ANTICANCER RESEARCH *40*: 3417-3421 (2020)
doi:10.21873/anticanres.14326

Intraluminal Brachytherapy in Unresectable Extrahepatic Biliary Duct Cancer: An Italian Pooled Analysis

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Abstract. *Background/Aim: To evaluate the outcome of patients with unresectable extrahepatic cholangiocarcinoma (CC) treated with external-beam radiotherapy (EBRT) and concurrent chemotherapy (CT) with or without intraluminal brachytherapy (ILBT) boost or with definitive ILBT. Patients and Methods: A pooled analysis of patients with non-metastatic unresectable CC was performed. They were treated in three different institution with EBRT plus CT with or without an ILBT boost. Some patients received only ILBT with curative dose. Results: Seventy-three patients were included in the analysis. Thirty-nine patients (53%) received EBRT treatment with ILBT boost (18 patients with CT during EBRT), while 28 patients (38%) were treated with EBRT (CT in 26 patients) and 6 patients (8.2%) with definitive ILBT (2 patients with CT). CT was administered including either the use of gemcitabine or 5-fluorouracil. With a median follow-up of 16 month (range=1-94 months), median overall survival (OS) was 16 months. Overall median LC was 16 months and patients who underwent ILBT had a better local control (LC) (p=0.018). Conclusion: The role of ILBT in unresectable CC is not yet supported by robust evidence in the literature. However, within this limit, preliminary results seem to suggest an improved local control in patients treated with ILBT, almost comparable to the ones of standard chemo-radiotherapy (CRT).*

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Key Words: Radiotherapy, biliary tract cancers, chemoradiation, brachytherapy, cholangiocarcinoma.

Cholangiocarcinoma (CC) is a rare cancer and represents 2% of all malignant tumors. The incidence is rising in the western world (1). Patients with CC are generally over 65 years of age, with a peak occurring in the seventh decade of life (2).

Complete surgical resection with negative margins is the gold standard treatment of extrahepatic CC. However, even in localized and resectable CC, nodal metastases and peri-neural invasion are predictors of poor prognosis (3, 4). Moreover, in patients who are not candidates for curative resection, due to poor physical compliance, locally advanced disease, or unfavorable tumor site, overall survival (OS) generally ranges between 6 and 12 months (5-7).

To improve CC treatment outcome, external-beam radiotherapy (EBRT) and/or intraluminal brachytherapy (ILBT) have been used either alone or in combination with concurrent chemotherapy (CT) (8-10). However, the specific role of radiotherapy (EBRT or ILBT) plus chemotherapy in locally advanced CC has not been yet clearly defined (1-5, 8, 9). Nevertheless, OS in patients with locally advanced CC treated with chemo-radiotherapy (CRT) seem to be improved compared to best supportive care alone, using both gemcitabine or 5-fluorouracile as CT (11). Furthermore, the combination of EBRT plus ILBT improved OS and QoL in patients who underwent percutaneous transhepatic biliary drainage (PTBD) (12).

Recently, Bisello and colleagues published a study suggesting that EBRT plus ILBT in patients with unresectable CC is well tolerated and able to achieve OS rates comparable to the current standard treatments (13). In order to verify these results, also including a group of patients undergoing ILBT alone, we retrospectively analyzed CC patients treated with EBRT+/-CT with or without an ILBT boost or with definitive ILBT alone.

Patients and Methods

Study design and eligibility criteria. We retrospectively analyzed patients with extrahepatic CC treated in 3 different institutions [Fondazione Policlinico Gemelli (FPG) - Gemelli ART-Roma; Ospedale Sant'Orsola-Malpighi-Bologna; Fondazione IRCCS Istituto Nazionale Tumori- Milano] from 1992 to 2017. All patients had inoperable CC at diagnosis as documented by CT scan, MRI, or surgical exploration. Patients treated with EBRT (+/- concurrent chemotherapy and +/- IBRT boost) or with definitive ILBT at curative doses were included in this analysis.

Treatment characteristics. External beam radiation was delivered to the tumor volume and the primary lymphatic drainage with different techniques such as: conventional 2 dimensional, (2D-CRT), conventional 3 dimensional (3D-CRT), intensity modulated radiotherapy (IMRT), and volumetric- modulated-arc-therapy (VMAT). ILBT was delivered as a boost after completion of EBRT or as definitive treatment. A 192Ir source was positioned through a percutaneous biliary drainage catheter or a nasobiliary catheter. ILBT was administered at both low dose (LDR) and high dose rate (HDR) and the dose was prescribed at 10 mm from the center of the source. Different concurrent schedules of CT were administered with EBRT: gemcitabine and capecitabine, 5-fluorouracile, gemcitabine and oxaliplatin, and capecitabine alone. All patients underwent radiologic and endoscopic exams to identify the tumor site and extension, and histologic confirmation of malignancy was obtained prior to start of the therapy. After treatment, patients were evaluated every 3 months by physical examination, complete blood count, blood chemistry, chest X-ray, and abdominal ultrasound or CT every 6 months. Acute and long-term toxicities were assessed using the Common Toxicity Criteria Adverse event (CTCAE) Version 3.0.

Statistical analysis. Statistical analysis was performed by MedCalc (14). Local control (LC) rates and OS curves were calculated using the Kaplan–Meier method (15).

Results

In this analysis, we included 73 patients treated in 3 different institutions. Median age was 64 years (range=32-88 years). All patients had a non-metastatic unresectable cancer, with or without nodal involvement. Forty-nine patients had a proximal duct CC and 24 patients a distal ductal CC. The patient characteristics are summarized in Table I. Thirty-nine patients (53.4%) received EBRT treatment with ILBT boost (18 patients with concurrent chemotherapy during external beam radiotherapy), while 28 patients (38.3%) were treated with EBRT (concurrent chemotherapy in 26 patients) and 6 patients (8.3%) with definitive ILBT (2 patients with concurrent chemotherapy). CT was administered including either the use of gemcitabine or 5-fluorouracil. The median dose of EBRT was 50 Gy (range=40-50.4 Gy). The median dose of ILBT boost was 20 Gy (range=14-25 Gy); instead, for definitive ILBT the median dose was 30 Gy (range=20-50 Gy). With a median follow-up of 16 months (range=1-94 months), median OS was 16 months and median progression free survival (PFS) was 13 months. Median LC was 16 months. At univariate analysis, patients who received exclusive ILBT as a boost or as definitive therapy showed improved LC compared to patients EBRT or CRT (Figure 1) (p=0.018). Median LC was 16 months and 1-yr LC and 2-yrs LC were 82% and 50%, respectively, in patients treated with EBRT ± CT + ILBT. Median LC was 11 months and 1-yr LC and 2-yrs LC were 41% and 23%, respectively, in patients treated with EBRT±CT. Median LC was 24 months and 1-yr LC and 2-yrs LC were 80% and 53%, respectively, for the patients treated with brachytherapy (Table II).

Table I. *Patient characteristics*.

Characteristics	No. of patients	% of total
Gender		
Male	47	64
Female	26	36
Bile duct segment		
Proximal	49	67
Distal	24	33
Treatment delivered		
EBRT	2	2.7
EBRT + CT	26	35.6
EBRT + ILBT boost	21	28.7
EBRT + CT + ILBT boost	18	24.6
ILBT alone	4	5.4
ILBT + CT	2	3

EBRT: External-beam radiotherapy; CT: concurrent chemotherapy; ILBT: intraluminal brachytherapy.

OS and PFS were similar in the 3 groups (Figure 2, p=0.51; Figure 3, p=0.18, respectively). The treatment was generally well tolerated. The incidence of acute hematologic and gastrointestinal toxicity (grade>2) is reported in Table III. No differences were observed between the 3 groups.

Discussion

Surgical resection is the treatment of choice in patients with extrahepatic CC. However, in a large number of patients, surgical intervention is not feasible. Several studies have been carried out in order to reduce the incidence of loco-regional recurrence of the disease with different treatments.

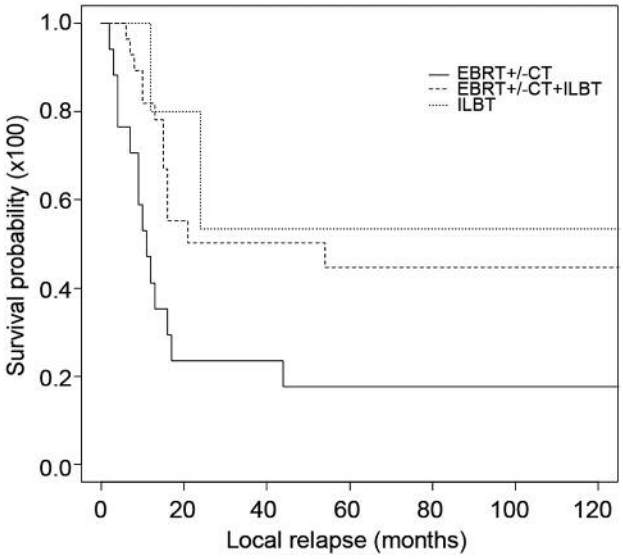

Figure 1. *Local control of patients treated with external-beam radiotherapy (EBRT)+/-CT or EBRT+/-CT +intraluminal brachytherapy (ILBT) or ILBT (p=0.018).*

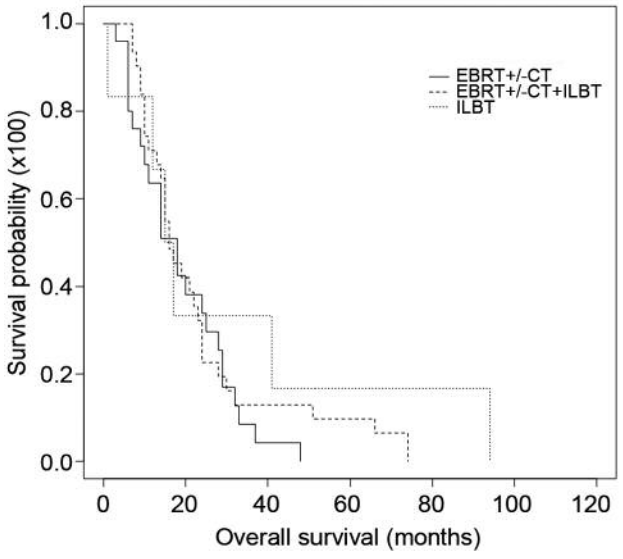

Figure 2. *Overall survival of patients treated with external-beam radiotherapy (EBRT)+/-CT or EBRT+/-CT+intraluminal brachytherapy (ILBT) or ILBT (p=0.51).*

Table II. *Local control.*

Treatment delivered	EBRT+CT	EBRT+CT+ILBT	ILBT
Median LC	11 months	16 months	24 months
1-yr LC	41%	82%	80%
2-ys LC	23%	50%	53%
Median OS	14 months	16 months	16 months
1-yr OS	63%	71%	67%
2-ys OS	34%	22%	33%
Median PFS	9.5 months	15 months	13 months
1-yr PFS	35%	62%	60%
2-ys PFS	10%	17%	20%

LC: Local control; EBRT: external-beam radiotherapy; CT: concurrent chemotherapy; ILBT: intraluminal brachytherapy; OS: overall survival; PFS: progression-free survival.

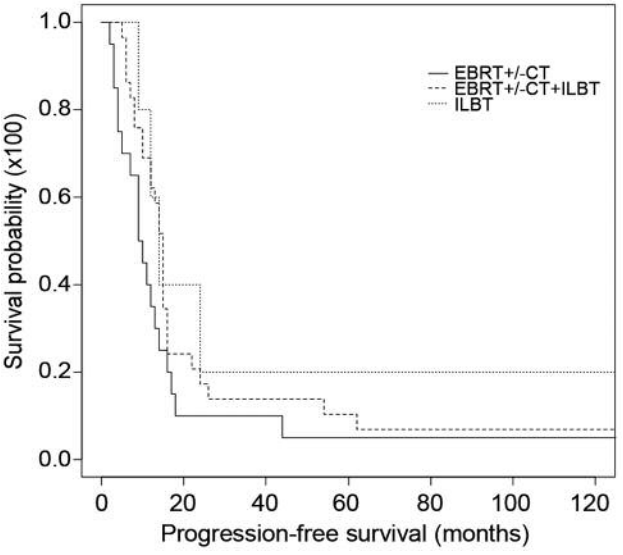

Figure 3. *Progression-free survival of patients treated with external-beam radiotherapy (EBRT)+/-CT or EBRT+/-CT+intraluminal brachytherapy (ILBT) or ILBT (p=0.18).*

It is difficult to detect any difference among the available therapeutic options due to the small sample size of published studies. Moreover, the advantages of CRT have not been established due to lack of randomized trials, despite the availability of some retrospective analyses on CRT even if based on different drugs and radiation doses of 40-54 Gy (16, 17). Therefore, the optimal radiation dose in the definitive treatment of CC has not been defined. However, there are strong limitations about the delivery of high radiation doses due to the close proximity to radiosensitive organs such as the gastrointestinal tract and the liver. In this scenario, ILBT may represent an effective strategy to escalate the dose to the tumor while sparing normal tissue. In fact, this technique allows the delivery of high radiation doses close to the source with rapid dose fall-off over a short

Table III. *Acute toxicity (Radiation Therapy Oncology Group Scale).*

Toxicity > G2	EBRT alone or CRT No. of patients (%)	EBRT+/-CT+ILBT No. of patients (%)	ILBT definitive No. of patients (%)
Acute toxicity GI	5 (4%)	0	1 (1%)
Acute toxicity hematological	4 (3%)	0	0

EBRT: External-beam radiotherapy; CRT: chemo-radiotherapy; CT: concurrent chemotherapy; ILBT: intraluminal brachytherapy; GI: gastrointestinal.

distance, with consequent sparing of adjacent normal tissues. Some authors have reported a correlation between the use of ILBT and OS, while others have shown no significant improvement (18-22).

In the recent analysis of Bisello and colleagues, an IBRT boost was delivered in some institutions to improve OS. According to these authors the OS was not improved in patients undergoing ILBT boost. However, in this group there was a higher rate of long-term survivors (>48 months) (13). Also the report of Deodato and colleagues showed similar results (23). Considering that local progression of disease is a major cause of treatment failure, increasing the dose to the tumor through ILBT boost can be considered a reasonable option to improve the outcome.

To increase the dose to the target stereotactic radiotherapy can be also used to deliver conformed radiation with high precision and accuracy, in a small number of fractions. Recently, several studies have been published about this treatment in CC. This technique has the advantage to be delivered in a very short time, with easy integration with systemic therapy. However, the optimal technique and dose in the definitive radiotherapy of CC has not yet been defined.

In conclusion, our analysis simply suggests an improved LC in patients treated with ILBT, even without a clear impact on OS. Moreover, it should be stressed that the treatments were safe and well-tolerated.

This study had obviously several limitations. The analysis was performed on a heterogeneous group of patients with CC in different sites of extrahepatic bile ducts. Patients were followed by different teams of radiologists, endoscopists, surgeons, and radiation oncologists. In particular, patients underwent radiation therapy with different procedures of EBRT, ILBT, and CT. In the future, the development of nomogram, or more general predictive models, could help the identification of patient groups who would most benefit from the delivery of CRT or CRT and ILBT in unresectable carcinoma.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Data collection: Dr. Privitera, Bisiello, Piccolo, Delle Curti; Data analysis: Masciocchi; Writing manuscript: Dr. Autorino, Bisiello, Pappalardi; Manuscript final approval: Dr Buwenge, Tagliaferri, Macchia, Luppatelli, Cerrotta, Morganti, Valentini, Mattiucci. All Authors read and approved the final manuscript.

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Received March 30, 2020
Revised April 19, 2020
Accepted April 30, 2020