 63 days) [63]. There are no published studies comparing percutaneous versus endoscopic intraluminal brachytherapy.

#### • Microwave ablation

Microwave ablation (MWA) is a thermal ablative technique that generates heat by creating an electromagnetic field [64]. Few articles have been published on its use in cholangiocarcinoma. Yu *et al.* published the first series of 15 patients with 24 histologically proven inoperable intrahepatic cholangiocarcinomas treated with ultrasound-guided percutaneous MWA [65]. They reported a technical success rate of 91.7% and a median OS after treatment of 10 months, although an undetermined number of patients went on to have other local or systemic treatments. Complications included two liver abscesses, one patient with needle-track tumor seeding and one patient with subcapsular bleeding. A similar trial used either RFA or MWA to treat 18 patients with histologically proven intrahepatic cholangiocarcinoma (eight primary and ten postoperative recurrences) [66]. In the six patients undergoing MWA (all with solitary nodules), median OS was 13.5 months with three patients surviving more than 5 years.

Yang *et al.* published a retrospective study investigating the safety and efficacy of percutaneous MWA with simultaneous TACE in patients with advanced or recurrent intrahepatic cholangiocarcinoma ( $n = 26$ , 39 tumors) [67]. Thirty-six tumors were completely ablated on follow-up imaging (92.3%). Median PFS and OS from treatment was 6.2 and 19.5 months respectively with a 2-year OS of 61.5%. No major complications occurred, with fever (88.5%), pain (84.6%) and thrombocytopenia (11.5%) being the most common minor complications. These encouraging results warrant RCTs comparing MWA versus MWA with TACE, as well as studies comparing MWA with other thermal ablative techniques such as RFA.

#### • Irreversible electroporation

Irreversible electroporation is a nonthermal ablative technique that uses pulsed electrical current to induce cellular apoptosis without disrupting the surrounding extracellular matrix, preventing damage to nearby vascular and biliary structures [68]. Data pertaining to

its use in cholangiocarcinoma are limited. An SRMA this year (nine studies,  $n = 300$ , 21 cases being cholangiocarcinoma) found a significant reduction in tumor diameter (standardized mean difference 0.447, 95% CI: 0.189–0.704) with transient rises in liver enzymes associated with the procedure [69]. There were seven major complications reported; four hepatic abscesses, one bile duct dilatation, one cardiac arrhythmia and one portal vein thrombosis. Survival data were not reported and the current data should be considered preliminary and experimental.

### Radiation oncological therapies

#### • External beam radiotherapy

The role of conventionally fractionated adjuvant radiotherapy remains unestablished. A recent retrospective analysis from the US National Cancer Database examined the effect on survival of postoperative radiotherapy for intrahepatic cholangiocarcinoma ( $n = 2897$ , 525 having had radiotherapy) [70]. Although there was a trend toward improved survival following radiotherapy in patients with negative lymph nodes but positive (R1/R2) resection margins, this disappeared after adjusting for other clinicopathological factors ( $p = 0.923$ ). The authors concluded that radiotherapy should not be routinely administered postoperatively. A systematic review in 2015 identified three retrospective analyses, one SRMA, two SEER studies and one prospective study investigating the role of adjuvant radiotherapy in cholangiocarcinoma [71]. Two of the retrospective analyses found higher 5-year OS following EBRT in perihilar cholangiocarcinoma versus resection alone (33.9 vs 13.5% and 19 vs 11%) and the SRMA (seven studies) found adjuvant radiotherapy to improve survival in extrahepatic cholangiocarcinoma (pooled hazard ratio 0.62, 95% CI: 0.48–0.78,  $p < 0.001$ ) [72–74]. The third analysis, although finding no increase in OS, found an improvement in disease-free survival favoring postoperative radiotherapy in patients with positive resection margins (5-year disease-free survival 13.9 vs 4.1%,  $p = 0.042$ ) [75]. However, this could be due to the small number (<10) of 5-year survivors and may not represent a true difference. In the two SEER analyses, one found adjuvant radiotherapy to increase OS in intrahepatic cholangiocarcinoma (median OS 6 vs 11 months,  $p = 0.014$ ,  $n = 1234$ ) whereas the other found no effect in extrahepatic cholangiocarcinoma (18 vs 18 months,  $p = 0.8$ ,

n = 1491) [76,77]. This may be due to patient selection bias, challenges in delivering higher radiation doses to extrahepatic tumors, or the unclear inclusion or exclusion of perihilar tumors in the latter study. A prospective study of EBRT to 50 patients with locally advanced perihilar cholangiocarcinoma found no survival benefit from the addition of radiotherapy (median OS 20 vs 20 in resected patients and 8 vs 12.5 months in palliated patients) [78].

Palliative radiotherapy is not widely used in cholangiocarcinoma. One SEER analysis (n = 2685) found palliative radiotherapy to be superior to no treatment in extrahepatic cholangiocarcinoma (9 vs 4 months) [79]. However, data on chemotherapy were not available making interpretation of the results difficult.

#### • Stereotactic body radiotherapy

Stereotactic body radiotherapy (SBRT) involves highly localized external beam radiotherapy with a high dose per fraction; typically 3–5 fractions of radiotherapy delivered over 2 weeks [80]. Because a much smaller margin of normal tissue is irradiated due to its specific targeting, higher doses of radiation can be delivered while limiting damage to surrounding normal tissue. Evidence for its use in cholangiocarcinoma is restricted to retrospective single institution studies. Jung *et al.* reported outcomes in patients with unresectable primary or recurrent postoperative intrahepatic cholangiocarcinoma treated with SBRT (n = 53) or conventional EBRT plus SBRT boost (n = 5) and found a median OS of 10 months [81]. Grade I/II complications occurred in 29% and grade III/IV complications in 10% with one mortality from gastric perforation. Mahadevan *et al.* used SBRT in 32 patients with unresectable or recurrent intrahepatic or perihilar cholangiocarcinoma and found SBRT to be associated with a median OS of 17 months [82]. Sandler *et al.* recently reported on the use of SBRT as a neoadjuvant therapy prior to OLT for unresectable intrahepatic or perihilar cholangiocarcinoma (n = 31) [83]. Of the 18 patients in the neoadjuvant subgroup, 14 were listed for OLT, of whom four patients underwent OLT and a fifth patient underwent surgical resection. Median OS was significantly higher in the five patients who underwent OLT or surgery (31.3 vs 12.7 months), with duodenal stricture/obstruction or hemorrhage being the most common major complications.

#### • Proton beam therapy

Instead of photon waves in EBRT, proton beam therapy (PBT) uses charged particles to deliver radiotherapy for greater dose conformation to the target volume. Like SBRT, this results in significantly reduced doses to surrounding tissues [84]. A retrospective analysis in 28 patients with new or recurrent inoperable cholangiocarcinoma undergoing PBT reported 1-year PFS and OS of 29.5 and 49%, respectively [85]. However, toxicities were common; 29 grade I, 16 grade II and eight grade III toxicities were reported. Grade III toxicities included duodenal ulceration/hemorrhage/stenosis, cholangitis and biliary stenosis. A prospective multicenter Phase II study of PBT (n = 83, 44 having cholangiocarcinoma) found a median PFS of 8.4 months and median OS of 22.5 months in the cholangiocarcinoma subgroup [86]. A similar study using curative-intent (n = 12) or palliative PBT (n = 8) for unresectable intrahepatic cholangiocarcinoma found curative-intent PBT achieved a median OS of 27.5 months with 1-year local disease control achieved in 88% [87].

#### Future perspective

Several prospective clinical trials are currently underway to try to establish the role of various locoregional therapies in cholangiocarcinoma, and the results of these may influence future use. Examples include the SIRCCA trial (chemotherapy ± SIRT), the DELTIC trial (chemotherapy ± DEB-TACE) and ABC-07 (chemotherapy ± SBRT). Due to the rarity of cholangiocarcinoma, a move away from RCTs and toward novel trial designs such as adaptive clinical trials or umbrella studies may allow for the simultaneous assessment of multiple therapies or treatment schedules, allowing for earlier identification of effective therapies. Novel trial design is especially important as the future management of advanced cholangiocarcinoma is likely to be multimodal and involve combined therapies, such as the combination of MWA and TACE by Yang *et al.* [67]. Exciting developments in nanomedicine may also augment existing therapies. For example, Spring *et al.* recently developed a nanoliposome containing a photosensitizer and a multikinase inhibitor that could be activated by near infrared light to provide simultaneous PDT and local release of biological agents [88]. Such treatments that exert their effects through

different mechanisms may provide patients with improved locoregional control and subsequent improved survival.

### Guidelines & conclusion

Due to a lack of prospective data and RCTs on the majority of locoregional therapies, recommendations for their use in guidelines are limited. The British Society of Gastroenterology cholangiocarcinoma guidelines (2012) did not recommend the use of PDT based on available data [9]. The International Liver Cancer Association guidelines (2014) did not recommend EBRT or HAI in the treatment of unresectable intrahepatic cholangiocarcinoma based on current evidence [89]. TACE, SIRT and RFA were acknowledged to provide some local tumor control, but could not be recommended as standard therapy until further clinical trials demonstrated their efficacy. The European Society of Medical Oncology guidelines (2016) state that radiotherapy and SIRT may be considered after first line chemotherapy [90]. Patients should be encouraged to participate in clinical trials investigating locoregional therapies to provide better evidence for their use. Trials should also not only focus on survival as a primary outcome but also on quality of life as a vital part of assessing the efficacy of any treatment. The results of several

ongoing trials will provide evidence for the use of locoregional therapies in the palliation of cholangiocarcinoma.

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