External Beam Radiation Therapy: 3D-Conformal, Intensity-Modulated, and Proton Beam

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Contents

Abstract

Radiation plays an important role in the treatment for gallbladder and biliary tract cancers. In the adjuvant setting, the goal of radiation is to provide local disease control and, by doing so, slow overall disease progression and prolong survival. Furthermore, local control is critical because of the morbidity of local progression in the biliary tract. Thus, radiation may help prevent or palliate symptomatic or uncontrolled local disease in both the adjuvant and unresectable settings. Historically, radiation has had a limited role in these malignancies. This was primarily related to the concern about radiation injury to organs at risk (OARs). With a better understanding of dose tolerances of OARs and improved conformality of treatment modalities, radiation has become more widely used.

1 Rationale for Radiotherapy

Several reports have examined the impact of radiation therapy on either the adjuvant or unresectable setting. Both external beam radiation therapy (EBRT) and, to a lesser degree, brachytherapy and intraoperative radiation therapy (IORT) were used in these series. The majority of the studies are retrospective, but several have comparison cohorts of patients who did not receive radiation. In the adjuvant series, the extent of resection (complete vs. partial) was variable. Neoadjuvant radiotherapy has been limited to unresectable disease prior to liver transplantation.

1.1 Adjuvant Radiotherapy

In 2012, a systemic review and meta-analysis of adjuvant therapy in biliary tract cancer presented data on twenty studies between 1960 and 2010 involving 6,712 patients with gallbladder and biliary tract tumors [1]. The vast majority of studies (19 of 20) in this meta-analysis did not

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Table 1 Adjuvant radiotherapy or chemoradiotherapy for extrahepatic cholangiocarcinoma

Study	No. of patients	R0 (%)	Radiotherapy	Chemotherapy	Locoregional failure (%)	Median survival (months)	*P* value
Kim et al. [29]	72	65	EBRT 40 Gy (split course, in 6 weeks)	Bolus 5-FU	47	25	–
Todoroki et al. [2]	29	4	IORT 21 Gy, EBRT 43 Gy, or the combination	None	21	32	0.01
	20		No radiation	None	69	10	
Schoenthaler et al. [28]	6	0	EBRT 54 Gy, 1.8 Gy/fraction	None	–	21.5	0.01
	15	60	No radiation	None		16	
Sagawa et al. [5]	39	49	EBRT 37 Gy + ILBT 37 Gy or EBRT 38 Gy	None	–	23	NS
	30		No radiation	None		20	
Gerhards et al. [3]	71	14	EBRT 46 Gy or EBRT 42 Gy + ILBT 10 Gy	None	–	24	<0.01
	20		No radiation	None		8	
Pitt et al. [49]	14	68	EBRT ± Ir-192 13 Gy	None	–	20	NS
	17		No radiation	None		20	
Nakeeb et al. [50]	42	75	EBRT (no details)	Bolus and CI 5-FU; gemcitabine	–	16.4	–
Ben-David et al. [12]	28	43	EBRT 54 Gy (median)	54 % of patients; 5-FU, gemcitabine, floxuridine, bromodeoxyuridine	39	24.1 (R0); 15 (R1)	–
Kim et al. [4]	115	78	EBRT 45 Gy (median), 1.8 Gy/fraction	Concurrent 5-FU-based chemo	41.5	36.4	0.007 (LRF); 0.049 (OS)
	53	38	No radiation	None	55.6	27.9	–
Nelson et al. [31]	45	80	EBRT 50.4 Gy (median); ILBT (4 patients)	5-FU-based	22	34	–
Hughes et al. [30]	34	24	EBRT 50.4 Gy (median), 1.8 Gy/fraction	5-FU-based	30	36.9	–

EBRT external beam radiation therapy; *IORT* intraoperative radiation therapy; *ILBT* intraluminal brachytherapy; *5-FU* 5-fluorouracil; *OS* overall survival; *LRF* locoregional failure; *NS* not significant; *CI* continuous infusion

include intrahepatic cholangiocarcinoma. Adjuvant therapy, which included chemotherapy, radiation, and chemoradiation, was associated with a borderline significant improvement in survival ($p = 0.06$). In patients who had undergone R1 resections, adjuvant radiation had a survival benefit ($p = 0.01$). The authors concluded that radiation therapy should be administered in margin-positive disease, but that the benefit after R0 resection was unclear.

Extrahepatic Cholangiocarcinoma The majority of the literature on radiation in cancers of the gallbladder and biliary tract is focused on adjuvant therapy for extrahepatic cholangiocarcinoma. In these studies, median survival is approximately 2 years (Table 1). Radiation was administered to the tumor bed and draining lymph nodes (see Target Definition) at a dose of 37–54 Gy in 1.8 Gy per fraction, sometimes in combination with intraoperative radiation or brachytherapy to total doses approaching 60 Gy.

Todoroki et al. [2] published a retrospective analysis of 63 patients who underwent resection of Klatskin tumors between 1976 and 1999. Forty-nine patients had R0 or R1 resections, of which 29 were treated adjuvantly with IORT, EBRT, or a combination. The 5-year survival was 33.9 % in the cohort that was treated with adjuvant radiation and 13.5 % in those who were observed ($p < 0.01$). Patients who had a combination of EBRT and IORT had better survival than those treated with either modality alone. Locoregional failure was diminished in the group that received adjuvant radiation: 20 % compared to 69 %. Initially, high toxicity rates were seen in the IORT group thought to be related to large single electron doses. These toxicities diminished after dose adjustment.

Likewise, a 2003 study by Gerhards et al. [3] suggested a survival benefit with adjuvant radiation. Ninety-one patients underwent mostly margin-positive surgical resection (86 %)

for hilar cholangiocarcinoma, of which 71 received EBRT, intraluminal radiation, or a combination. The median survival for those that received radiation was 24 months, compared to 8 months in those observed ($p < 0.01$).

Most recently, Kim et al. [4] reported on 168 patients with extrahepatic biliary tract cancer who underwent resection between 2001 and 2009, of which approximately 70 % were margin negative. Postoperative chemoradiation with EBRT and concurrent 5-fluorouracil-based chemotherapy was administered to 115 of 168 patients. After a median follow-up of 33.8 months, the median survival was 36.4 months in the adjuvant treatment group, versus 27.9 months in the observation group, which was statistically significant on univariate analysis ($p = 0.049$) and multivariate analysis ($p = 0.005$). Likewise, locoregional failure was lower in the adjuvant treatment group on univariate analysis (41.5 vs. 55.6 %, $p = 0.007$) and multivariate analysis ($p = 0.001$). Other significant poor prognostic indicators on multivariate analysis included perineural invasion, vascular invasion, poor differentiation on histology, and positive resection margin.

Other series, however, were more equivocal in regard to benefit of adjuvant radiation therapy. Sagawa et al. [5], who reported on patients with hilar cholangiocarcinoma who underwent surgical resection, did not reveal an overall survival benefit in a subset that received adjuvant radiation. Of the 69 patients reported, approximately 50 % had R0 resections. Thirty-nine patients received EBRT with or without brachytherapy, and the others were observed. After a median follow-up of 32 months, 3-year survival was 40.9 % in the adjuvant therapy group compared to 33.3 % with surgery alone ($p = 0.554$).

Population studies have not demonstrated a clear benefit from adjuvant radiotherapy. In a Surveillance, Epidemiology and End Results (SEER) analysis by Shinohara et al. [6], 4,758 patients with extrahepatic cholangiocarcinomas treated with surgery or radiation between 1998 and 2003 were assessed for overall survival. Of these patients, 28.8 % underwent surgery alone, and 14.7 % underwent surgery and radiation therapy. Although the median survival was 16 months in the surgery and radiation group compared to 9 months with surgery alone ($p < 0.0001$), this did not hold after adjusting for potential confounders. A similar SEER analysis of patients with resected extrahepatic cholangiocarcinoma, which excluded patients with less than 3 months of follow-up, demonstrated no benefit from adjuvant radiation in local or locally advanced disease [7].

Gallbladder Cancer In the case of gallbladder cancer, there are fewer studies of adjuvant radiotherapy (Table 2). Like studies in extrahepatic cholangiocarcinoma, median survival in the majority of studies was approximately 2 years. Balachandran et al. [8] published a report on 117 patients with gallbladder cancer, of which only 37 underwent extended resections. Of the 117 patients, 73 received adjuvant chemoradiotherapy. Although no details were given regarding adjuvant chemoradiotherapy, the median survival for the adjuvant treatment group was 24 months compared to 11 months in the surgery-alone group ($p = 0.001$). Those patients who did not have extended surgical resections or had node-positive or T3 disease appeared to benefit more from adjuvant chemoradiotherapy.

A more recent study by Gold et al. [9] of 73 patients with stage I and II gallbladder cancer who underwent R0 resection reported a median survival approaching 5 years. In the 25 patients that received adjuvant chemoradiotherapy, which involved 50.4 Gy in 1.8 Gy per fraction with concurrent bolus 5-FU, the median survival was 4.8 years (vs. 4.2 years for surgery alone). Although not significant on univariate analysis ($p = 0.56$), overall survival was statistically improved with adjuvant chemoradiation on multivariate analysis, adjusting for T and N stages as well as pathologic diagnosis.

In 2008, Wang et al. [10] described a prediction model for gallbladder cancer using SEER data of 4,180 patients with resected disease, of whom 18 % received adjuvant radiation. In addition to factors such as age, histology, and stage of disease, adjuvant radiation was associated with a significant survival benefit on multivariate analysis. The median survival of those who received radiation therapy was 15 months, versus 8 months in those who did not. In the prediction model, the greatest benefit from adjuvant radiation therapy occurs in patients with T2 or node-positive disease.

1.2 Definitive Radiotherapy

In the series of definitive radiotherapy for unresectable disease, which included patients with gallbladder cancer as well as intrahepatic and extrahepatic cholangiocarcinoma (Table 3), the median survival was approximately 1 year. Although there were no direct comparison cohorts in most series, there was an improvement compared to historical data where the median survival for untreated patients with unresectable cancers of the gallbladder and biliary tract had been only 6–9 months.

Alden and Mohiuddin [11] described 48 patients with extrahepatic cholangiocarcinoma in one of the earliest reports of radiation in the unresectable setting. Of these patients, 24 were treated with radiation therapy (EBRT, brachytherapy, or combination) or chemoradiotherapy, 6 underwent resection, 7 were treated with chemotherapy alone, and 11 were untreated. The median survival of the untreated group and chemotherapy-alone group was 4 and 9 months, respectively. The median survival of the group receiving radiation was 12 months, compared to 5.5 months for the 24 patients that did not receive radiation ($p = 0.01$).

Table 2 Adjuvant radiotherapy or chemoradiotherapy for gallbladder cancer

Study	No. of patients	Radiotherapy	Chemotherapy	Median survival (months)	*P* value
Kresl et al. [32]	21	54 Gy EBRT	5-FU bolus	31.2	–
Czito et al. [51]	22	45 Gy EBRT ± 5.4 to 50 Gy boost (5 patients)	5-FU bolus or CI (82 % of patients)	22.8	–
Balachandran et al. [8]	44	None	None	11	0.001
	73	Yes; no details	Yes; no details	24	
Ben-David et al. [12]	14	54 Gy EBRT	Mostly 5-FU-based (54 % of patients)	23	–
Duffy et al. [52]	16	No details	Mostly 5-FU-based during radiotherapy; 8 received additional systemic therapy	23.4	0.4
	99	None	None	30.3	
Gold et al. [9]	25	50.4 Gy EBRT	5-FU bolus	4.8 years	0.56
	48	None	None	4.2 years	

Table 3 Definitive radiotherapy or chemoradiotherapy for unresectable cholangiocarcinoma

Study	No. of patients	Radiotherapy	Chemotherapy	Median survival (months)
Hayes et al. [53]	14	63.5–108.2 Gy; EBRT + ILBT	None	12.8
Alden and Mohiuddin [11]	24	46 Gy EBRT + 25 ILBT	5-FU ± adriamycin; 5-FU ± mitomycin	12
Morganti et al. [15]	20	39.6–50.4 Gy EBRT ± 30–50 Gy ILBT (12 patients)	5-FU CI days 1–4 in 19 patients	21.2
Shin et al. [54]	31	50.4 Gy EBRT ± 15 Gy ILBT (14 patients)	None	7
Crane et al. [34]	52	30–85 Gy; EBRT ± ILBT	5-FU CI in 38 patients	10
Buskirk et al. [55]	34	45–55 Gy EBRT ± ILBT (20–25 Gy; 10 pts) or IORT (15–20 Gy; 7 patients)	5-FU in 7 patients	12
Urego et al. [37]	34	49.5 Gy (median) EBRT ± ILBT (4 patients)	5-FU + INFa (27 patients)	14
Ben-David et al. [12]	52	23–86.3 Gy (median 60.2 Gy) EBRT	Mostly 5-FU-based	13.1
Habermehl et al. [13]	15	EBRT 45 Gy (median; 25.2–69 Gy); brachytherapy boost in 3 patients	Gemcitabine or FU-based chemotherapy	12.0
Polistina et al. [16]	10	SBRT 30 Gy to 80 % isodose in 3 fractions (CyberKnife)	Gemcitabine	35.5
Kopek et al. [18]	27	SBRT 45 Gy to isocenter in 3 fractions over 5–8 days	–	10.6
Momm et al. [17]	13	SFRT 32-56 Gy, in 4 Gy/fraction given 3 times a week	Gemcitabine or FU-based in 6/13 pts	33.5
Leong et al. [14]	20	EBRT 46 Gy (median) in 1.8–2.0 Gy/fraction	Cisplatin/5-FU and gemcitabine	20.4

In a retrospective study by Ben-David et al. [12], a subset of 52 patients with extrahepatic cholangiocarcinoma and gallbladder cancer had unresectable or gross residual disease and underwent radiation therapy. The median overall survival in this group was 13.1 months, similar to the study by Alden and Mohiuddin [11]. More recent studies have reported similar median survival times with chemoradiation in the unresectable setting [13, 14].

Long-term survival has also been reported with definitive radiotherapy. In a cohort of 20 patients who received EBRT for extrahepatic cholangiocarcinoma or gallbladder cancer reported by Morganti et al. [15], 2 patients survived beyond 5 years. The majority of patients also received concurrent chemotherapy (5-fluorouracil) and intraluminal brachytherapy.

Studies using hypofractionated or stereotactic body radiotherapy reported promising results, achieving median

survival exceeding 30 months in the unresectable setting [16–18] (Table 3). However, these studies report only a limited number of patients and toxicity, at least in some, has been high. This approach requires further investigation. This will be discussed in more detail in the next chapter entitled Emerging Techniques in Image-Guided Radiation Therapy and Stereotactic Body Radiation Therapy.

2 Radiation Technique

The vast majority of the studies supporting the use of radiation therapy in cancers of the gallbladder and biliary tract used 3D-conformal technique. In this chapter, we will discuss this technique in detail including target definition, organs at risk (OARs), and dose selection. We will then introduce the use of intensity-modulated RT (IMRT) and proton beam radiotherapy in the treatment for gallbladder and biliary tract cancers.

2.1 3D-Conformal Radiotherapy

External beam radiotherapy using 3D-conformal technique relies on cross-sectional imaging and three-dimensional reconstruction to define target structures and OARs. Current radiation planning systems use CT-based imaging. Simulation CT scans are obtained with intravenous and oral contrast to (1) delineate vasculature structures around which nodal basins are defined, (2) identify gross tumor volume (GTV), and (3) delineate liver, stomach, duodenum, and small bowel. Preferably, 4D-CT scans are obtained to assess tumor and organ motion. Magnetic resonance imaging (MRI) may also be obtained at time of simulation to assist in target delineation. Hepatobiliary structures are better visualized on MR-based imaging. In particular, the extent of tumor and nodal involvement, proximity to biliary and vascular structures, and proximity to small bowel are better defined on MRI.

Target structures include the GTV, which is defined by gross disease on imaging, and clinical target volume (CTV), which includes the GTV as well as any potential microscopic disease. Finally, dose is prescribed to a planning target volume (PTV), which is the CTV plus an additional margin (typically 1 to 1.5 cm) to account for motion and setup uncertainty. When an internal tumor volume (ITV) is generated incorporating motion as determined by 4D-CT planning, the PTV will only consist of setup uncertainty (0.5 mm in all directions, when daily image guidance is used).

In the adjuvant setting, appropriate postoperative healing should occur prior to starting radiation therapy. A rule of thumb is to begin radiation planning approximately 4 weeks after surgery. In the adjuvant or definitive setting, radiation may be administered concurrently with chemotherapy, or sequentially. One common approach is to begin with systemic chemotherapy and follow with chemoradiotherapy. The initial preradiation chemotherapy allows for the selection of patients who do not have early distant failure, akin to approaches used in pancreatic cancer [19].

Target Definition Target definition depends primarily on two factors: (1) goals of treatment and (2) disease failure patterns. In the definitive setting, the aim is to eradicate all gross and microscopic locoregional disease. Disease failure patterns dictate the extent of regional nodal irradiation.

In the adjuvant setting, gross disease is not present unless the resection was grossly incomplete. Thus, the CTV is defined by the surgical bed and the lymphatic drainage basin. The surgical bed is best defined by careful examination of the operative report and may be highlighted on imaging by radio-opaque clips or staples left by the surgeon. It is important to note that normal anatomic relationships may be disrupted postoperatively.

For hilar cholangiocarcinoma, surgery requires resection of the involved extrahepatic biliary structures and adjacent hepatic parenchyma. Thus, the surgical bed follows along the medial aspect of the remaining liver, within a reasonable radius around the surgical clips. Reconstruction of the tumor and surgical bed on the simulation scan is difficult because of the major change in anatomy and the considerable deformation typically encountered. Careful study of the preoperative scans and detailed discussion with the surgeon are critical. Any gross residual disease on imaging is the GTV and should be delineated separately and included within the CTV.

For distal extrahepatic cholangiocarcinoma, resection consists of the involved extrahepatic biliary ducts, with or without a pancreaticoduodenectomy. The postoperative bed is centered on the new anastomosis between the biliary tree and small bowel, and guided by surgical clips and an appropriate margin. For gallbladder cancer, surgery requires radical or extended cholecystectomy, which involves resection of a margin of hepatic tissue around the gallbladder. This relates to the tendency of gallbladder cancers to infiltrate through Rokitansky–Aschoff sinuses and the gallbladder wall into adjacent hepatic tissue. Thus, the tumor bed includes a rim of hepatic tissue in the space previously occupied by the gallbladder (as indicated by surgical clips). In each case, the CTV encompasses the tumor bed.

In the adjuvant setting, the regional lymph nodes are included in the CTV. Compared to intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinomas have higher rates of lymph node metastasis [20, 21]. This pattern of lymphatic drainage for extrahepatic and hilar cholangiocarcinomas has been described in a study using blue dye technique [22]. The first site of drainage is the pericholedochal lymph node station. The lymphatic drainage then

descends along the portal vein into the surrounding nodes, along the common hepatic artery into the surrounding nodes, or along the biliary tree to the pancreaticoduodenal node station. Notably, lymph flow does not ascend toward the hepatic hilum. The tertiary nodal stations include the nodes surrounding the celiac axis and superior mesenteric artery as well as the aortocaval nodes.

This flow pattern is supported by clinical studies. In a study by Kitagawa et al. [23], 110 patients underwent lymph node dissection in addition to surgical resection, of which 52 % of patients had nodal disease. The pericholedochal lymph node group was the most frequent site of lymph node metastasis (42 %), followed by the nodes along the portal vein (31 %), nodes along the common hepatic artery (27 %), and the pancreaticoduodenal nodes (15 %). Another study examined failure patterns based on imaging in 76 patients with hilar cholangiocarcinoma who had undergone resection [20]. Of the 52 patients who had disease recurrence, 59 % failed with isolated locoregional disease. Sites of local recurrence included the hepatic resection margin (12/59), porta hepatis (7/59), and bilioenteric anastomosis (5/59), while others recurred regionally in retroperitoneal lymph nodes (14/59).

The CTV for extrahepatic and hilar cholangiocarcinoma therefore includes the pericholedochal lymph nodes. For hilar cholangiocarcinomas, these nodes are within the hepatic hilum and porta hepatis. The CTV also extends to a 1-cm margin around the portal vein from the hepatic hilum to its junction with superior mesenteric and splenic veins to include the surrounding nodes. To encompass the pancreaticoduodenal nodes, the CTV will also include the area surrounding the groove between the pancreatic head and duodenum and, in particular, its posterior aspect. The celiac trunk and the proximal superior mesenteric artery, typically with a 1-cm margin, are also within the CTV to include corresponding lymph nodes.

For intrahepatic cholangiocarcinoma, the lymphatic drainage is similar with a few exceptions. Because the tumor originates intrahepatically, the first echelon pericholedochal lymph nodes lie within hepatic tissue. These nodes lie within the tumor bed volume and corresponding CTV. Subsequent lymph drainage occurs in a pattern similar to extrahepatic cholangiocarcinoma: to nodes in the hepatic hilum, along the common hepatic artery, to retropancreaticoduodenal region, the celiac axis, and the root of the superior mesenteric artery. These findings were confirmed in study of 39 patients who had undergone surgical resection as well as radical lymph node dissection for intrahepatic cholangiocarcinoma [24]. The study also found that intrahepatic cholangiocarcinoma in the left peripheral biliary tract also spreads to the left gastric nodes along the lesser curvature of the stomach. However, for intrahepatic cholangiocarcinoma, prophylactic irradiation of the regional lymph node basin is more limited and typically does not include second echelon lymphatics.

Gallbladder carcinoma likely has a lower rate of isolated locoregional recurrence compared to hilar cholangiocarcinoma. In a study of 80 patients with gallbladder carcinoma after surgical resection, only 8 patients had isolated locoregional recurrence at a median follow-up of 24 months [20]. However, there are no confirmatory reports of this finding and other series suggested a local control and possibly a survival benefit with adjuvant chemoradiotherapy. When such therapy is administered, the CTV typically includes regional nodes. The nodal areas are those described above.

For unresectable disease, the benefit of radiotherapy is unknown. Radiation therapy, though not curative, is administered to decrease tumor size, slow progression, prevent local complications, and perhaps prolong survival. For intrahepatic tumors, the CTV includes gross disease with a margin for microscopic extension. For extrahepatic tumors, the regional nodes have typically also been included in the CTV. However, given the pattern of failure (primarily within the PTV of the primary), the rationale for this practice is questionable.

Organs at Risk Ultimately, target dose is limited by the dose to OARs. The primary OARs in the hepatobiliary region include the liver, small bowel, and ipsilateral kidney. The acute toxicities arising from radiation include nausea and vomiting, abdominal pain, and fatigue. Subacute and late toxicities can occur in the liver and gut. Radiation-induced liver disease, which pathophysiologically resembles veno-occlusive disease, can occur between 4–6 weeks and 3–4 months postradiation. The incidence of RILD is related to the mean dose of radiation to the liver and volume of normal liver spared from radiation [25, 26]. In the absence of underlying cirrhosis, mean liver dose is limited to 30 Gy.

Patients with preexisting liver conditions (e.g., cirrhosis) are also at risk for liver failure. Unlike hepatocellular carcinoma, the majority of patients with cancers of the gallbladder and biliary tree do not have underlying cirrhosis. Cirrhotic livers are more sensitive to radiation injury and require more stringent constraints [27].

Stomach and small bowel are also at risk for radiation injury, including ulceration, bleeding and perforation and obstruction. Difficulty meeting the dose–volume constraints of these organs (Table 4) is naturally more common when treating hilar and distal extrahepatic cholangiocarcinomas.

Dose There are limited data to guide dose selection in radiation therapy of cancers of the gallbladder and bile ducts. Most series support radiation doses consistent with other tumors of the gastrointestinal tract because of shared OARs. The use of concurrent chemotherapy should also be considered in dose determination.

For extrahepatic and hilar cholangiocarcinoma in the adjuvant setting, most studies using external beam

Table 4 Dose constraints for organs at risk

Organ at risk	Maximum tolerated dose	Volume constraint	Mean dose constraint
Liver		700 cc less than 15 Gy	<30 Gy
Stomach		95 % less than 50 Gy	
		75 % less than 45 Gy	
Small bowel	60 Gy	98 % less than 55 Gy	
		75 % less than 45 Gy	
Duodenum	60 Gy	95 % less than 50 Gy	
		66 % less than 45 Gy	
Large bowel	60 Gy	95 % less than 55 Gy	
Kidney, right		50 % less than 18 Gy	
		25 % less than 20 Gy	
Kidney, left		50 % less than 10 Gy	
		25 % less than 15 Gy	
Spinal cord	45 Gy		
Gallbladder	60 Gy	75 % less than 55 Gy	

radiotherapy alone report median doses ranging from 45 to 54 Gy in 1.8–2.0 Gy per fraction [4, 12, 28–31]. One acceptable approach is to treat the entire CTV, including the tumor bed and lymph node basin, to one dose (e.g., 45 Gy) and administer an additional dose (e.g., 9–14 Gy) to the tumor bed. This is based on the higher risk for residual disease at the site of the primary lesion and allows for compliance with normal tissue constraints (e.g., bowel). Similar doses were utilized in studies of adjuvant radiation in gallbladder cancers [9, 12, 32].

In the unresectable or definitive setting, for typical fractionated radiotherapy, most recent studies have reported similar doses—45–60 Gy in standard 1.8–2.0 Gy per fraction [12–14, 33]. Crane et al. [34] reported that the first site of local failure in a cohort of 52 patients with unresectable cholangiocarcinoma treated with definitive radiotherapy (with or without chemotherapy) was local in 72 % of cases. Some studies of conventionally fractionated radiotherapy have shown a correlation between dose delivered and survival outcomes for hepatic malignancies [34–36]. In a study conducted by Alden and Mohiuddin [11], radiation doses greater than 55 Gy in the definitive setting were associated with improved survival in patients with extrahepatic cholangiocarcinoma. Others did not find an association between dose and survival [34, 37]. Given the pattern of failure and the stated goal of delaying progression for as long as possible, a reasonable approach would be to deliver as high a dose as safely possible given the OAR constraints discussed above.

A number of groups have investigated the use of stereotactic fractionated (SFRT) or stereotactic body radiotherapy (SBRT)—a highly conformal technique that allows delivery of high biologically effective dose to the tumor by delivering increased dose per fraction.

Momm et al. [17] reported their experience of 13 patients with unresectable Klatskin tumors treated with SFRT—32–56 Gy in 4 Gy per fraction three times a week. They reported a median progression-free survival of 32.5 months. Adverse events included one grade 3 toxicity (nausea) as well as infectious cholangitis in 5 of 13 patients. A few groups have reported variable experience using SBRT for unresectable cholangiocarcinoma. One study used a dose of 30 Gy in 3 fractions and reported median time to progression of 30 months [16]. Another study used 45 Gy in 3 fractions, reported only 7-month median progression-free survival, and reported a significant rate of late duodenal toxicity in the 27 patients treated (6 with ulceration, 3 with stenosis) [18]. Given this toxicity, we believe that the use of SFRT and SBRT remains investigational in this setting.

2.2 Intensity-Modulated Radiation Therapy

IMRT typically refers to inverse radiation planning based on dose-volume goals and constraints to target and normal structures. After target goals and OAR constraints are defined, multiple radiation fields are placed. Planning software then optimizes the radiation dose distribution by varying the intensity of multiple beamlets within each beam. The technique results in dose distributions that tightly conform to the shape of the target.

Compared to 3D-Conformal radiation, IMRT allows sparing of high dose to nearby critical structures (Fig. 1). For hepatobiliary radiation, this is advantageous because it limits high doses to the spinal cord, kidneys, bowel, and liver. Because of the steep dose gradient, higher radiation doses may be delivered to the target [38]. However, inherently, this technique delivers a higher low-to-intermediate dose to

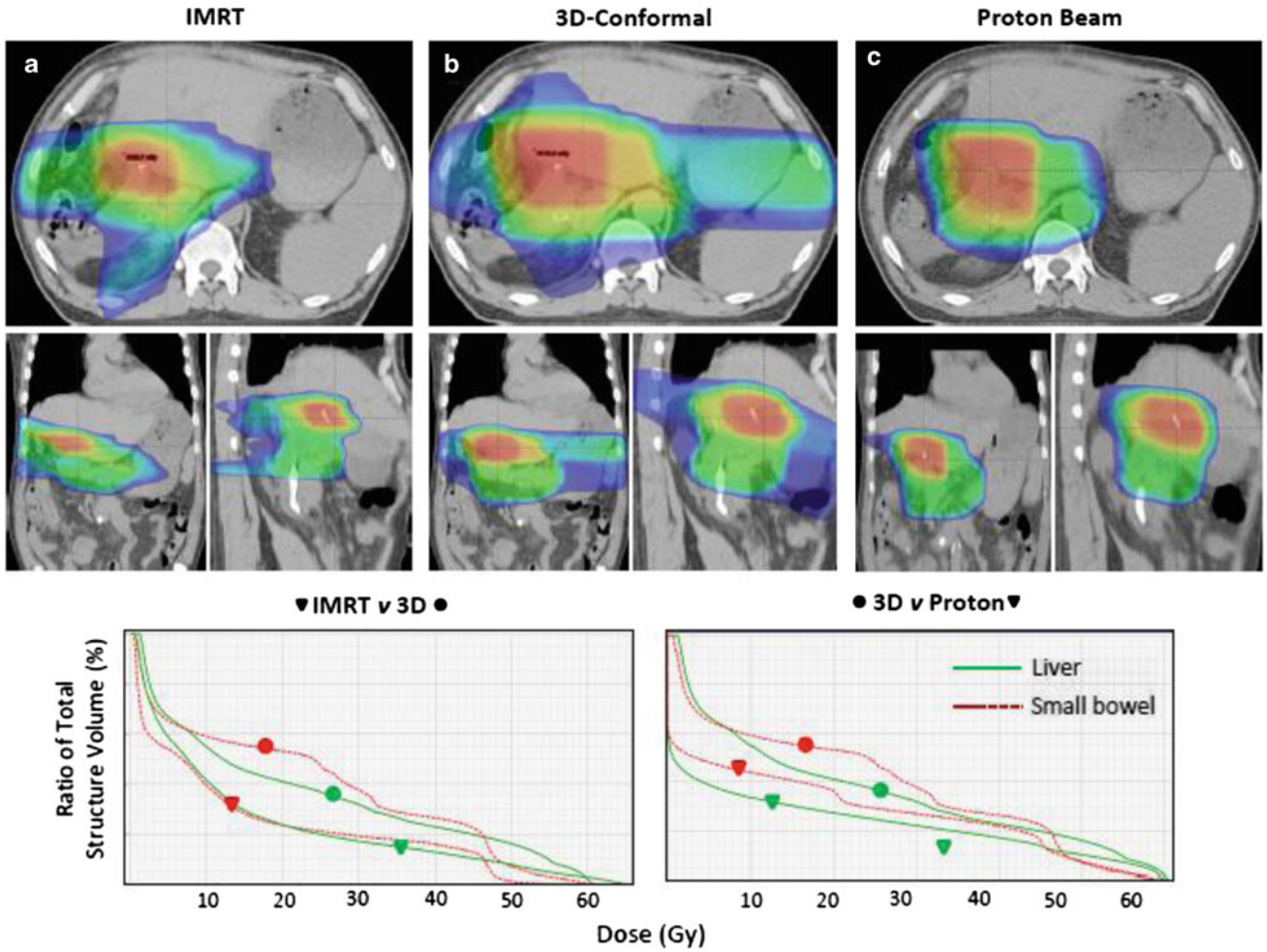

Fig. 1 Dose distribution for postoperative treatment for extrahepatic cholangiocarcinoma using **a** IMRT, **b** 3D-conformal therapy with four fields, and **c** proton radiotherapy with two fields. Axial (*top panel*), coronal, and sagittal (*middle panel*) views are shown. A dose gradient of 25 Gy (*blue*) to 64 Gy (*red*) is shown. In the *bottom panel*, dose–volume histograms comparing 3D with IMRT (*left*) and proton therapy (*right*) show sparing of liver and small bowel with IMRT or proton radiotherapy

normal tissues around the target (but not immediately adjacent to it).

IMRT is widely used in pancreatic tumors [39], which have similar anatomic considerations to hepatobiliary malignancies, and consensus guidelines in pancreatic cancer recommend either 3D-conformal technique or IMRT [40]. A number of studies have demonstrated the dosimetric benefits of IMRT compared to 3D-conformal technique in pancreatic and bile duct malignancies. In pancreatic cancer, there is emerging prospective data, suggesting that high-dose radiotherapy delivered with IMRT may improve survival and local control [41]. Although no such data exist for cholangiocarcinoma, existing evidence does suggest that the use of IMRT in bile duct malignancies improves the rate of acute and/or late toxicity [42, 43].

Fuller et al. [44] reported on the use of IMRT (with ultrasound image guidance) for both gallbladder carcinoma and biliary adenocarcinoma. For 10 patients with gallbladder carcinoma, adjuvant or definitive IMRT achieved a median dose of 59 Gy, while limiting mean liver dose to 28.8 Gy, mean right kidney dose to 14.3, and mean spinal cord dose to 10.6 (all median values). Another series of 24 patients treated with IMRT for biliary tract cancers (extrahepatic cholangiocarcinoma and gallbladder cancer) were compared to a similar cohort of 24 patients treated with 3D-conformal technique [45]. In the IMRT group, median target dose was 59 Gy, compared to 48 Gy in the 3D-conformal group. No significant differences were noted in clinical toxicity between the two modalities.

2.3 Proton Beam Radiotherapy

Proton beam radiotherapy, a form of heavy-charged-particle therapy, does not have a clinically proven benefit for cancers of the gallbladder and biliary tract at this time. Because of its

unique physical properties, protons have a finite penetration within tissue and deliver the majority of their energy at narrow depth window within tissue (i.e., Bragg peak). Historically, proton beam radiotherapy was limited to malignancies adjacent to critical structures (e.g., spinal cord) and pediatric malignancies. However, as the ability to deliver proton beam radiotherapy has advanced with isocentric gantry systems, its potential use in other malignancies has broadened.

In hepatic tumors, where restricting integral liver dose is critical, proton beam radiotherapy is of particular interest. Compared to a high-energy photon beam (e.g., 15 MV), each modulated proton beam delivers less radiation to normal surrounding liver in its path to the target and past the target. Dosimetric studies of proton beam radiotherapy in hepatobiliary malignancies have suggested an advantage in achieving maximal target coverage while limiting dose to nearby OARs (Fig. 1).

In a dosimetric analysis of four pancreatic or biliary large-volume treatment plans, proton beam radiotherapy (using "spot-scanning" technique) achieved target coverage while meeting dose constraints in all 4 patients [46]. IMRT plans with 9 fields were not able to simultaneously achieve large-volume target coverage and meet dose constraints in the same 4 patients. Likewise, in a dosimetric comparison between photon and proton plans in 9 patients with liver tumors, proton plans spared more liver of doses $\geq$30 Gy, decreased the mean liver dose, and reduced the volume of high-dose radiation to the stomach, duodenum, heart, and spinal cord [47]. And by limiting the number of beams from the contralateral side of the patient, the left kidney is better spared with proton radiotherapy [48].

The conformality of proton beam radiotherapy depends on the delivery technique. Less-conformal delivery techniques such as double scatter and uniform scanning do not achieve the same conformality as spot-scanning or pencil beam proton beam radiotherapy. Limitations of proton beam radiotherapy include range uncertainties related to tissue inhomogeneity and dose distribution at the distal edge of the Bragg peak.

Although clinical data have shown the feasibility of proton beam radiotherapy for hepatobiliary malignancies, there are no clinical data to suggest that proton beam radiotherapy is superior to photon-based treatments in terms of disease control or toxicity. There is currently an ongoing phase II trial to assess local control and safety of the use of proton beam radiotherapy in hepatocellular carcinoma and intrahepatic cholangiocarcinoma at the Massachusetts General Hospital (MGH), University of Pennsylvania, and MD Anderson Cancer Center.

3 Conclusion

Despite the lack of prospective data, the retrospective literature on the effects of radiation on cancers of the biliary tract suggests a benefit in the adjuvant and definitive setting in terms of local control and perhaps survival. Multiple external beam radiation technologies are now available to deliver target doses safely, including 3D-conformal, intensity-modulated, and proton beam radiotherapy. SBRT has been associated with a high rate of complications and needs further development in clinical trials. Although head-to-head comparisons of these modalities are unlikely, prospective clinical data on efficacy and toxicity will guide modality selection. In the meantime, assessment of each individual tumor and its relationship to surrounding structures, as well as the clinical context, is critical to the selection of target, dose, and technology.

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