Unresectable hilar cholangiocarcinoma: percutaneous multimodal palliative treatment

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Purpose

Cholangiocarcinoma (CLCA) is a rare tumor of the bile ducts, with high local invasiveness and occasional distant metastases (1, 2, 3). Worldwide, it accounts for 3% of all primary gastrointestinal malignancies and 10% of primary hepatobiliary malignancies (4). The topographic classification distinguishes three types of CLCA, all with different prognoses: CLCA in the lower third of the bile duct; CLCA in the middle third of bile duct; CLCA in the upper third of the bile duct, located at the hepatic ducts confluence. The latter, also called a Klatskin tumor and accounts for more than 50% of cases (5,6), has been divided into four types by Bismuth (1), according to the location and extent of the tumor.

Due to the natural rapid progression of the tumor and its low chemosensitivity, surgery remains the gold standard for treatment; in past decades, only a minority of patients were surgical candidates but surgical management of hilar CLCA has evolved since its original description; in fact, the large series recently reported in the literature showed resectability rates varying from 50 to 80% (7) with 1, 3, and 5-year overall survival rates of 74.4%, 47.3%, and 34.1% respectively (7, 8). However, when biliary cancers are unresectable at the time of diagnosis or metastatic at the first clinical observation, the mortality rate for untreated CLCA ranges from 50 to 70% within 12 months (9); therefore, this category of patient can only undergo palliative treatment.

Given that the natural history of hilar CLCA is guided by liver complications rather than metastatic disease, local palliative treatments are a rational option. Many therapeutic protocols using radiotherapy (intraluminal (brachytherapy (BT) and external beam radiotherapy (EBRT) and chemotherapy (ChT) combined with biliary decompression have been advocated to provide a resolution of the jaundice associated with the elective treatment of tumor stenosis (10-17). To date, the role of these therapies, still considered experimental treatment options, is poorly defined since data from controlled clinical trials are lacking. Studies to support treatment recommendations are insufficient, mainly due to the low incidence of CLCA, which has precluded large randomised studies examining the role of radiation and ChT.

The aim of the present study was to evaluate the outcome and survival of multimodal percutaneous treatment (drainage of the right and left biliary systems, Iridium-192 intraluminal BT, positioning of metallic stents and EBRT associated with systemic chemotherapy) in unresectable CLCA.
Methods and Materials

**Patient population:** From April 2003 to April 2010, 32 patients [22 male; mean age 68 years (range: 32-88)] with obstructive jaundice due to malignant biliary stenosis were evaluated. All patients underwent the following diagnostic examinations:

- Magnetic resonance cholangiopancreatography (MRCP) to evaluate stenosis location, morphology and extent (Figure 1a);

- Abdominal CT or MR to detect hepatic, lymphatic or peritoneal metastases, and to detect arterial or portal infiltration (Figure 1b);

- Percutaneous transhepatic cholangiogram (PTC) (Figure 1c) to define the precise extension of tumor infiltration or to perform a biopsy for histological confirmation preliminary to the placement of double internal biliary drainage (PTBD) to palliate jaundice (Figure 1d).

Resectability was determined by individual surgeons but according to the following standard criteria: patients in poor clinical condition, or patients with tumor invasion of the common hepatic artery or infiltration of the controlateral branch of the portal vein or of the hepatic artery (as determined at the time of abdominal imaging) are considered inoperable. Of the 32 patients, 30 (93.75%) had a Klatskin tumor: 1 patient (3.12%) with type I, 1 patient (3.12%) with type II, 9 patients (28.13%) with type III B, 10 patients (31.26%) with type III A and 9 patients (28.13%) with type IV. One (3.12%) patient had a gallbladder carcinoma involving the biliary confluence and 1 (3.12%) had a CLCA of the middle third of the common bile duct.

The mean total bilirubin values before the biliary decompression were 12.35 mg/dL (range 0.48 -33.13 mg/dL).

**Multimodal treatment.** Percutaneous transhepatic cholangiography (PTC) (Figure 1c) was performed in all patients, demonstrating malignant biliary stenosis and, in the same session, an intraluminal forceps biopsy was carried out in the main ductal stenosis to obtain histological confirmation of CLCA; the percutaneous procedure was completed by placing internal-external biliary drains for PTBD, both on the right and the left biliary tree (Figure 1d). Detailed PTC also defined the exact radiation field of the subsequent intraluminal BT, corresponding to a cylindrical volume of 2 cm in diameter with a length including the whole neoplastic stenosis plus a proximal and distal tumor-free margin of 15 mm; this strategy is indicated for the control of any submucosal tumor frequently undetected at cholangiography (Figure 1e). One to two days after PTBD placement, BT was performed by inserting, within the right or the left or both internal biliary drains, Iridium-192 sources in two consecutive weekly sessions (on days 7 and 14) with a dose of 7 Gy each (total dose: 14 Gy) or of 4 Gy each (total dose: 8 Gy).
All patients underwent PTC, PTBD and BT, in 29 patients (90.63%) with a total dose of 14 Gy and in 3 patients (9.37%) with a total dose of 8 Gy. After BT, in all patients, the biliary drains were percutaneously replaced with bare metallic stents (Wallstent, Boston Scientific, Medi-Tech, Watertown, MA, USA) with diameters ranging from 7 to 10 mm (Figure 1f). The patients subsequently underwent a follow up with laboratory tests and ultrasound examinations every 3 months.

Two weeks after the end of BT, 18 patients (56.26%) also received EBRT at the day hospital in 5 week cycles (46 Gy; 25 administrations of 1.8 cGy each). In 7 patients, systemic ChT was also administered: 3/7 (42.86%) received 5-fluorouracil (300 mg/day at week 1 and 5 during EBRT, 1/7 (14.28%) Gemcitabine and Oxaliplatin (Gemcitabine 1000 mg/mq at day 1 and Oxaliplatin 100 mg/mq at day 2 every 14 days), 2/7 (28.58%) Capecitabine (500 mg x2/day every day) and 1/7 (14.28%) Gemcitabine alone (1000 mg/mq at day 1, 8 and 15 every 28 days). Therefore, the patient population was divided into 3 groups, according to the completion of the protocol: Group A (14 patients = 43.75%) received only BT without EBRT or ChT; Group B (11 patients = 34.37%) received BT plus EBRT without ChT; Group C (7 patients = 21.88%) received BT, EBRT and ChT.

Statistical evaluation: Statistical analysis was carried out with the SPSS test (SPSS/PC User’s guide, ver. 13.0, 1998; SPPS, Chicago, IL). Survival curves were estimated by the Kaplan-Meier method which provided mean and median survival of the overall group and of each individual group. Comparisons of the curves were made using the logrank test and the Breslow test. A p value < 0.05 was considered statistically significant.
Fig. 1: Klatskin’s III a tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f ) Two self-expandable bare stents inserted after the completion of BT treatment.

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Fig. 2: Figure 1. Klatskin's IIIa tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f ) Two self-expandable bare stents inserted after the completion of BT treatment.

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**Fig. 3:** Figure 1. Klatskin's III a tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f) Two self-expandable bare stents inserted after the completion of BT treatment.
Fig. 4: Figure 1. Klatskin's III a tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f ) Two self-expandable bare stents inserted after the completion of BT treatment.

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Fig. 5: Figure 1. Klatskin's III a tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f) Two self-expandable bare stents inserted after the completion of BT treatment.

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**Fig. 6**: Figure 1. Klatskin's III a tumor. A): MR Cholangiography; b) abdominal MR showing a right hepatic artery thrombosis (arrow) and infiltration of the right portal vein (arrowhead), thus confirming tumor unresectability. c) PTC confirms the diagnosis and is followed by bilateral PTBD positioning (d). E) Brachytherapy planning, with a measuring catheter inserted percutaneously within the biliary drainages. f) Two self-expandable bare stents inserted after the completion of BT treatment.

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Results

All patients had complete remission of jaundice at the end of the BT.

No patient developed acute complications from BT and EBRT during the first two weeks. Generally, chemo-radiotherapy was reasonably well tolerated, and all patients completed the intended treatment course. Severe post-radiotherapy complications (digestive haemorrhage and hepatic abscesses development) occurred in one patient (3%), five months after EBRT, leading to the death of the patient. The median survival of the entire population was 12 months (range 7.76-16.24 months) (Figure 2). Cumulative 6 month, 1 year and 2 year mean survival rates were 78.12%, 53.12 % and 15.62%, respectively. The median survival rate for Group A (14 patients who received only BT) was 7 months (range 3.33-10.66 months), for Group B (11 patients who underwent BT with EBRT without ChT) was 14 months (range 4.28-23.71 months), for Group C (7 patients who underwent the complete protocol of BT, EBRT and ChT) was 15 months (range 7.3-22.69 months): the differences among the 3 groups was not statistically significant (p=0.128) (Figure 3). Mean 6 month, 1-and 2-year survival rates were 57.14%, 28.57 % and 7.14% for Group A; 81.81%, 63.63% and 27.27% for Group B; 85.71%, 71.42% and 0% for Group C, respectively. On univariate analysis, the patients who received EBRT + BT (Groups B+C) with or without ChT (n= 18) had a median survival of 14 months (range 9.84-18.15 months), significantly higher (p = 0.049) than that of 7 months (range 3.33-10.66 months) for the patients treated with BT alone (Group A) (Figure 4). Age, gender, type of CLCA, BT dose and bilirubin level before treatment were not found to affect patient outcomes.

Twenty-seven patient deaths (84.38%) were cancer-related while 3 patients (9.38%) died from other causes (2 patients died from cardiovascular disease and 1 from post-radiotherapy complications), and the cause of death was not assessable in 1 patient (3.12%). One patients (3.12%) was alive at the last follow-up.

The mean duration of hospital of the entire cohort was 15 days (range 8-17), without differences among the groups.

Four patients (12.5%) required a percutaneous revision of the metallic stent due to stenosis for tumor ingrowth after the completion of the protocol (median 14 months; range 5-19 months); a stent-in-stent procedure was carried out, successfully restoring stent patency.
Fig. 7: Figure 2: Survival of the entire study population

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Fig. 8: Figure 3: Kaplan-Meier median survival curves for the three groups, according to the therapy protocol (p=0.128)

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Fig. 9: Figure 4: Kaplan-Meier median survival curves for the patients in Groups B+C (treated with EBRT + BT with or without ChT: continuous line) and those in Group A (who received BT without EBRT and ChT: broken line) with statistically significant difference between the two groups (p = 0.049).

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Conclusion

In conclusion, in unresectable hilar CLCA, a multimodal treatment consisting of high dose (up to 60 Gy) radiation therapy obtained by combining intraluminal BT and EBRT, followed by percutaneous metallic stent positioning and combined with systemic ChT represents the-state-of-the-art regimen. This protocol achieved significant improvement in overall survival, low morbidity and a short hospital stay, and it represents a valid substitute for surgical palliation. However, prospective randomised trials are still needed to adequately determine which patients may benefit from this approach.
References


