Examining the Use of Radiation Therapy for Cholangiocarcinoma: Benefits through Modern Techniques

Michael Oertel a  Felix Gattermann a  Hartmut Schmidt b  Hans Theodor Eich a

a Department of Radiation Oncology, University Hospital of Münster, Münster, Germany; b Department of Gastroenterology and Hepatology, University Hospital of Münster, Münster, Germany

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Abstract

Background: Cholangiocarcinoma (CCA) is a rare malignant tumor of the bile duct epithelium. At first diagnosis, only a minority of patients are eligible for surgery, which is regarded as the only curative treatment. This study examines the role of radiation therapy (RT) and chemoradiotherapy (CRT) in the definitive and adjuvant treatment situation.

Methods: The monocentric, retrospective analysis included 39 patients with CCA undergoing 53 RT courses. Data were collected from January 2005 to September 2018. There were 11 cases of CRT, 6 of which were definitive. Surgery was either palliative (n = 6) or radical (n = 15).

Results: After RT, the median overall survival (OS) was 10.4 months (m), median progression-free survival was 5.6 m, and median duration of local control (DOLC) was 8.9 m. There was a significant difference in survival between patients with and without locoregional lymph node metastasis (OS: 4.3 vs. 15.4 m, p = 0.031). After treatment of a primary tumor, DOLC was about twice as long as in the recurrent situation (10.4 vs. 5.4 m, p = 0.032). Conservative therapy significantly elevated the risk of local recurrence compared to radical surgery in univariate and multivariate analyses. Side effects were mostly classified as mild to moderate. Termination of RT and increased alanine aminotransferase were significantly less frequent after stereotactic body radiation therapy and hypofractionation.

Conclusion: RT can achieve local control in patients with CCA. Toxicities of RT are manageable but require close clinical and laboratory follow-up.

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Introduction

Cholangiocarcinoma (CCA) is a rare malignant tumor of the bile duct epithelium with an annual incidence between 0.35 and 2 per 100,000 in the Western world [1, 2]. Surgery is regarded as the only curative treatment [3, 4], but prognosis remains dismal, with a median overall survival (OS) of months (m) to a few years without adjuvant treatment [5, 6]. However, only a minority of patients with CCA are eligible for surgery at first diagnosis, as symptoms usually do not occur until the disease is in an advanced stage. Additionally, CCA reveals an aggressive behavior with up to 60% local recurrences after curative resection [1], calling for additional treatments.

External beam radiation therapy (RT) can be used in the definitive or adjuvant treatment setting, ameliorating survival significantly [1, 3, 7, 8]. Data from the Surveillance, Epidemiology, and End Results database demonstrate an improvement of cancer-specific survival for definitive RT [9]. Furthermore, an analysis including patients with unresectable intrahepatic CCA from the National Cancer Database found an advantage of chemoradiotherapy (CRT) compared to chemotherapy alone in the definitive treatment situation [10]. In the postoperative setting, a prospective clinical trial investigating CRT yielded a promising median OS of 35 m [11]. Similarly, adjuvant RT enhances median OS compared to surgery alone [5]. In contrast, another study suggested a survival
advantage for adjuvant RT only in the first 14 m after to-
tal resection and the first 21 m after subtotal resection
[12].

Overall, the role of RT in the context of CCA demands
further analysis. Due to the low incidence of CCA, pro-
spective trials assessing the impact of RT are sparse, and
there is limited evidence for choosing a specific dose,
technique, or fractionation schema. Consequently, we
attempted to provide further insight into the role of RT in
the treatment of patients with CCA and to identify prog-
nostic factors.

Materials and Methods

This monocentric, retrospective analysis included 39 patients
with intrahepatic (n = 11), hilar (n = 26), or both intra- and extra-
hepatic (n = 2) CCA, showing a total of 53 lesions treated with RT
in either definitive or adjuvant setting at our institution from Jan-
uary 2005 to September 2018. Data were collected from the depart-
ment’s clinical files and data management systems. The mean du-
ration of follow-up after the last day of RT was 13.6 m. Statistical
analyses were performed using the software SPSS® version 24.0
(IBM®, Armonk, USA), and differences with a p value below 0.05
were considered statistically significant. Time-dependent event
curves were created by the Kaplan-Meier method, and different
curves dependent on a categorical variable were compared by
means of the log-rank test. The duration of OS, duration of local
control (DOLC), and progression-free survival (PFS) were calcu-
lated from the first day of RT to the respective event. If a patient
underwent RT several times due to progressive disease, he or she
was included only once in the calculation of OS, PFS, DOLC, and
the corresponding Kaplan-Meier plots. In order to determine
whether a local relapse had occurred in the planning target vol-
ume, plan and follow-up images before and after RT were ana-
yzed. The Cox proportional hazards model was applied to assess
the impact of noncategorial variables on the occurrence of death,
metastases, or local relapse and to perform a multivariate analysis.
Fisher’s exact test was applied to analyze the relationship between
2 categorial variables like treatment characteristics and toxicities.
The latter were graded according to the Common Terminology
Criteria for Adverse Events (CTCAE) [13].

Results

The median age was 68 years both at first diagnosis
(range: 40–83 years) and at the beginning of RT (range:
41–83 years). Locoregional lymph node status was nega-
tive in 14 patients, positive in 11 patients, and unknown
in another 14 patients. The median time from first diagnosis
to start of RT was 4 m. If possible, surgery was radical (n = 15), but in
some cases, only palliative (n = 6) intervention was feas-
able, and 17 patients were inoperable. Total tumor resec-
tion was achieved in 3 patients, whereas microscopic or
macroscopic residual disease was found in 6 and 7 pa-
tients, respectively. Eleven patients received chemother-

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Table 1. Cox proportional hazards model

|          | Death (OS)  | Progression/death (PFS) | Local recurrence/death (DOLC) | Local recurrence (LC) |
|----------|-------------|-------------------------|-------------------------------|-----------------------|
|          | HR 95% CI   | p value                 | HR 95% CI                    | p value               | HR 95% CI   | p value |
| Univariate          |            |                         |                              |                       |            |         |
| Rec. versus Prim.    | 1.7 0.57–4.87 | 0.348 | 2.7 0.95–7.54 | 0.063 | 2.87 1.05–7.89 | 0.041 | 1.33 0.33–5.33 | 0.691 |
| N1 versus N0         | 2.9 1.17–7 | 0.022 | 5.39 2.07–14.04 | 0.001 | 3.29 1.32–8.21 | 0.011 | 12.25 2.34–64.05 | 0.003 |
| T4 versus T1         | 6.07 1–37.1 | 0.051 | 2.71 0.48–15.42 | 0.262 | 5.38 0.88–32.78 | 0.068 | <0.0005 <0.0005 | 0.994 |
| Inoperable versus radical surgery | 1.48 0.66–3.32 | 0.344 | 1.8 0.82–3.93 | 0.143 | 2.22 0.97–5.09 | 0.058 | 11.04 2.2–55.32 | 0.004 |
| Palliative versus radical surgery | 2.92 0.87–9.76 | 0.082 | 1.95 0.61–6.22 | 0.26 | 3.01 0.9–10.1 | 0.075 | <0.0005 <0.0005 | 0.99 |
| SW IMRT versus tomo   | 3.6 1.19–10.66 | 0.023 | 4.01 1.32–12.17 | 0.014 | 2.6 0.89–7.58 | 0.082 | 4.85 0.41–56.91 | 0.208 |
| VMAT versus tomo      | 2.9 0.98–8.39 | 0.055 | 2.22 0.77–6.39 | 0.138 | 2.83 0.95–8.5 | 0.063 | 3.78 0.31–45.77 | 0.295 |
| S&S IMRT versus tomo  | 2.13 0.82–5.53 | 0.122 | 1.26 0.5–3.15 | 0.629 | 0.054 0.003–1.08 | 0.46 | 0.58 0.03–11.32 | 0.32 | <0.0005 |
| 3D CRT versus tomo    | 4.41 0.53–36.79 | 0.17 | 1.84 0.23–14.6 | 0.564 | 0 0 0.985 | 0 0 0.996 |

Median and 95% CI are given in months. Significant values (p < 0.05) are given in bold. OS, overall survival; PFS, progression-free survival; DOLC, duration of local control; CI, confidence interval; HR, hazard ratio; Prim., primary tumor; Rec., recurrence; N, nodal status; T, tumor size; 3D CRT, three-dimensional conformal radiation therapy; SW, sliding window; S&S, step and shoot; tomo, tomotherapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.
apy, predominantly gemcitabine, either as monotherapy \( (n = 2) \) or in combination with a platinum agent (gemcitabine and cisplatin, \( n = 5 \); gemcitabine and oxaliplatin, \( n = 1 \); unknown chemotherapy, \( n = 3 \)). CRT was adjuvant in 5 cases and definitive in 6 cases and was carried out for a median of 3.5 cycles (data on duration available for 6 patients). There were 2 cases of second-line chemotherapy, one using gemcitabine monotherapy after gemcitabine and oxaliplatin and 1 case of capecitabine followed by 5-fluorouracil, folinic acid, and irinotecan after first-line cisplatin and gemcitabine. Most RT courses were targeted at primary tumors \( (n = 34) \), followed by metastases \( (n = 12) \) and recurrences \( (n = 7) \). Regarding RT series, the majority \( (n = 36) \) were stereotactic body RT (SBRT). In these cases, target volume was covered by the 65% isodose. Treatment courses were carried out as helical tomotherapy \( (n = 24) \), sliding window intensity-modulated radiation therapy (IMRT, \( n = 7) \), step and shoot IMRT \( (n = 9) \), volumetric modulated arc therapy (VMAT, \( n = 12) \), and three-dimensional conformal RT (3D-CRT, \( n = 1) \). Hypofractionation \( (n = 40) \) encompassed treatment doses of 21–45 Gray (Gy) in fractions of 3–12.5 Gy, whereas normofractionated \( (n = 13) \) treatments varied between 14 and 55.8 Gy in fractions of 1.8–2 Gy. In 4 cases of normofractionated RT, a radiation boost was applied. The most frequently applied treatment regimens were 5 fractions of 7 Gy \( (n = 19; \text{biologically effective dose [BED]}: 59.5 \text{ Gy, equivalent dose [EQD}2\text{]}: 49.58 \text{ Gy}) and 3 fractions of 12.5 Gy \( (n = 12; \text{BED}: 84.4 \text{ Gy, EQD}_2: 70.31 \text{ Gy})). At the end of follow-up, 31 of 39 patients \( (79.5\%) \) were deceased. Eight patients \( (20.5\%) \) were alive, of whom one \( (2.6\%) \) had a local recurrence and another one had a distant metastasis after RT. Overall, 19 patients \( (48.7\%) \) had at least one documented metastasis following RT. There were 10 hepatic, 7 lymph node, 5 pulmonary, and 2 bone metastases. In addition, 6 cases of peritoneal carcinomatosis and a single case of spinal cord involvement were registered. Local recurrence was noted after 10 of 53 RT courses \( (18.9\%) \). In the entire cohort, 1-year local control (LC) rate and 1-year OS were 69.7 and 44.7\%, respectively. The median OS was 10.4 m \( (95\% \text{ CI 6.6–14.2}; \text{Table 1, shown in Fig. 1})\). Median PFS was 5.6 m, and median DOLC was 8.9 m.

Adjuvant chemotherapy prolonged median OS from 9.8 to 18.8 m, without statistical significance \( (p = 0.257) \). After treatment of a primary tumor, median OS, PFS, and DOLC were about twice as long as those after treatment of a recurrent tumor \( (11.9 \text{ vs. } 5.6 \text{ m, } 7 \text{ vs. } 2.9 \text{ m, and } 10.4 \text{ vs. } 5.4 \text{ m}) \), which was significant for median DOLC \( (p = 0.032) \). Additionally, locoregional lymph node metastasis prior to RT resulted in a significantly worse outcome \( (4.3 \text{ vs. } 15.4 \text{ m, } p = 0.031; 2.1 \text{ vs. } 11.5 \text{ m, } p < 0.0005; \text{and } 4.2 \text{ vs. } 12.3 \text{ m, } p = 0.02 \text{ for OS, PFS, and DOLC, respectively; see Fig. 2}).

Fig. 1. Kaplan-Meier plots for OS (a), PFS (b), and DOLC (c) of the entire patient collective. OS, overall survival; PFS, progression-free survival; DOLC, duration of local control.
Locoregional lymph node involvement was also associated with a worse prognosis according to the Cox proportional hazards model, in both univariate analysis (HR 2.9, \(p = 0.022\); HR 5.39, \(p = 0.001\); HR 3.29, \(p = 0.011\); and HR 12.25, \(p = 0.003\) for OS, PFS, DOLC, and LC) and multivariate analysis (HR 2.33, \(p = 0.146\); HR 5.39, \(p = 0.001\); and HR 2.1, \(p = 0.206\) for OS, PFS, and DOLC), as shown in Table 1.

Conservative therapy was associated with significantly higher risk of local recurrence than radical surgery in univariate (HR 11.04, \(p = 0.004\)) and multivariate (HR 98.34, \(p = 0.024\)) analyses. Similarly, palliative surgery was associated with a significantly higher risk of death than radical surgery (HR 6.04, \(p = 0.016\)) according to multivariate analysis. Interestingly, a palliative surgical procedure was associated with a higher risk of local relapse or death than no surgery at all (multivariate analysis: HR 5.81, \(p = 0.019\) vs. 3.72, \(p = 0.04\)).

Tomotherapy appeared to be a favorable prognostic factor regarding OS, PFS, DOLC, and LC in both univariate and multivariate analyses (see Table 1). Neither total radiation dose nor dose per fraction had a significant impact on OS, PFS, or DOLC in univariate Cox regression.

Acute toxicities were predominantly fatigue (4× CTCAE grade 1, 4× grade 2), stomach pain (6× grade 1, 2× grade 2), heartburn (\(n = 3\)), and nausea or emesis (10× grade 1, 1× grade 2). Chronic side effects were rare and never exceeded CTCAE grade 2 during follow-up, with chronic fatigue being the most frequent (\(n = 7\)). Nine patients had at least one acute side effect of grade 3 or 4. Altogether, 13 acute high-grade elevations (9× grade 3, 4× grade 4) in liver parameters such as bilirubin (\(n = 5\)), alkaline phosphatase (AP, \(n = 3\)), gamma-glutamyltransferase (\(\gamma\)-GT, \(n = 1\)), alanine aminotransferase (ALT, \(n = 1\)), or aspartate aminotransferase (AST, \(n = 3\)) were registered. Often, laboratory values were already elevated prior to RT, which prompted us to calculate the pre- and post-RT difference. An acute increase by 3 CTCAE grades occurred only once, when elevated bilirubin worsened from grade 1 to grade 4. An increase by 2 grades was identified for ALT (\(n = 1\)), AST (\(n = 4\)), and \(\gamma\)-GT (\(n = 3\)).

Three patients did not complete RT due to side effects. One of them received RT after radical surgery and developed hemorrhage (type Forrest IIa) from an inflamed anastomosis. Another patient refused to continue definitive RT after experiencing cholangitis with fever, loss of appetite, and elevated laboratory values to grade 1 or 2. The third patient, undergoing RT after palliative surgery, also suffered from grade 1 fever and loss of appetite. In addition, he had leukocytopenia grade 3 and elevated liver parameters, that is, bilirubin (grade 3), AP (grade 4), ALT (grade 3), and AST (grade 3).

According to Fisher’s exact test, termination of RT (\(n = 3/23.1\%\) vs. \(n = 0, p = 0.012\)) as well as an increase in...
SBRT prolonged median DOLC (8.9 vs. 5.6 m), albeit not in relationship regarding RT for CCA [15, 16]. In our study, there is evidence for a positive dose-response rate of SBRT (100% [3, 7] vs. 67.9%), enabling dose escalation. This difference may be attributable to the higher and 83.4% [7], respectively, compared to 69.7% in our review articles estimated a pooled 1-year LC of 78.6% [3] in another randomized trial [14]. Anyhow, comparability is limited due to preselected patient collectives. Two review articles estimated a pooled 1-year LC of 78.6% [3] and 83.4% [7], respectively, compared to 69.7% in our work. This difference may be attributable to the higher rate of SBRT (100% [3, 7] vs. 67.9%), enabling dose escalation. There is evidence for a positive dose-response relationship regarding RT for CCA [15, 16]. In our study, SBRT prolonged median DOLC (8.9 vs. 5.6 m), albeit not statistically significant (p = 0.645).

Radical surgery remains the cornerstone of local therapy and constitutes a favorable prognostic factor [1, 3, 5, 7]. Nevertheless, potential advantages and disadvantages of surgery have to be carefully considered, especially as our investigation found palliative surgery to be associated with poorer outcome in comparison with radical surgery and conservative treatment. A possible explanation may be an inadequate recovery time before initiation of RT. However, the median duration from palliative surgery to the start of RT (76 days) was longer than that in the radical surgery group (61 days), thus contradicting this hypothesis.

The apparent superiority of conservative treatment over palliative surgery may also be influenced by the more frequent use of chemotherapy in the nonsurgical group (n = 6, 37.5% vs. n = 1, 16.7%), although other studies found a benefit of adjuvant chemotherapy only for patients with positive resection margins or locoregional lymph node metastasis [4, 17]. Another potential bias may be an impaired performance status preventing the use of chemotherapy. Unfortunately, data concerning performance status were sparse, preventing definitive conclusions.

Helical tomotherapy might be superior to IMRT and 3D CRT regarding death and local recurrence (Table 1), due to its dose homogeneity and conformity even for irregularly shaped carcinomas. These features are enabled by the large number of beamlets resulting from 51 different beam directions per gantry rotation [18, 19]. However, randomized controlled trials are needed to confirm potential advantages of this RT technique.

Chronic toxicities like fatigue may be influenced by the malignant disease itself with only a minor impact of RT. Despite that, side effects after RT of CCA are common. Overall, SBRT is frequently associated with high-grade elevation of liver enzymes within the first 3 m after initiation of RT (20–55.5% [20, 21]). Correspondingly, 11.3% of our RT courses and 8.3% of our SBRT treatments produced similar findings, with SBRT also featuring a lower rate of other toxicities (see Results). This may be explained by the steep dose gradients and narrow safety margins in SBRT, which delivers high doses to the tumor volume while sparing the surrounding tissue [22, 23]. Tumor size may bias this finding, since the median planning target volume of our RT courses was 39.5 cm³ for SBRT compared to 225.5 cm³ without SBRT. Being a hypofractionation regimen, SBRT requires fewer treatment days, which makes a combination with systemic therapies (e.g., SBRT between chemotherapy cycles) feasible and attractive.

Our study has limitations due to its monocentric and retrospective character. Together with the low incidence of CCA, this results in a smaller and more inhomogeneous patient collective than analyses of large databases. Furthermore, the cause of death was unknown in some cases so that several patients may not have died from their malignant disease. The duration of OS, PFS, DOLC, and survival until the occurrence of local relapse was calculated from the first day of RT in each case, a method prone to lead-time bias. Moreover, as this study was meant to generate new hypotheses and not to prove a previously observed association, the significance level α was not adjusted although the influence of multiple variables was tested.

Ongoing and future clinical trials, like 2 prospective randomized phase III trials comparing adjuvant chemotherapy with CRT in extrahepatic CCA or gall bladder cancer (NCT02798510) and definitive chemotheraphy with definitiveCRTforunresectableCCA(NCT02773485), will hopefully shed more light on the role of RT for this malignancy.
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Conclusion

RT has proven to be an effective therapy for CCA, providing good LC. Moreover, helical tomotherapy seems to be superior to other irradiation techniques regarding OS, DOLC, and LC. Outcome deteriorates for patients with locoregional lymph node metastasis, in the recurrent treatment situation or with palliative surgery. Toxicities seem to be less likely after SBRT and are manageable but require close clinical as well as laboratory surveillance. Randomized clinical trials are necessary to improve combination therapies for CCA, which is still an orphan disease with poor prognosis.

Statement of Ethics

Ethical approval for this study was given by the local institutional review board (ethical review board: Ethikkommission der Ärztekammer Westfalen-Lippe; Reference number: 2018-669-f-S). With the study being a monocentric, retrospective analysis, all data analyzed were already been stored within the department’s clinical files and data management systems. Additional patient consent was not required.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.G. collected the data and performed the statistical analysis. The manuscript was written by F.G. and M.O. M.O., H.S., and H.E. contributed to the treatment of the patients included in this study. All authors read, corrected, and approved the final manuscript.

Availability of Data and Material

Raw data will not be deposited in a repository.

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