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Impact of radiotherapy in the management of locally advanced extrahepatic cholangiocarcinoma

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Abstract

Background: Optimal therapy for patients with unresectable locally advanced extrahepatic cholangiocarcinoma (ULAC) remains controversial. We analysed the role of radiotherapy in the management of such tumors.

Methods: We retrospectively reviewed the charts of patients treated in our institution with conformal-3D external-beam-radiotherapy (EBRT) with or without concurrent chemotherapy.

Results: Thirty patients were included: 24 with a primary tumor (group 1) and 6 with a local relapse (group 2). Toxicity was low. Among 25 patients assessable for EBRT response, we observed 9 complete responses, 4 partial responses, 10 stabilisations, and 2 progressions. The median follow-up was 12 months. Twenty out of 30 patients (66%) experienced a relapse, which was metastatic in 75% of cases in the whole series, 87% in group 1, 60% in group 2 (p = 0.25). Twenty-eight patients (93%) died of relapse or disease complications. Median overall survivals in the whole group and in group 1 or 2 were respectively 12, 11 and 21 months (p = 0.11). The 1-year and 3-year progression-free survivals were respectively 38% and 16% in the whole series; 31% and 11% in group 1, 67% and 33% in group 2 (p = 0.35).

Conclusion: EBRT seems efficient to treat ULAC, with acceptable toxicity. For primary disease, the high rate of metastatic relapse suggests to limit EBRT to non-progressive patients after induction chemotherapy.

Keywords: Inoperable cholangiocarcinoma, Radiotherapy, Chemotherapy, Outcome

Background

Extrahepatic cholangiocarcinoma (EHCC) is an uncommon cancer comprising almost 3% of all gastrointestinal carcinomas and accounting for 4000 new cases diagnosed each year in France [1]. Most of patients are diagnosed with locally advanced or metastatic disease with 5-year overall survival rates of less than 10% [2,3]. To date, there is no curative therapy apart surgery, but unfortunately only a minority of tumors are resectable at diagnosis, and there is no standard therapy for advanced disease. Optimal therapy for patients with unresectable locally advanced disease remains controversial. Palliative irradiation following biliary decompression can prolong survival, with median survival rates between 9 and 14 months [4-7]. In this study, we have retrospectively reviewed our experience in the EBRT-based management of main

duct cholangiocarcinoma in the settings of unresectable locally advanced primary disease and local relapse after resection. Our goals were to determine the tolerance of treatment, the pattern of failure, and the patients' outcome.

Methods

Patients

Between February 1995 and December 2008, 30 patients with unresectable main duct tract cholangiocarcinoma were treated with EBRT in our institution (Paoli-Calmettes Institute, Marseille, France): 24 for a primary tumor (group 1) and 6 for a local relapse occurring in a mean delay of 16.3 months [range, 12–27] after surgical resection of the primary tumour (group 2). Extrahepatic cholangiocarcinoma was defined by radiologic and endoscopic studies as arising from the right and/or left hepatic ducts, the common hepatic duct, and the common bile duct. Patients with intrahepatic cholangiocarcinoma, gallbladder carcinomas, as well as patients with metastatic

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disease at diagnosis were not included in the analysis. Histological confirmation of diagnosis was obtained for all patients prior to initiation of treatment. The non-resectability was defined by surgeons and radiologists as a coeliac invasion, or a mesenteric or hepatic arterial invasion, or a portal veinous invasion exceeding 180° 27 patients), and/or non-operability for medical reasons (3 patients). Patient and tumor characteristics are described in Table 1. The three patients who presented a T1 or T2 tumor were treated by exclusive radiation therapy because they were considered medically non operable. All data reported in this study have been performed with the approval of our institutional review board ("Comité d'Orientation Stratégique, COS").

Treatment

Pretreatment biliary drainage was performed in 25 out of 30 patients, by using endoscopic procedure (n = 23) or percutaneous transhepatic procedure (n = 2). All patients received a conformal 3D EBRT, delivered to a median dose of 48.25 gy [range, 30–78], at standard fractions of 1.8 to 2 Grays, using 6 to 18 MV photons, with all fields treated five days a week. The clinical target volume (CTV) was designed to adequately cover the tumour volume (with at least a 1.5-cm margin) and the primary lymphatic drainage. The planning target volume encompassed the CTV with a 1-cm margin in all dimensions. Eighteen patients (60%) received a concomitant chemotherapy (12 in group 1 and 6 in group 2) with cisplatin and/or

Table 1 Patients' and tumor characteristics

	All patients (n=30)	Locally advanced cholangiocarcinoma (n=24)	Local relapse of cholangiocarcinoma (n=6)
Age at diagnosis (years) Median (range)	68,3 (46–84)	71,2 (46–84)	59,6 (50–68)
Gender			
Male	19 (63%)	14 (58%)	5 (83%)
Female	11 (37%)	10 (42%)	1 (17%)
Performance status			
0	1 (3%)	1 (4%)	0
1	21 (70%)	15 (63%)	6 (100%)
2	5 (17%)	5 (21%)	0
3	3 (10%)	3 (12%)	0
Tumor size (mm) Mean (range)	-	36 (12–83)	-
Location			
Hilar	-	16 (67%)	-
Intermediate	-	2 (8%)	-
Distal	-	6 (25%)	-
T (TNM classification)			
T1	-	1 (4%)	-
T2	-	2 (8%)	-
T3	-	12 (50%)	-
T4	-	6 (25%)	-
ND	-	3 (13%)	-
N (TNM classification)			
N0	-	11 (46%)	-
N1	-	11 (46%)	-
ND	-	2 (8%)	-
Bismuth classification			
I	-	9 (38%)	-
III	-	4 (16%)	-
IV	-	11 (46%)	-
Follow-up (months)			
Median (range)	61,7 (5–180)	54,8 (5–131)	117 (58–180)
Alive at last follow-up: N	2	2	0

5FU-based regimens (Table 2). Twelve patients received radiotherapy alone.

Statistical analysis

Toxicity was graded according to the NCI-CTC scale (CTC v3.0). Tumour response was assessed by CT scan, using the RECIST 1.0 criteria, 2 months after the end of radiation therapy. Then, patients were followed-up using clinical examination, blood sample analysis and CT scan every 3 months during the 2 first years, then every 6 months. The follow-up was calculated from the date of diagnosis (primary tumor for group 1 and local relapse for group 2) to the date of last follow-up. The progression-free survival (PFS) was defined as the interval between the date of diagnosis and the date of first relapse (local and/or metastatic) or death. Local progression-free survival (LPFS) was defined as the interval between the date of diagnosis and the date of first local recurrence or the date of death resulting from any cause. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death resulting from any cause. Actuarial survival rates were computed using the Kaplan-Meier method and compared using the log-rank test [8]. A 3-months landmark analysis was realized, excluding patients who presented a relapse or were died before 3 months after the end of the treatment. To compare the distribution according to categorical variables, the Fisher's exact test was used. Univariate and multivariate analyses for PFS and OS were done using Cox regression analysis. Univariate analysis tested the following variables: age, sex, performance status, patients group, T stage, N stage, Bismuth classification, tumor size, chemotherapy. Mutivariate analysis was applied to variables with a p-value inferior to 0.2 in univariate analysis. A two-sided p-value inferior to 0.05 was considered significant. Statistical analysis was performed using the survival package (version 2.30) in the R software (version 2.9.1).

Results

Toxicity

All 30 patients were assessable for toxicity. Eight of them had no toxicity, among which 3 improved their performance status during treatment. Acute toxicity was observed as follows: grade 1 (9 patients), grade 2 (13 patients), grade 3 (7 patients), and grade 4 (2 patients: one who presented a major systemic infection, and one a febrile neutropenia). Details of grade 3 and 4 toxicities are given in Table 3. Given the small number of patients exhibiting grade 3–4 toxicity, no statistical analysis was done. As expected, nausea and vomiting were more frequent when chemotherapy was associated. Five out of 30 patients experienced acute cholangitis during radiotherapy, which was adequately addressed with stent desobstruction (n = 2) or change (n = 3), and antibiotics. One patient experienced an ischemic cerebral accident during treatment. One patient definitively stopped the treatment because of grade 4 toxicity. No toxic death was observed.

Radiological response to radiation therapy, pattern of failure, and clinical outcome

Among the 30 patients, 25 were assessable for the radiological response 2 months after EBRT completion (Table 4). Nine out of 25 patients experienced a complete response, 4 patients a partial response, 10 patients a stable disease, and 2 patients experienced disease progression. The objective response rate was 52% and the overall disease control rate was 92%.

In the whole population, the median follow up was 12 months (range, 1–83). Twenty out of 30 patients (66%) experienced a disease progression that was metastatic (15 patients, 50%), local (4 patients, 13%), or both local and metastatic (1 patient, 3%). Within the 16 patients who presented distant metastasis, the metastatic site was peritoneum (n = 10), liver (n = 4), lung (n = 1), and both liver and bone (n = 1). The 1-year and 3-year PFS were 38.4 ± 9% and 15.7% ± 7% respectively (Figure 1a); the median PFS was 9 months (range, 1–11). Twenty-eight patients (93%) died: 20 died of disease recurrence (66%), 6 (17%) of complications (detailed below), and 2 of unknown cause. The 1-year and 3-year OS were 52% ± 9.3% and 15.3% ± 6.9% respectively (Figure 2a). The median OS was was 12 months (range, 1–15).

In the group 1, the median follow up was 10 months (range, 1–70). Fifteen out of 24 patients (62.5%) experienced a recurrence, which was metastatic (12 patients, 50%), local (2 patients, 8.5%), and both local and metastatic

Table 2 Details of concomitant chemotherapy regimens

Chemotherapy schedules	N
Cisplatin (80 mg/m^2) d1 + 5 Fluorouracil (1000 mg/m^2/d) d1-d4, weeks 1 and 5	7
Cisplatin (40 mg/m^2/week), 5 weeks	4
Carboplatin (AUC 2, bi-weekly), 5 weeks	5
Capecitabine 1600 mg/m^2/d, 5 d/week, 5 weeks	2

Table 3 Grade 3 or 4 toxicity according to treatment

	Radiation therapy alone (n = 12)		Radio-chemotherapy (n = 18)	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea and vomiting			4 (22%)	
Pain			1 (5%)	
Fever		1 (8%)		1 (5%)
Asthenia	1 (8%)		1 (5%)	
Total	1 (8%)	1 (8%)	6 (32%)	1 (5%)

Table 4 Radiological response to radiotherapy

Response	All patients (n = 30)	Group 1 (n = 24)	Group 2 (n = 6)
Complete response	9	8	1
Partial response	4	3	1
Stable disease	10	6	4
Progressive disease	2	2	0
Not Available	5	5	0

(1 patient, 4%). Out of the 13 patients who experienced metastatic relapse, 9 developed a peritoneal carcinosis, 2 developed liver metastasis, one developed lung metastasis, and one developed both liver and bone metastases. The 1-year and 3-year PFS were 31.1% ± 9.7% and 10.7% ± 6.9% respectively; the median PFS was 9 months (range, 7–11) (Figure 1b). Twenty-two patients died: 15 of recurrence (62.5%), 5 (21%) of complications including sepsis following hepatic abscess (2 patients), infectious ascitis (1 patient), and angiocholitis (2 patients), and 2 of unknown cause. The 1-year and 3-year OS were 44% ± 10.4% and 10.2% ± 6.7% respectively (Figure 2b). The median OS was 11 months (range, 7–15).
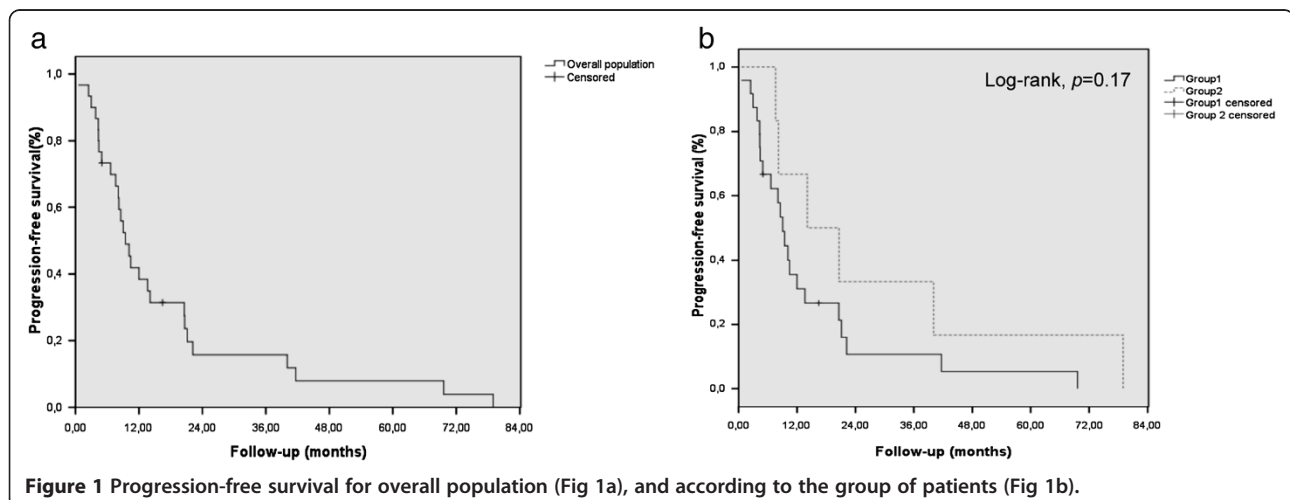
In the group 2, the median follow up was 23 months (range, 8–83). Five out of 6 patients (83%) experienced a recurrence: local (2 patients, 33%) and metastatic (3 patients, 50%). The relapse site was metastatic in 3 out of 5 relapses (2 patients relapsed in the liver and one patient developed a peritoneal carcinosis). The 1-year and 3-year PFS were higher than in group 1, but not significant (p=:0.17, log-rank test): 66.7% ± 19.2% and 33.3% ± 19.2% respectively; the median PFS was 14 months (range, 0–29) (Figure 1b). All patients died: 5 following disease recurrence, whereas 1 patient died in complete remission because of an upper digestive-tract bleeding (Child C cirrhosis with rupture of oesophageal varices). Like PFS, the 1-year and 3-year OS were not significantly

better than in group 1: 83.3% ± 15.2% and 33% ± 19.2% respectively (Figure 2b). The median OS was was 21 months (range, 5–38) *versus* 11 in group 1. The 1-year LPFS was not significantly different between both groups (75 ± 15.3% in group 1 versus 83.3 ± 15.2% in group 2; p = 0.67, log-rank test). The results of univariate and multivariate analyses for PFS and OS are summarized in Table 5. For PFS, both performance status (PS) and age were significant in univariate analysis, but PS remained the sole independent factor in multivariate analysis. For OS, both PS and age were significant in univariate and multivariate analyses.

Landmark analysis with exclusion of patients who presented a relapse or died before 23 months after the end of the treatment was done: median PFS of patients was 10.5 months [4-17], with 1- and 3-years PFS rates equal to 50% ± 13.4% and 14.3% ± 9.4% respectively. Median OS was 13 months [7.5-18.4] and 1- and 3-years OS rates were 71.4% ± 12.1% and 14.3% ± 9.4% respectively.

Discussion

In this study we evaluated the role of EBRT +/– concomitant chemotherapy in patients with extrahepatic cholangiocarcinoma in the settings of unresectable locally advanced primary disease and local relapse after resection. Toxicity was mild to moderate and no toxic death was observed, suggesting that EBRT can be safely administered to such patients. The response rate of loco-regional disease to EBRT and the overall disease control rate were high, 52% and 92% respectively. In literature, the response rate to EBRT is rarely described, but seems relatively high. For example, Lu et al. reported a 56% response rate in 18 patients treated with high-dose radiotherapy [9], and McMasters et al. reported partial (2 patients; 22%) and complete (3 patients; 33%) pathological response in 9 patients treated with neoadjuvant chemoradiation [10]. In a series of 35 patients with unresectable intrahepatic cholangiocarcinoma,
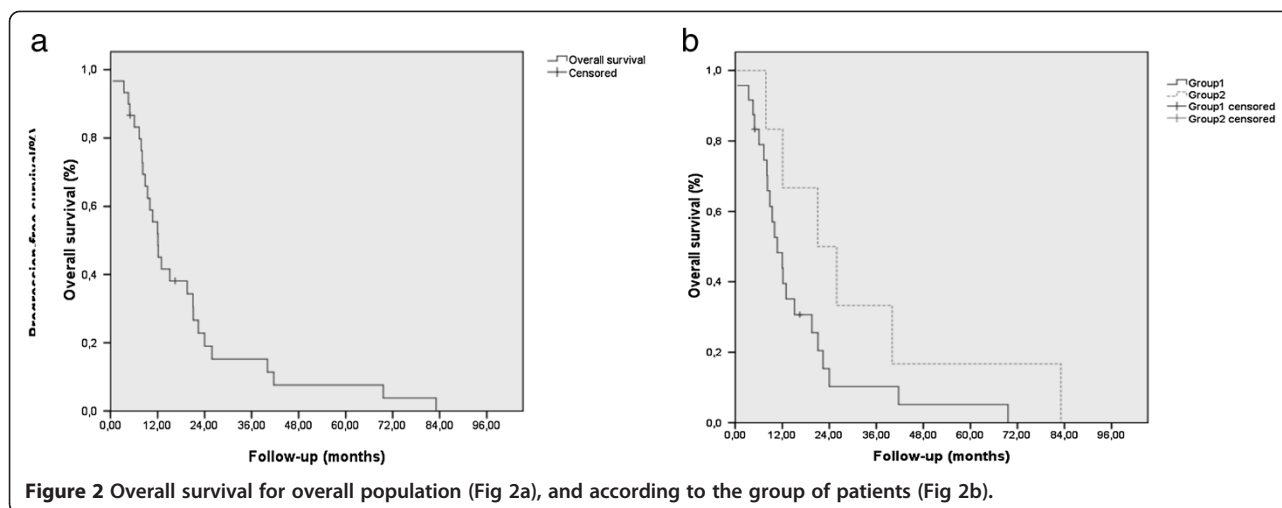

Figure 1 Progression-free survival for overall population (Fig 1a), and according to the group of patients (Fig 1b).

Figure 2 Overall survival for overall population (Fig 2a), and according to the group of patients (Fig 2b).

Chen et al. reported 37% of objective response and 86% of overall disease control [11]; Jiang et al. reported a 75% objective response rate after EBRT for concurrent regional lymph node metastases in 24 patients with resected intra-hepatic cholangiocarcinoma [12]. Despite the response rate, 66% of our patients experienced progression disease. The first site of disease progression was metastatic, mainly hepatic and peritoneal, in agreement with recent studies [5,13]: Ghafoori et al. showed that the majority of patients with unresectable extra-hepatic disease treated with EBRT had local control at the time of death with 18 out of 21 disease progressions occurring firstly in metastatic sites and only 3 in loco-regional sites [5]; similarly, in a German study [13] including 15 patients treated with primary chemoradiation, 53% of first treatment failures were metastatic and 40% were loco-regional. By contrast, the studies, which have reported a prominence of loco-regional progressions as first treatment failure, mainly concern the adjuvant setting [14]. In the study reported by Ben-David and colleagues, the first site of failure was locoregional but corresponded in fact to the 28 patients treated by adjuvant radiotherapy after R0/R1 surgical resection [15]. In our series, OS was poor (median 12 months) as previously reported in literature.

Regarding clinical outcome, we differentiated two populations, those with a locally advanced disease and those with a local recurrence after curative resection. These two populations had different clinical outcome after treatment with RT or RT-CT alone: the first group of patients treated for a locally advanced primary extrahepatic cholangiocarcinoma, with a median OS of 11 months, and a metastatic progression in 87% of patients who relapsed, and the second group of patients similarly treated for an unresectable local relapse after primary surgery, with a median OS of 21 months and 60% of distant failure. In our study, patients with primary extrahepatic cholangiocarcinoma have a poor prognosis, with a high number

of metastatic relapses when the relapse occurs, resulting in a high disease-related mortality. The survival rates described here are in accordance with those published in the literature for unresectable patients treated with RT or RT-CT [5,9,10,13,15-17] and superior to survival rates observed with historical controls and symptomatic palliation. However, this therapeutic strategy has not been widely adopted for all patients. Considering the frequent metastatic evolution of such tumors, and the potential side effects of RT and RT-CT, many patients are treated with CT alone. Recently, in a phase III randomized study, patients (most had metastases) treated with CT alone (gemcitabine and cisplatin) experienced median OS of 11.7 months [18]. Most of the trials investigating the role of chemotherapy in the management of cholangiocarcinomas include patients with locally advanced tumors as well as those with metastatic disease [19-21]. The survival rates obtained in our study are in the same range as the survival rates published for patients treated with RT-CT alone (9 to 14 months) [4,5,9,10,13,15-17,22,23]. Such a comparison should be cautiously taken into account, because data for RT-CT come mainly from old studies with small sample sizes, longer accrual periods, and lack of CT scan imaging for staging, as compared with the CT studies. Furthermore, some patients included in the CT studies could have benefited from RT-CT after induction CT and/or second-line therapies.

Anyway, in our series as well as in others published series, the prognosis of such patients remains poor, with an important metastatic relapse rate frequently resulting in rapid disease-related mortality, suggesting the necessity to integrate new treatment approaches such as systemic agents [19-21]. For locally advanced pancreatic cancers (LAPC) patients, primary CT helps to identify those who may then potentially benefit from RT-CT, therefore sparing almost 30% of them from this unuseful and heavy treatment; furthermore, the outcome of patients

Table 5 Univariate (5a) and multivariate analysis (5b) for PFS and OS

	n risk	n events	PFS		OS	
			1 year-PFS (%) (± SE)	p	1 year-OS (%) (± SE)	p
a						
PS						
0–1	22	21	50 ± 10.7	0.001	63.6 ± 10.3	0.006
2–3	8	7	0		15.6 ± 14.2	
Age						
≤68 years	15	14	58.2 ± 13.1	0.06	79.4 ± 10.6	0.017
>68 years	15	14	20 ± 10.3		26.7 ± 11.4	
Sex						
M	19	18	31.8 ± 14.9	0.3	52.6 ± 11.5	0.4
F	11	10	42.1 ± 11.3		60.6 ± 15.4	
Group 1	24	22	31.1 ± 9.7	0.17	44 ± 10.4	0.11
Group 2	6	6	66.7 ± 19.2		83.3 ± 15.2	
T stage						
T1-2	3	2	66.7 ± 27.2	0.2	66.6 ± 27.2	0.25
T3-4	18	17	18.3 ± 9.5		35.9 ± 11.7	
N stage						
N0	11	9	31.8 ± 14.9	0.8	41.6 ± 15.6	0.7
N1	11	11	27.3 ± 13.4		45.5 ± 15	
Bismuth						
I-II	9	8	33.3 ± 15.7	0.9	44.4 ± 16.6	0.6
III-IV	15	14	29.3 ± 12.2		43.3 ± 13.3	
Tumor size ≤ 36 mm	12	10	27.8 ± 13.6	0.8	36.7 ± 14.6	0.3
>36 mm	9	9	33.3 ± 15.7		55.6 ± 16.6	
Chemotherapy						0.15
Yes	18	18	44.4 ± 11.7	0.3	66.7 ± 11.1	
No	12	10	28.6 ± 13.8		27.5 ± 13.5	
b						
factors			PFS		OS	
			HR [CI95%]	p	HR [CI95%]	p
PS 0–1 *vs* 2-3			3.9 [1.4-11.1]	0.01	3.9 [1.4-10.9]	0.01
Age ≤68 years *vs* >68 years			1.5 [0.56-4]	0.4	4.9 [1.2-18.9]	0.02
Group 1 vs 2			0.7 [0.2-2.3]	0.6	0.8 [0.2-2.]	0.7
Chemotherapy yes *vs* no			–	–	2.4 [0.7-8.2]	0.16

Abbreviations: PS, performance status; SE standard error; T stage and N stage according to TNM classification; Bismuth: Bismuth classification; *vs*: versus; CI 95%: 95% Confidence interval.

not experiencing disease progression after 3 months of induction CT seems better if subsequent RT-CT is administered as compared with continuation of CT [24]. This therapeutic strategy, currently widely adopted in the management of LAPC and tested in a large randomized trial (LAP 07), could be applied to the management of unresectable main bile duct cholangiocarcinoma, which presents almost the same natural history, with a high and rapid metastatic potential. RT or RT-CT could be reserved to non-progressive patients after induction CT in order to increase the local control. In our study, with the use of a landmark analysis, with the exclusion of early relapse, we did not observe any difference in terms of overall survival, which does not support this hypothesis but the small effective of our study does not allow drawing any definitive conclusion. In this study, RT with or without concomitant CT seems efficient to ensure local control, with 79% of local controls observed at 1 year for such advanced disease, similar to published rates in the literature [5]. The optimal radiation dose in

the definitive treatment of biliary malignancies remains unknown, but some authors recommend dose level over 45 to 50 Gy in 5 weeks [25,26]. Since larger volumes will not tolerate a higher dose administrated with external beam irradiation, internal irradiation with iridium-192 seems to be an attractive approach to boost the area where more tumor burden exists [27-30]. More recently, stereotactic fractionated radiotherapy was shown promising to increase the rate of local control [31]. The role of CT in combination with RT remains undefined. The use of 5FU-based CT in combination with RT is extrapolated from the survival benefit demonstrated with other gastrointestinal malignancies, including pancreatic cancer [32-34]. The number of patients reported to be receiving combined therapy is too small to draw conclusions about the benefit of concomitant CT, with reports showing conflicting results [5,22,35,36]. In our study, RT-CT was well tolerated with an acceptable incidence of acute side effects, not very different from patients treated by exclusive RT. Based on the lack of significant toxicity added with CT in published series, and the proven benefit of this treatment in other gastrointestinal malignancies, the use of concomitant RT-CT can be recommended in biliary tract cancers [23].

However, our second group of patients, treated by RT for an unresectable local relapse of disease after primary surgery, experienced better outcome, with a median OS of 21 months after RT (+/−CT). The differences in PFS, OS and site of relapses between the 2 groups 1 and 2, were not statistically significant, likely because of an insufficient number of patients, but this difference has still been reported in the literature, in a small series where patients treated for a local relapse after primary surgery had better outcome [25]. Local relapse represents 33% of all relapses of patients treated by primary surgery for extrahepatic cholangiocarcinomas, most of patients developing distant metastasis at the time of recurrence [37]. The median OS described in this study for this specific group of patients is superior to that described in series of patients treated by exclusive surgery [7,38]. Even though these results should be cautiously taken into account because of the small size of this group, they suggest a potential benefit of such aggressive loco-regional treatment for this specific selected population. Tumors initially resectable and who recurred only locally had certainly a less aggressive behaviour than most of biliary tract cancers, likely explaining in part the better outcome when compared to initially locoregional advanced cancers. These findings are comforted by Yoon and colleagues who reported two cases of patients treated by curative reoperation for recurrent cancer of the extrahepatic bile duct, both alive at 46 and 9 months [39]. The authors concluded that a surgical curative re-resection is possible in selected patients with recurrent bile duct cancer, mostly of the papillary type, and such aggressive treatment should be considered whenever possible in case of recurrence.

Our study presents some limitations. The first one its retrospective nature and the small number of patients included. In fact, this limitation is due to the scarcity of disease: to our knowledge, all studies reported in literature [4,5,9,10,13,15-17,22,23] are retrospective and small, the largest one including 54 patients [17]. No prospective randomized study is available in literature regarding the role of radiation therapy in unresectable patients. The second limitation is the absence of control group that would include unresectable patients not treated with radiotherapy. In fact, based on several older publications for review see [6,7] that suggested that EBRT offers effective palliation of symptomatic disease and improves survival, it has been our institutional policy for more than 10 years to routinely recommend radiotherapy to patients with unresectable extrahepatic cholangiocarcinomas, and the aim of our study was to report our experience during the conformal 3D RT period between 1995 and 2008. Similarly, most of published retrospective studies do not include any control group [4,5,9,10,13,15-17,22,23].

Conclusion

Despite the retrospective nature of our study, the absence of control group and the size limitation that of course limit the statistical power, 3D conformal radiation therapy, ideally combined with concomitant chemotherapy, seems to be efficient in the loco-regional management of locally advanced non-operable extrahepatic cholangiocarcinomas, with an acceptable tolerance. However, the rate of distant relapse remains high, suggesting the need to develop new drugs efficient to treat micrometastatic disease. For locally advanced disease, concomitant radio-chemotherapy should not be administrated initially, but should be delayed after induction chemotherapy and reserved to patients with non-progressive disease. On the contrary, because of a better survival observed for patients presenting a local relapse after primary surgery, concomitant radio-chemotherapy seems to be a promising treatment for this group of patients.

Consent

Written informed consent was obtained from our patients and family for publication of this report and any accompanying images.

JRD managed patients. MR, JLR, MG, GP, JRD, and FP drafted the manuscript. All authors read and approved the final manuscript.

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