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LETTER TO THE EDITOR

Clinical outcomes after stereotactic ablative radiotherapy in locally advanced cholangiocarcinoma

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Introduction

Cholangiocarcinoma (CC) is a rare, aggressive malignancy, representing ∼3% of all gastrointestinal cancers [1], and each year, ∼200 new cases of CC are diagnosed in Denmark [2].

CCs are classified anatomically into intrahepatic and extrahepatic [3].

The only curative treatment is resection, however most patients present with non-resectable, locally advanced, or metastatic disease at the time of diagnosis and carries an extremely poor prognosis with a median survival of 7–12 months with chemotherapy [3–5] and 2–4 months with best supportive care.

In Denmark, each patient is discussed in a multidisciplinary tumor board (MDT) to determine the most optimal treatment. If a patient is deemed non-resectable or medically inoperable, the standard treatment is palliative chemotherapy with cisplatin/gemcitabine based on a randomized phase III trial suggesting survival benefit after combination chemotherapy compared to monotherapy (11.7 *vs*. 8.1 months) [6].

However, other non-surgical local treatments, including radiotherapy, might also be possible in selected patients [7,8]. The use of radiotherapy in the treatment of CC is challenged by the anatomical location close to dose-limiting organs (e.g., duodenum) and respiratory motion; however, techniques, such as 4DCT based planning, respiratory gating, breath-hold, abdominal compression, and daily cone-beam CT (CBCT) guidance might decrease these problems [9].

Stereotactic ablative radiotherapy (SABR) is a non-invasive advanced technique of radiotherapy that permits accurate delivery of high radiation doses in few fractions while critical normal tissues are spared. Gkika et al. [10] showed, that SABR could be considered in fragile patients not suitable for chemotherapy with the benefit of short treatment time and acceptable toxicity. Several other studies suggest an increased overall survival after SABR in combination with standard chemotherapy [4,6,10]. However, there is a lack of phase III randomized trials and it remains to be determined whether SABR alone or in combination with chemotherapy increases overall survival.

The purpose of this retrospective study was to investigate survival and toxicity after SABR in a Danish cohort of patients with cholangiocarcinoma treated during a 10-year period at Aarhus University Hospital.

Material and methods

Patients

The Danish Patient Safety Authority (case number 3-3013-2856/1) and the Danish Data Protection Agency (case number 1-16-02-140-17) approved the study. Patients were identified in the Eclipse treatment planning system and data was retrieved retrospectively from medical records.

Patients eligible for the study included patients with CC treated with SABR from 2009 to 2018 at Aarhus University Hospital. In our institution, SABR was offered to selected patients with non-resectable, locally advanced, and non-metastatic tumors located more than 1 cm from the intestines of patients who were medically inoperable. Patients should have a performance status $\leq$3, and life expectancy $\geq$6 months. All patients were discussed at the MDT before the treatment decision. If blood samples showed compromised liver function, patients were individually evaluated before initiation of SABR. All patients had a contrast-enhanced CT scan and a clinical examination at baseline and after 3, 6, 12, 18, and 24 months, if suitable.

SABR technique

From 2015 Patients were immobilized in a custom-made vacuum pillow supported by a rigid frame (SBF, Elekta Oncology Systems, Crawley, UK, or an in-house developed frame). The treatment planning was based on the mid-ventilation phase of a 4-dimensional CT scan.

The gross tumor volume (GTV) was identical to the clinical target volume (CTV) and contoured by a radiation oncologist and a liver radiologist using available imaging including CT,

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MRI, MRCP, and ERCP. The planning target volume (PTV) was created using a uniform expansion of the CTV with 5 mm in the transversal and 10 mm in the cranio-caudal directions Treatment planning was performed in Eclipse (Varian Medical Systems Palo Alto, CA, USA), using either 3D-conformal, IMRT or VMAT techniques.

Organs at risk included the liver, kidneys, duodenum, esophagus, stomach, bowel cavity, and spinal cord. The biliary tree was not delineated. A minimum of 700 mL of the liver should receive a total dose lower than 15 Gy, the mean liver dose should be below 15 Gy when 3 fractions were used and below 20 Gy when 6 fractions were used. The dose to the liver outside PTV should be as low as possible. The spinal cord received a maximum dose of 18 Gy (23 Gy) and a maximum of 1 cm^3 of bowel, duodenum, or stomach were allowed to receive >21 Gy (28 Gy) when treated with 3 (6) fractions.

Treatments were based on daily CBCT-guidance, typically aided by the position of a biliary drain.

The dose was prescribed as the mean dose to the CTV following the Nordic tradition of in-homogenous dose prescription [11]. The CTV was enclosed by the 95% isodose surface and the PTV by the 67% isodose surface. The maximum dose was kept below 107%.

Endpoints and statistical analysis

The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), local control (LC), and acute and late radiation-induced toxicity. Overall survival was calculated from the date of the first SABR fraction to death by any cause reported in the Danish Civil Registration (CPR) system. Local control was defined as the absence of tumor growth within the PTV of the irradiated tumor detected by imaging (CT and/or MR scans). PFS was defined as the time from first SABR fraction to any progression (based on either imaging, clinical symptoms, or verified by biopsy) or death (calculated as cancer death unless another reason was given) whichever came first.

Co-morbidity was evaluated by the Charlson Comorbidity Index and performance status (PS) by the WHO PS criteria. All toxicity registered within 90 days after the first fraction of SABR was defined as acute toxicity while toxicity after 90 days was defined as late toxicity. Data on toxicity were extracted from the medical records. No formal scoring was done.

Descriptive statistics were used to analyze patient, tumor, and treatment characteristics. Data were analyzed using SPSS 20. Survival analysis was assessed using the Kaplan–Meier method. Data were compared using the log-rank test and chi-square test. Tests were two-sided and a p-value ≤ 0.05 was considered significant.

Results

Patient characteristics

Baseline patient and tumor characteristics for the cohort are listed in Table 1.

Forty-one patients diagnosed with CC and treated with SABR at our institution between 2009 and 2018 were included. Forty patients had histologically verified CC. In one patient repeated biopsies were inconclusive and the diagnosis was based on imaging and clinical symptoms.

Total prescribed radiation dose varied between 42 and 60 Gy, delivered in either 3 or 6 fractions with 2 or 3 fractions per week. Three patients did not complete the planned radiotherapy treatment due to cholangitis (1 pt), hospitalization due to unknown causes (1 pt), and chest pain (1 pt).

According to national guidelines, patients were candidates for subsequent chemotherapy if treated with SABR from 2015 and onwards. In our cohort, 19 patients were treated after 2015 but only 5 patients received adjuvant chemotherapy with either cisplatin/gemcitabine ($n = 2$), oxaliplatin/gemcitabine ($n = 1$), or gemcitabine as monotherapy ($n = 2$). Two patients were treated with chemotherapy before SABR. Reasons not to administer chemotherapy were poor performance status ($n = 10$), patient choice ($n = 2$), and unknown/lost to follow-up ($n = 2$).

Overall survival and local control

The median follow-up was 9.5 months (0–66.5 months). Five patients were followed up at other institutions and therefore data was lost to follow-up a short time after SABR.

Median OS was 11.8 months with 1- and 2-year OS of 48.8 and 19.5%, respectively (Figure 1(A)).

One-year local control was 85.4% and six patients experienced local recurrence inside PTV (Figure 1(B)). One and 2-year progression-free survivals were 31.7 and 9.8%, respectively, and median time to progression 5.8 months (Figure 1(C)).

At the time of analysis, five patients were still alive including two patients surviving more than 5 years after SABR.

We demonstrated a significant correlation between overall survival time and small tumor size (<3.6 cm) with a p-value of 0.004 in Kaplan–Meier log-rank test. There was no correlation between survival and performance status, location, or total dose.

Toxicity

Nine patients were either lost to follow-up ($n = 4$) or dead ($n = 5$) before the first follow-up at 3 months. Acute and late toxicity registered for the remaining 32 patients are listed in Table 1.

Overall, the treatment was well-tolerated. No patients were diagnosed with hepatic failure and no toxicity-related deaths were observed.

Twenty-one patients experienced acute toxicity with the most common toxicity being cholangitis ($n = 9$).

The most common late toxicity was recurrent cholangitis ($n = 8$).

All dose constraints to OAR were met, but two patients were diagnosed with liver abscess and had in common a high dose in few fractions (56.25 Gy in 3 fractions).

Table 1. Clinical characteristics and toxicity.

Patient and tumor characteristics for SABR treated patients, $n = 41$	
Gender	
Female	15 (37%)
Male	26 (63%)
Age median (range)	69 (39–82)
Performance status	
0	16 (39%)
1	11 (27%)
2	6 (15%)
3	5 (12%)
Not reported	3 (7%)
Charlson score	
0	18 (44%)
1	5 (12%)
2	11 (27%)
3	4 (10%)
4	1 (2%)
5	0 (0)
6	2 (5%)
Tumor localization	
Intrahepatic	15 (37%)
Extrahepatic	26 (63%)
Tumor size median mm (range)	22 mm (5–65)
Missing $n = 13$	
Prior treatment	
Resection	5 (12%)
RFA	2 (5%)
Chemotherapy	5 (12%)
None	29 (71%)
GTV diameter (median cm)	3.6 (2–7.4)
GTV volume (median cm^3)	24.41 (3.93–213)
PTV volume (median cm^3)	71.2 (24.9–468.3)
Total dose	
42/6	2 (5%)
45/3	9 (22%)
45/6	1 (2.5%)
47,75/3	1(2.5%)
48/6	11 (27%)
54/6	5 (12%)
56,25/3	5 (12%)
60/6	7 (17%)
Acute and late toxicity, $n = 32$ (9 lost to follow up or death shortly after SABR)	
Acute toxicity ≤90 days	
Cholangitis	9
Vomiting/nausea/loss of appetite	8
	8
Fatique	6
Abdominal pain	1
Liver abscess	1
Pancreatitis	1
Diaré	1
Late toxicity >90 days	
Cholangitis	8
Abdominal pain	4
Liver abscess	2
Ascites	2
Vomiting/nausea/loss of appetite	2
	1
Fatique	1
Pancreatitis	1
Duodenal ulcus	1
Fistula	1
Ventrikel retention	1
Ileus	1

In univariate analysis, a significant correlation was found between the presence of any toxicity and age (<69 years) ($p = 0.02$), as well extrahepatic localization ($p = 0.02$). There was no significant correlation between toxicity and gender, performance status, size of GTV, total dose, or co-morbidity score.

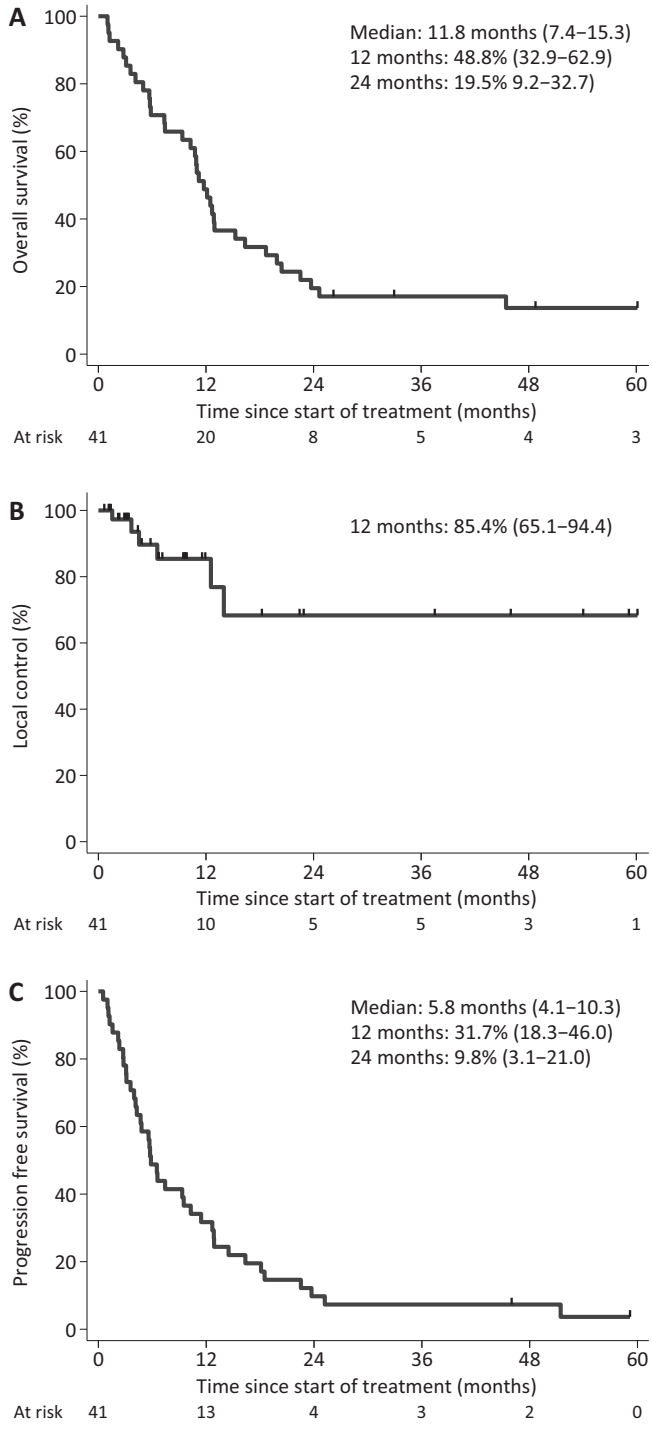

Figure 1. Overall survival (A), local control (B), and progression-free survival (C) from the start of radiotherapy.

Discussion

This study reported on survival and toxicity for a Danish cohort of 41 patients with locally advanced CC treated with SABR over a 10-year period. We found a median overall survival of 11.8 months. The toxicity to SABR was acceptable.

Other studies investigating SABR in CC patients demonstrated a similar median OS of 10–17 months and LC rates at 1 year of 55–100% [3–5,8,12–14]. However, the comparison is difficult due to differences in dose and fractionation regimes, GTV definition, inclusion/exclusion criteria, prior treatments,

adjuvant chemotherapy, etc. Overall survival varies greatly in published studies, likely reflecting patient selection bias [5]. Most of the published studies have small sample sizes and retrospective study designs. A systematic review by Frakulli et al. [15] reports a high heterogenicity in 10 studies (231 patients) showing a pooled 1-year OS of 58.3% and 2-year OS of 35.5%, respectively.

Another systematic review by Lee et al. [16] (11 studies, 226 patients in total) reported a pooled 1-year OS rate of 53.8% and a median overall survival of 13.6 months while Ibarra et al. [12] demonstrated a low 1-year OS rate of 45% in a cohort with heavily pretreated patients.

In our study, SABR was in general well-tolerated. Unfortunately, we were not able to grade the toxicity according to CTCAE (Common Terminology Criteria for Adverse Events) criteria due to the retrospective design and the risk of misinterpretation if scoring toxicity from medical records. The most common acute and late toxicity was cholangitis; however, cholangitis is a common complication in patients with CC regardless of radiotherapy. Nine patients were lost to follow-up before 3 months evaluation, which is the first follow-up visit according to our guidelines. Those patients might have experienced potentially severe toxicity without our knowledge.

Duodenum is the main dose-limiting OAR and a frequently reported severe toxicity is ulceration and bleeding. In our study, only one patient experienced an ulcer, but an earlier paper from our institution [17] reported severe toxicity with ulceration or stenosis in 30% of the patients, which might be due to a high dose per fraction and a lack of daily CBCT-guidance in the early days of SBRT. Today, patients at our institution are treated with 6 fractions instead of 3, and patients are more carefully selected. Other studies report an increased risk of bleeding from duodenal ulcers in extrahepatic tumors [3,10].

Only a minority of patients in our cohort were treated with standard chemotherapy due to poor performance status or comorbidity. Despite this, we found a median OS comparable to published data in international randomized studies of 10–12 months [6,18].

Unpublished data from our institution examining 41 patients treated with standard chemotherapy (cisplatin/gemcitabine) for locally advanced, non-metastatic CC from 2016 to 2018 demonstrated an OS of 10.8 months. These patients had larger and more advanced tumors but better performance status compared to the SABR group. Most of the patients (27 out of 35 patients evaluated with CT scans) treated with chemotherapy alone had local recurrence. Interestingly, only six patients in our study had local recurrence, and the local control after SABR was 85.4%. On the other side, only a few patients treated with chemotherapy alone had a distant failure while the majority of patients treated with SABR had a distant failure or regionally failure outside PTV. In general, most patients treated with SABR had metastasis regionally in the liver outside PTV (at least 1/3) and distant failures were predominantly lymph nodes, lungs, carcinomatosis, or bones.

The present study was too small to describe any difference between those treated with SABR alone compared to those treated with SABR and chemotherapy. Anyhow, our data suggest that a potential increase in disease control and survival might be obtained with a combination of SABR and chemotherapy with SABR leading to high local control rates and chemotherapy controlling disease outside PTV. Today, the majority of patients in our institution receive SABR combined with chemotherapy. The combined approach was examined by Frakulli et al. [15] who reported a higher pooled 1-year OS rate for patients receiving adjuvant chemotherapy after SABR with a 1-year OS of 73% compared to 53% for patients treated with SABR only. Pooled 1-year LC was 83.4%.

Eight patients (20%) in this cohort lived for more than 2 years. The only curative treatment is resection but high dose radiation combined with chemotherapy or other promising systemic treatments like immunotherapy might lead to long-term responders [8]. Prospective studies in this area are urgently needed.

Our study is limited by the retrospective design, small sample size, incomplete follow-up, and the risk of selection bias. Data in this study should be interpreted with caution due to the low patient number, and for the same reason, it was unfortunately not possible to perform a multivariate analysis.

In conclusion, SABR for patients with non-resectable CC is a promising local, non-invasive treatment option with the benefit of short treatment time and acceptable toxicity. SABR should be considered for fragile patients not suited for standard chemotherapy and not eligible for clinical trials.

Future studies should consider the identification of subgroups who benefit from SABR, the impact of additional chemotherapy or other promising systemic treatment as immunotherapy, and patient-reported quality of life.

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Disclosure statement

The authors report no conflicts of interest.

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