Radiotherapy and Chemotherapy as Therapeutic Strategies in Extrahepatic Biliary Duct Carcinoma

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Purpose: This report aims to provide an overview on radiotherapy and chemotherapy in extrahepatic biliary duct carcinoma (BDC).
Patients and Methods: A PubMed research identified clinical trials in BDC through April 1, 2010 including randomised controlled trials, SEER analyses and retrospective trials. Additionally, publications on the technical progress of radiotherapy in or close to the liver were analysed.
Results: Most patients with cholangiocarcinoma present with unresectable disease (80–90%), and more than half of the resected patients relapse within 1 year. Adjuvant and palliative treatment options need to be chosen carefully since 50% of the patients are older than 70 years at diagnosis. Adjuvant radiotherapy or chemotherapy after complete resection (R0) has not convincingly shown a prolongation of survival but radiotherapy did after R1 resection. However, data suggest that liver transplantation could offer long-term survival in selected patients when combined with neoadjuvant chemoradiotherapy in patients with marginally resectable disease. For patients with unresectable biliary tract carcinoma (BTC), palliative stenting was previously the treatment of choice. But recent SEER analyses show that radiotherapy prolongs survival, relieves symptoms and contributes to biliary decompression and should be regarded as the new standard. Novel technical advances in radiotherapy may allow for dose-escalation and could significantly improve outcome for patients with cholangiocarcinoma.
Conclusion: Both the literature and recent technical progress corroborate the role of radiotherapy in BDC offering chances for novel clinical trials. Progress is less pronounced in chemotherapy.

Key Words: Bile duct cancer · Radiotherapy · Chemotherapy · Chemoradiotherapy · Review

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Radiotherapie und Chemotherapie als therapeutische Strategien bei extrahepatischen Gallenwegstumoren

Ziel: Dieser Bericht gibt eine Übersicht über die Rolle der Radio- und Chemotherapie beim extrahepatischen Gallengangskarzinom (BDC).
Patienten und Methodik: Eine PubMed-Suche identifizierte klinische Studien zum BDT bis 1. April , 2010 und schloss randomisierte kontrollierte Studien, SEER Analysen und retrospektive Studien ein. Außerdem wurden Arbeiten zum technischen Fortschritt der Radiotherapie in und nahe der Leber analysiert.
Ergebnisse: Die Mehrzahl der Patienten mit cholangiozellulärem Karzinom befindet sich zum Zeitpunkt der Diagnose bereits in fortgeschrittenen irresektablen Tumorstadien, und auch unter den primär operablen Patienten kommt es in den meisten Fällen zum Rezidiv innerhalb eines Jahres. Adjuvante und palliative Behandlungsoptionen müssen sorgfältig gewählt werden, weil 50% der Patienten bei Daignose älter als 70 Jahre sind. Die adjuvante Radio- bzw. Chemotherapie zeigt nach R0-Resektion keinen überzeugenden Überlebensvorteil, hingegen die Radiotherapie nach R1-Resektion. Bei sorgfältig selektierten Patientengruppen gibt es Daten zum Langzeitüberleben nach neoadjuvanter Radiochemotherapie mit anschließender Lebertransplantation. In der palliativen Situation war bislang die Einlage von Endoprothesen Methode der Wahl. Jedoch zeigen neueste SEER-Analysen, dass die Radiotherapie nicht nur eine Besserung der Lebensqualität durch Besserung der Cholestase bewirkt, nsondern auch das Überleben verlängert, weshlab sie als neue Standardtherapie angesehen werden sollte. Neueste technische Entwicklungen in der Strahlentherapie eröffnen die Perspektive einer Dosiseskalation und könnten die Ergebnisse bei Patienten mit cholangiozellulären Karzinomen dramatisch verbessern.
Schlussfolgerung: Sowohl die Literatur als auch der jüngste technische Fortschritt stärken die Rolle der Radiotherapie beim BDC und eröffnen Chancen für klinische Studien. Für die Chemotherapie ist der Fortschritt weniger ausgeprägt.

Schlüsselwörter: Gallenwegstumoren · Radiotherapie · Chemotherapie · Radiochemotherapie · Übersicht

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Introduction

Currently, the only curative therapeutic option in biliary carcinoma is resection. However, only a minority of the patients can be operated and even if a clear resection (R0 resection) is possible, the rate of relapse is as high as 60–75% [50]. Even multimodal therapeutic concepts were not successful to achieve major progress. In addition, the assessment of the respective therapeutic modalities is impeded by the paucity of data (low patient numbers, only with perspective studies, rarely randomised control groups). This review aims to deliver an overview of the current knowledge of radiotherapy and chemotherapy in biliary duct carcinoma but also to give an outlook to the high potential for radiotherapy with the advent of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT).

Methods

We conducted a PubMed research on articles published in English, German and French until April 1, 2010 (open start date) with the major MeSH headings biliary tract neoplasms and cholangiocarcinoma. The two headings were then combined with other search terms and the following numbers of articles were identified with the two major MeSH terms respectively: "radiotherapy" 397 and 355, "randomized controlled trials" 83 and 8, "clinical trial (phase III)" 5 and 0, "clinical trial (phase II)" 118 and 24, "retrospective studies" 1165 and 355, "SEER" 24 and 11. The two authors independently selected the articles based on the content of titles and abstracts and decided by consensus which articles to include in the analysis.

Adjuvant Therapeutic Options

Adjuvant Radiotherapy

The majority of relapses after resection with curative intent is located in the primary tumor site [34]. Therefore, local adjuvant treatment in terms of an intraoperative, external-beam or internal irradiation appears to be a reasonable approach. Nevertheless, there are almost no clinical studies with sufficient patient numbers which compare in a controlled manner resection only and resection followed by radiation. The largest piece of evidence advocating the use of adjuvant radiotherapy after complete resection is a recent SEER analysis (1973–2005) on a total of > 1500 patients with locoregional extrahepatic cholangiocarcinoma indicating a modest but significant prolongation in survival (mean overall survival (mOS) 26 vs 25 months, Table 1) [24]. Survival benefit was maximal within the initial 1–2 years after therapy. Patients with incomplete resections had a more distinct prolongation of survival after adjuvant radiotherapy compared with surgery alone (mOS: 25 vs. 21 months). Another recent SEER analysis [58] confirmed the survival benefit of adjuvant radiotherapy however with lower overall survival rates in both groups.

This is in contrast with the results of a retrospective analysis of 294 US American patients [53]: neither external-beam radiotherapy (48 Gy) nor combined external/intraluminal radiotherapy resulted in a positive effect after R0 resection. Though limited in number, there are a few retrospective series reporting on clearly improved survival rates after adjuvant radiotherapy. For example, Todoroki et al. [66] report a 5-year overall survival rate (5-y OS) of 34% after R1 resection with adjuvant intraoperative ± external radiation vs. 13% after resection only. Survival was longest (39% 5-y OS) when combined radiotherapy was applied. Similar results are reported in a large Dutch study including 91 patients (1983–1998) [26], where a significant prolongation of the median overall survival (24 vs. 8 months) could be achieved by the use of post-operative external-beam radiotherapy (46 ± 11 Gy total dose). In this (adjuvant) setting brachytherapy did not increase survival rates but dramatically increased toxicity. Importantly, this series had a low number of margin-free resections (14%) which might well be relevant for the survival advantage of adjuvant therapy in this study. For intrahepatic cholangiocarcinoma a recent SEER analysis in over 3,800 patients showed that the combination of surgery and adjuvant radiation therapy results in the greatest benefit and median overall survival time (9 vs 6 months, p = 0.014) [57].

Table 1. Adjuvant therapy. adj: adjuvant, Gy: Gray, mOS: median overall survival time, n: patient number, n.a.: not available, neo: neoadjuvant, R+: positive margins, R–: clear margins, RT: radiotherapy, SEER: surveillance, epidemiology and end results.

Tabelle 1. Adjuvante Therapie. adj: adjuvant,Gy: Gray, mOS: medianes Gesamtüberleben, n: Patientenzahl, n.a.: nicht angegeben, neo: neoadjuvant, R+: positive Schnittränder, R–: tumorfreie Schnittränder, RT: Radiotherapie, SEER: Beobachtung, Epidemiologie und Endergebnisse.

Study	n	Clear resections	RT	RT dose (Gy)	mOS (months)	3-year survival rate
Fuller (SEER) [24]	379	275 (73%)	yes	n.a.	R– 26, R+ 25	–
	651	464 (71%)	no	–	R– 25, R+ 21	–
Shinohara (SEER) [58]	701	n.a.	yes		16	
	1372		no		9	
Kopelson [39]	13	n.a.	yes	38–72.25	12.7	–
Gerhards [26]	71	11 (15%)	yes	42/46	24	36
	20	2 (10%)	no	–	8	10
Cameron [7]	63	all pts:	yes	50–80	–	21
	33	71 (74%)	no	–	–	0
Pitt [53]	23	9 (39%)	yes	51/54	20	–
	27	12 (44%)	no		20	–
Hughes [31]	34	25 (74%)	yes	40–54	37	35
	30	28 (93%)	no	–	22	27
Nelson	33	all pts:	adj	50.4 Gy	34 [all pts]	23 [5 years]
	12	36 (80%)	neo			53 [5 years]

Adjuvant Chemoradiation (CRT)

On the basis of the radiosensitising effect of several chemotherapeutic agents (for instance 5-fluorouracil (5-FU)) several trials tested the efficacy of adjuvant simultaneous chemoradiation. In an analogy to the data on radiation only the results are conflicting for this approach. Serafini et al. [56] reported on an increase of median overall survival times from 25 to 41 months and Kim et al. [37] achieved a 5-year overall survival of 36% for patients after R0 as well as R1 resection combining external radiotherapy (40 Gy) with 5-FU bolus. On the other hand, CRT could not prolong survival in a retrospective analysis from the University of Barcelona [20] in 28 patients after clear resections. Recently, Nelson et al. [45] performed a retrospective analysis of patients with tumor resection who had undergone chemoradiotherapy in 45 patients. They were treated with a median dose of 50.4 Gy and concurrent fluoropyrimidine-based chemotherapy. The 5-year overall survival and locoregional control rates were 33% and 78%, respectively. The median survival was 34 months. No patient died perioperatively and toxicity was mostly fatigue, nausea and anorexia. The resection margins were negative in 80% of the patients in this study, 13% had microscopically involved margins and 7% had gross residual disease. Hughes et al. [31] compared the 5-year overall survival after post-operative chemoradiotherapy (50.4 Gy, concomitant 5-FU) with that after surgery alone in distal cholangiocarcinoma and confirmed a slight benefit of 35% vs 27%. Most of the above given results apply for distal extrahepatic cholangiocarcinoma whereas the evidence to support the use of adjuvant chemoradiation for intrahepatic cholangiocarcinoma is very limited.

Adjuvant Chemotherapy

Adjuvant chemotherapy has largely failed to show significant survival benefits [65, 66]. A large study including 139 patients from Japan achieved negative results [61]. This trial tested adjuvant systemic combined chemotherapy with 5-FU and mitomycin C compared to resection only in biliary duct carcinoma. Among the 508 patients included 118 had resected bile duct carcinoma (58 receiving chemotherapy vs 60 in the control group) and no survival benefit was observed in either the subgroup with clear resections or in the subgroup with residual disease. Similar observations were made for patients (n = 49) with resected ampullary carcinoma whereas patients with resected gallbladder cancer had a significant prolongation of survival after adjuvant chemotherapy (5-y OS 26% vs 14%).

Taking into account that the majority of the relapses occur locally or regionally, the approach of another group from Japan appears to be more promising: postoperative intraarterial application of 5-FU (hepatic artery) achieved a significant improvement of 1-y OS (76% vs 52% compared with resection only) as well as the median overall survival [63].

Neoadjuvant Therapy: Especially in the case of peri-hilar tumor localizations, a clear resection is often not possible even in early stages. In a subgroup of patients the combination of radiation and chemotherapy can achieve a down-staging with subsequent resection in curative intent. The only trial reporting on this approach is a retrospective study published by McMasters et al. [42] in 9 primary inoperable patients. After preoperative chemoradiation (total dose (TD) 50.4 Gy/5-FU continuous infusion), a rate of clear resections of 100% was reported compared to only 54% in the control group of 40 non-pretreated patients with primary operable tumors. Of note, in 3 patients a complete response was observed at pathohistological evaluation. Another option for selected patients with non-resectable stage I–II peri-hilar cholangiocarcinoma and a negative operative nodal staging is chemoradiation to bridge the gap for liver transplantation. A very recent study reported by Heimbach et al. [29] described 1- and 5-year survival rates of 88 and 82% after neoadjuvant combined percutaneous/intraluminal irradiation (45 Gy/20–30 Gy) and concurrent 5-FU-based chemotherapy. In a report by Nelson et al. [45], despite having more advanced disease at presentation, 12 patients treated neoadjuvantly had a longer survival (5-year survival 53% vs. 23%, p = 0.16) and similar rates of grade 2–3 surgical morbidity (16% vs. 33%, p = 0.24) compared with the 33 patients treated in the postoperative setting.

Palliative Therapy

More than half of the patients with cholangiocarcinoma are only suitable for palliative treatments because of the advanced stage of their disease at diagnosis. Due to short survival times therapy for patients with inoperable cholangiocarcinoma is required to lead to an improvement of quality of life and at the same time to minimise treatment-related complications, e.g. cholangitis. Cholestatic liver failure is the most important fatal complication in patients with inoperable cholangiocarcinoma. The only established method to obtain biliary drainage is the implantation of (metal) stents. As for operable tumors there are conflicting data with regards to the choice of therapeutic regimen as well as the efficacy of palliative (chemo)radiation. Tissue diagnosis should always be obtained when possible to direct palliative treatment choice. Drainage can be achieved endoscopically, percutaneously or with a surgical bypass. Biliary decompression is to relieve jaundice, pain, pruritus and to prevent cholangitis and cholestatic liver failure.

As for stenting, usually, the percutaneous approach is performed when an endoscopic drainage fails or cannot be performed. The disadvantage of this form of biliary drainage is more discomfort and reduced quality of life as well as the disadvantage of draining bile without the ability of enteric recycling. As for endoscopic stents, there is a choice between metallic or plastic (polyethylene) stents. Several randomised controlled trials have compared metallic stents with plastic stents to treat

patients with irresectable cholangiocarcinoma [35, 59]. These studies showed that metal stents are more cost effective for patients with an expected survival time of more than 5 months as an effect of a lower number of interventions and shorter hospitalizations. Plastic stents however often need to be changed at 2–3 month intervals, whereas patency can remain up to 9 months with metal stents [11]. A multicenter prospective trial evaluated covered metal stents as it was hypothesised that a lower occlusion rate could be achieved [25]. However, this hypothesis could not be confirmed with an increased risk of cholecystitis related with covered stents [25, 49].

Systemic Chemotherapy

To date, no chemotherapeutic regimen has consistently shown activity against cholangiocarcinoma. A large number of chemotherapeutic agents have been tested as monotherapy or in combination to treat distantly metastasised cholangiocarcinoma. Similar to earlier stages of the disease the level of evidence of these studies is often limited due to low patient numbers, lack of control groups or a mixture of intra-/extrahepatic cholangiocarcinoma with gallbladder cancers or papillary cancer.

Initially, 5-FU was the most often used chemotherapeutic agent and response rates of only 10% were reported [27]. Response rates could be increased to about 30% using combinations of 5-FU with leucovorin, cisplatin and/or epirubicin hence achieving median overall survival times between 6 and 11 months [9, 17, 44, 51]. The combined approach of 5-FU with IFN-α in a study comprising 32 patients [51] achieved partial remissions in 34%. However a subsequently tested triple or quadruple combination with cisplatin and doxorubicin was only related to higher rate of toxicity without further improvement of overall survival. Similarly, the combined administration of 5-FU with doxorubicin and mitomycin C did not improve the efficacy.

In contrast to these data, the results of gemcitabine mono or combination therapy are more promising. The use of gemcitabine only was reported to result in response rates of up to 60% (median 30%), and the median overall survival time in a prospective phase II study reported by Penz et al. [52] was 11.5 months (Gemcitabine 2200 mg/m^2 d1,15). While combinations of gemcitabine with irinotecan or docetaxel did not result in increased activity, the combination of gemcitabine with oxaliplatin in patients with a good performance status and sufficient hepatic and renal function resulted in a median overall survival time of 15.4 months [2]. The results of the first randomized phase III trial for patients with metastatic cholangiocarcinoma were presented at ASCO in 2009. The ABC trial compared first-line chemotherapy with gemcitabine plus cisplatin versus gemcitabine alone, finding a statistically significant improvement in overall survival (11.7 months vs. 8.2 months) and progression-free survival (8.5 months vs. 6.5 months) with the combination therapy [68].

Intraarterial Chemotherapy

Chemotherapy administered via a catheter placed in the hepatic artery reaches the tumor area directly due to anatomic reasons (most of the biliary tree is directly perfused by the hepatic artery). Furthermore, chemotherapeutic agents are enriched in the biliary canaliculi after hepatic excretion.

The simultaneous administration of EBRT and 5-FU into the hepatic artery in 22 patients resulted in a progression-free survival of 50% after 2 years and an overall survival of 20% after 4 years [54]. Cantore et al. [8] reported on 30 patients with locally advanced/metastasised cholangiocarcinoma treated with combined intraarterial (epirubicin, cisplatin) and systemic (5-FU) chemotherapy and achieved remission rates and stable disease in 40% (mPFS 7 months) and 1y- and 2y-OS of 54% and 20%, respectively.

Palliative (Chemo)Radiation

There are no large randomised clinical trials in cholangiocarcinoma and many of the reports show therapeutic inhomogeneities (Table 2), however a very recent large SEER analysis allows to estimate the effect of radiotherapy [24]. This analysis compared patients with locoregional extrahepatic cholangiocarcinoma who had no treatment vs. patients with EBRT showing a mOS of 9 vs 12 months. Another SEER analysis on almost 400 patients with radiotherapy compared with more than 2200 patients with observation showed also a clear survival benefit for the patients who underwent radiotherapy (mOS 9 vs 4 months, $p < 0.0001$)[57]. Of course these data were collected over more than 30 years and do not reflect therapeutic progress. On the other hand, the SEER data show that even radiotherapy with simple treatment techniques was able to improve survival giving rise to the prospect of further improvement with modern radiotherapeutic techniques.

Brachytherapy: The key advantage of intraluminal brachytherapy (BT) is the focal delivery of high radiation doses with rapid dose falloff over a short distance from the radioactive source thus avoiding hepatotoxicity. After identification of the location and length of the malignant bile duct stricture at cholangiography brachytherapy with sources such as Ir-192 can be performed preferably in a transduodenal endoscopic approach or where this is not possible in a transhepatic technique. In both cases a guide wire is advanced through the malignant stricture under fluoroscopy. A remote afterloading machine is used to give high-dose rate (HDR) brachytherapy increasingly replacing the former low-dose rate (LDR) techniques. Often, 5 Gy per HDR fraction are prescribed at 1 cm from the center of the catheter. If the patient is being treated by brachytherapy alone, 30 Gy in six fractions over 3 days may be given. In case of BT in conjunction with EBRT (combined radiotherapy), a total dose of up to 20 Gy in four fractions over 2 days can be given (20–30 Gy at 0.5–1 cm from the source with LDR) [3]. Due to the lack of sufficiently large clinical trials it is difficult to estimate the true therapeutic benefit of BT in addition to EBRT.

Table 2. Palliative therapy. B: brachytherapy, E: external beam radiotherapy, Gy: Gray, I: intraoperative radiotherapy, mOS: median overall survival time, n: patient number, n.a.: not available, RT: radiotherapy, SEER: surveillance, epidemiology and end results.

Tabelle 2. Palliativtherapie. B: Brachytherapie, E: externe Radiotherapie, Gy: Gray, I: intraoperative Radiotherapie, mOS: mediane Gesamtüberlebenszeit, n: Patientenzahl, n.a.: nicht angegeben, RT: Radiotherapie, SEER: Beobachtung, Epidemiologie und Endergebnisse.

Study	*n*	RT	RT dose (Gy)	mOS (months)	3-year survival (%)
Fuller (SEER) [24]	146	yes	n.a.	12	11
	393	no	–	9	6
Shinohara (SEER) [58]	475	yes	n.a.	9	–
	2210	no	–	4	–
Grove [28]	19	yes	12.6–64.0	12.2	10
	9	no	–	2.2	
Veeze-Kuijpers [70]	42	yes	30–65	10	14
Crane [10]	52	yes	30–85	10	13
Brunner [5]	25	yes	50.4	16.5	26 (2 years: 37)
	39	no	–	9.3	5 (2 years: 12)
Foo [21]	24	E + B	50.4 B: 20	12.8	14 (5 years)
Buskirk [6]	17	I/B	≥ 45 + I 15–20/B	12	B: 30 – I: 43 (1.5 years)
	17	no	20–25	11	
			≥ 45 + 5–15		12
Fields [19]	8	E + B	n.a.	15	–
	12	E	?	7	–
Fritz [22]	30	E + B	E: 30–45 B:20–45	10	18
Iwasaki [33]	6	I	n.a.	–	33 (1 year)
	21	no	–	–	5 (1 year)
Takamura [62]	93	E + B	E 50 B 27–50	12	10

Combined Radiotherapy and Chemoradiotherapy Combined Radiotherapy: Several small studies described a positive effect on quality of life with combined external and intraluminal radiation because they improved biliary drainage and reduced pain [48], however its impact on overall survival time was inconsistent. Kuvshinoff et al. [40] reported prolongation of the median survival time to 14.5 months after combined external/intraluminal radiotherapy (similar data is reported by Foo [21]), whereas Bowling et al. [4] did not observe a significant survival advantage when they compared this approach with a control group which had no radiotherapy 7 vs 10 months) in a retrospective study on 56 patients. One of the problems with combined radiotherapy is an increased rate of cholangitis of 40–50% [21, 26, 32, 40, 69]. In addition, some studies could not confirm a survival benefit from combined radiotherapy [62]. Another option to deliver a high local dose to a tumor or a tumor bed while sparing normal tissue is intraoperative radiotherapy (IORT). A small trial in unresectable carcinoma compared the survival of patients with laparotomy only with that of patients who had IORT additionally (9 patients per arm) and reported mOS of 9.4 vs 23.3 months [36]. IORT doses range from 10–20 Gy in a single fraction.

Chemoradiation: More than 3 decades after the first study on CRT by Kopelson [39], there is still only a small number of trials reporting on CRT. While most of these trials concluded a survival benefit mediated by the addition of chemotherapy [1, 5, 16, 21, 39] no significant benefit was reported in a trial from the MD Anderson Cancer Center [10]. Median survival times for patients who had CRT ranged from 10–22 months. Most of these trials used 5-FU or gemcitabine-based CRT schedules without clear demonstration of the superiority of a regimen to 5-FU. In summary, retrospective, nonrandomized data suggest a prolongation of survival after CRT compared to stenting alone or radiotherapy alone as suggested by survival times reported in the SEER analysis [24].

Dose-Response Relationship: The relationship between the median overall survival time and the total dose used was reported by Alden et al. [1]. Following combined radiation with a total dose > 55 Gy, median overall survival time amounted 24 months, with doses less than 55 Gy mOS dropped to 6 months, being identical with a control group without radiation. A phase I–II study of combined radiotherapy with three BT dose cohorts (once, twice or thrice 7 Gy BT) achieved median survival of 9, 12.2 and 20.3 months in the three dose groups although this did not reach statistical significance [41]. These two analyses suggest a dose–response relationship in cholangiocarcinoma and therefore one can expect that dose escalating concepts involving novel techniques like IMRT may be more efficient. Tumor size was described to be strongly related to overall survival after chemoradiation with a mOS time of 20.5 months for patients with smaller tumors ≤ 4 cm vs 8.5 months for those with larger tumors > 4 cm, clearly addressing the need for high total doses to optimise local outcome [5].

In summary, radiotherapy should be considered for patients with locally advanced tumors without distant metastasis to improve local control. This can be achieved with conventional external (chemo)radiotherapy, with a combination of external (chemo)radiotherapy, intraoperative radiotherapy (IORT) and intraluminal brachytherapy with Ir-192 HDR as well as stereotactic radiation.

Future Perspectives in External Beam Radiotherapy (EBRT) for Cholangiocarcinoma

In the past the application of sufficient doses to tumors in the region of the hepatic hilum and in the liver with EBRT was severely restricted by technical difficulties to deliver high

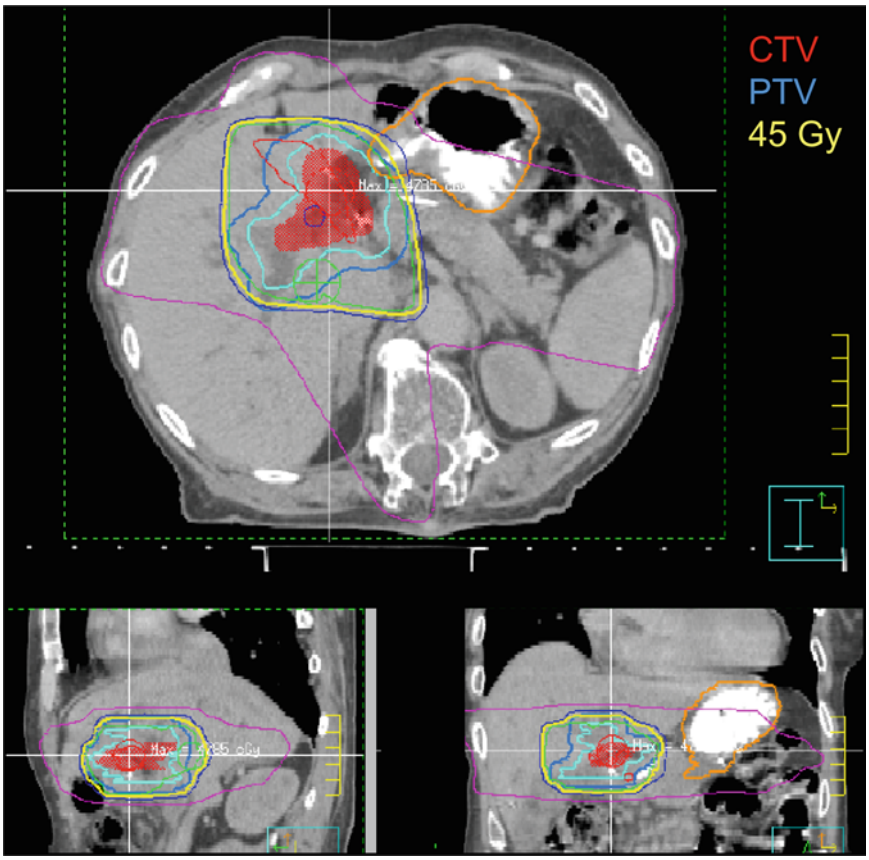

Figure 1. Intensity modulated radiotherapy (IMRT) of a patient with an intrahepatic cholangiocarcinoma to demonstrate protection of the liver with advanced radiotherapy techniques. This is an example of a forward planned segmentally modulated plan. The patient had two lesions treated with nine beam angles and three segments. The mean liver dose (liver minus GTV) was less than 14 Gy. Beam angles minimised path-lengths through normal liver as opposed to a set number of equidistant beams as other early IMRT studies have reported. Structures: Red = gross tumor volume (GTV), light blue = clinical target volume (CTV), blue = planning target volume (PTV), orange=stomach. Isodoses: yellow = 100% (45 Gy in 6 fractions), blue 95% (42.8 Gy), green = 102% (45.9 Gy), red = 105% (47.3 Gy), pink = 40% (18 Gy). Diagram is courtesy Dr Laura Dawson, Princess Margaret Hospital, Toronto.

Abbildung 1. Intensitätsmodulierte Radiotherapie (IMRT) eines Patienten mit einem intraheptischem Cholangiokarzinom zur Demonstration der Leberprotektion mit modernen Techniken der Strahlentherapie. Dies ist ein Beispiel für einen vorwärts geplanten segmentmodulierten Plan. Der Patient hatte zwei Läsioinen, die mit neun Strahlwinkeln und drei Segmenten behandelt wurden. Die mittlere Leberdosis (Leber minus GTV) lag unter 14 Gy. Die Strahlwinkel waren so gewählt, dass die Wegstrecken durch die gesunde Leber minimiert wurden, was sich von anderen Phase I/II-IMRT-Studien unterscheidet, in denen eine fest vorgegebene Zahl von Einstrahlrichtungen in regulären Winkelabständen verwendet wurde. Strukturen: Rot = makroskopisches Tumorvolumen (GTV), hellblau = klinisches Zielvolumen (CTV), blau = Planungszielvolumen (PTV), orange = Magen. Isodosen: gelb = 100% (45 Gy in 6 Fraktionen), blau 95% (42.8 Gy), grün = 102% (45.9 Gy), rot = 105% (47.3 Gy), rosa = 40% (18 Gy). Mit freundlicher Genehmigung von Dr Laura Dawson, Princess Margaret Hospital, Toronto.

doses to the region whilst sufficiently sparing the liver. Radiation-induced liver disease (RILD) can occur when the whole liver dose is > 30 Gy in 2-Gy fractions [71]. However recent technical advances have allowed dramatic progress to safely treat such tumors: intensity-modulated radiotherapy (IMRT), breathing motion management (assisted breath-hold, abdominal compression or respiratory gating) and image-guided radiotherapy (IGRT) are key to this development [30, 43, 60].

Forward planned 3D-conformal radiotherapy plans with multiple segments are labour intensive and time-consuming whereas automated optimization and inverse IMRT planning have proved useful in the generation of treatment plans for partial liver radiation [64]. In order to overcome difficulties with planning target volume (PTV) inhomogeneities the use of the concept of an equivalent uniform dose (EUD) can be useful [46]. Optimization using the generalised EUD is superior to dose–volume-based optimizations with equal or better target coverage and improved sparing of organs at risk [72]. The comparison of direct machine parameter optimization IMRT with conventionally planned conformal radiotherapy showed an improved PTV coverage in about 75% of the patients and dose escalation with an average of 3.8 Gy in 33% of the patients [18].

The potential significance of dose escalation in hepatobiliary cancer is well illustrated in a phase I trial where the patients receiving total doses in excess of 70 Gy had an excellent response rate, prolonged local control and improved survival compared to patients with lower doses [13]. Fuller et al. [23] have reported on a series of 24 patients with primary adenocarcinoma of the biliary tract treated using IG-IMRT ± surgical resection using a prescription of 59 Gy resulting in a median survival rate of 17.6 months. In the same study undergoing conventional radiotherapy 24 patients had a median survival of 9.0 months. The advantages of IG-IMRT are the ability to safely deliver higher, tumoricidal dose to a tightly confined area around the tumor, or resection bed, while avoiding toxicity to normal uninvolved structures such as the visceral organs of the gastro-intestinal tract and the liver (in particular RILD) [14].

Tse et al. [67] report on a phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC). All patients underwent a six-fraction individualized radiotherapy

treatment with prescription doses ranging from 24–54 Gy. Technical details of the individualized treatments are described by Dawson et al. [15] and had the advantage of facilitating treatment (palliation) of large tumors not amenable to other types of therapy. Overall, the 10 IHC patients had a median survival of 15 months and a 58% 1-year survival rate with no significant toxicity. Figure 1 demonstrates a highly conformal treatment plan for a patient with cholangiocarcinoma, treated on the Princess Margaret Hospital phase I/II protocol of highly conformal radiotherapy for hepatobiliary carcinoma and liver metastases [12] with 45 Gy in six fractions, showing excellent avoidance of the liver and visceral GI structures.

The limitations of these studies are the small patient numbers and lack of standardized radiotherapy treatments. Moreover, as shown in a recent report, great care must be taken to avoid late effects such as duodenal ulceration [38] and technical details such as respiratory motion control methods gain high importance in hypofractionated schedules. Even if reported acute toxicities can be lower with hypofractionated schedules [38, 47], the opposite can be true for late toxicities.

Charged particle radiotherapy was also used to treat biliary cancers. The most important study employing charged particles in the adjuvant setting is from UCSF where the 18 patients treated with this novel method survived 23 months compared to 16 months after surgery ± conventional radiotherapy [55].

Conclusion

1. In the light of conflicting data and the generally low level of evidence it is difficult to give therapeutic recommendations but the recent SEER analyses corroborate the role of radiotherapy in the treatment of extrahepatic cholangiocarcinoma.
2. The early data on neoadjuvant chemoradiation are very promising even if the reported patient numbers are low. At this time, this therapeutic approach should only be used in clinical studies after careful selection of patients (laparoscopic staging).
3. Patients who have undergone a resection without clear margins (R1 resection) and who are in a good performance status should be offered adjuvant (chemo)radiation, if possible in clinical trials. At this time there is no indication for adjuvant chemoradiation after clear resection (R0 resection).
4. For patients in the palliative situation the following treatment options are at hand: palliative stenting, radiotherapy (IMRT-IGRT and/or brachytherapy) with or without concurrent chemotherapy. The respective decision for the approach should be taken based on the performance status of the patient and the tumor characteristics (size and location of the primary tumor, absence or presence of distant metastasis). Again, we highly recommend to include these patients into clinical trials.

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