Abstract. Klatskin-type cholangiocarcinoma is a rare tumor, bearing a very poor prognosis: at diagnosis, most patients can only undergo palliation. Evaluation of outcome, mean survival and quality of life was performed in patients with unresectable hilar cholangiocarcinoma treated with multimodality approach in comparison with surgical palliation, biliary stenting or brachytherapy alone. Twenty-six patients with hilar cholangiocarcinoma were studied: 16 patients were enrolled in the multimodality protocol (bilateral biliary drainage; Iridium-192 brachytherapy; plastic endoprosthesis or metallic stent positioning and external radiotherapy plus systemic chemotherapy), 5 patients underwent surgical palliation and 5 percutaneous decompression alone. Nine patients completed the protocol and 7 were treated with brachytherapy followed by biliary stenting alone. The multimodality approach obtained mean survival (10 months) similar to that for surgery and higher than that of the brachytherapy and metallic stenting groups (6 and 2.75 months, respectively). The average hospital stay (15 days) was lower than that of the surgical group (20 days). A multimodality approach is a suitable alternative to palliative surgery of unresectable hilar cholangiocarcinoma.

Cholangiocarcinoma (CLCA) is a rare tumor, accounting for 2 to 6% of all cancer patients, originating from the extrahepatic bile ducts, with high local invasiveness but uncommon distant metastases (1-3). The topographic classification has major prognostic value and identifies three types of cholangiocarcinoma: (i) CLCA in the lower third of the bile duct; (ii) CLCA in the middle third of the bile duct (common bile duct); and (iii) CLCA in the upper third of the bile duct, located at the hepatic duct confluence. The latter, also called Klatskin tumor, account for more than 50% of cases (4, 5) and are divided into four types by Bismuth (1), according to the location and extent of the tumor and carry a poorer prognosis since surgical resection is possible in only 0 to 47% of cases (5-7). Therefore, at the time of diagnosis, most patients can only undergo palliative treatments.

Many therapeutic protocols using radiotherapy (intraluminal brachytherapy and external beam) combined with biliary decompression have been advocated to provide a resolution of jaundice associated with elective treatment of neoplastic stenosis (8-12).

The aim of this study was to evaluate outcome and mean survival of the multimodality approach (percutaneous drainage of both right and left biliary systems; Iridium-192 intraluminal brachytherapy; replacement of the drainages with plastic endoprosthesis or metallic stents and external radiotherapy associated with systemic chemotherapy) in comparison with palliative surgical treatment, percutaneous decompression or brachytherapy alone.

Patients and Methods

From January 1998 to December 2005, 26 patients with obstructive jaundice due to hepatic hilar cholangiocarcinoma were evaluated. All patients underwent the following diagnostic examinations: abdominal spiral CT to detect hepatic, lymphatic or peritoneal metastases; angiography of the celiac trunk and hepatic artery to detect arterial or portal infiltration; percutaneous transhepatic cholangiogram (PTC) to detect stenosis location, morphology and extent and position internal biliary drainage (PIBD) to obtain jaundice remission.

According to the diagnostic findings (vascular infiltration, neoplastic extension to intrahepatic bile ducts and hepatic metastases), 16 patients with >3 cm tumor extension were considered unresectable and were enrolled in our multimodality protocol. Out of the remaining patients, five with a favourable
anatomical (<3 cm tumor extension) and clinical condition, underwent surgical palliation (hepatic-jejunostomy) and five patients, unresectable due to advanced disease and in poor clinical conditions, were treated with biliary decompression alone, by inserting definitive metallic stents.

**Multimodality treatment.** Percutaneous cholangiography demonstrated the neoplastic infiltration of the bile ducts confluence in all patients and was followed by the percutaneous placement of two internal biliary drainages, on the right and left sides (Figure 1a-b). Cholangiography also allowed definition of the correct irradiation field of brachytherapy corresponding to a cylindrical volume 2 cm in diameter with a length including the neoplastic stenosis plus a proximal and distal tumor-free margin of 15 mm; this strategy warrants the control of any submucosal tumor spread frequently undetected at cholangiography.

Intraluminal brachytherapy was performed by inserting, two Iridium-192 sources within both right and left internal biliary drainages (Figure 1c), in two consecutive weekly sessions (on days 7 and 14) with a dose of 7 Gy each (total dose: 14 Gy).

After brachytherapy, the biliary drainages were replaced with plastic endoprostheses (12 patients) (Figure 1d) or with permanent metallic stents (4 patients).

The first phase required an average hospital stay of eight days; the plastic endoprostheses were left in place for three months to stabilize the post-radiation cicatisation and were then endoscopically removed (Figure 1e). In the last four patients permanent metallic stents were positioned (Figure 1f), which guarantee longer patency rates compared to plastic endoprostheses, with no further revisions or endoscopic removal requirement, thus, improving the patient’s quality of life.

Two weeks after the end of intraluminal brachytherapy, patients received external radiotherapy (46 Gy) at the outpatient’s clinic in 5-week cycles (26 administrations of 180 cGy each), associated with systemic chemotherapy (5-fluorouracil, 300 mg/day at week 1 and 5 during radiotherapy).

Three months later, the biliary endoprostheses were removed by endoscopic or percutaneous transhepatic approach or by a combined technique, after a cholangiogram performed to control biliary ducts patency (Figure 1d). The patients with definitive metallic stents were submitted to a follow-up with laboratory tests and ultrasound examinations every 3 months.

**Results**

Nine patients completed the multimodality protocol while 7 patients were treated with brachytherapy and biliary stenting alone, due to rapid clinical worsening. The last three patients who completed the protocol received bilateral metallic stents, without immediate complications.

No patient treated by radiotherapy developed acute complications during the first two weeks. Chronic post-radiotherapy complications (digestive haemorrhage and hepatic abscesses) occurred in one patient five months after treatment, causing the exitus.

All patients treated with the multimodality approach had complete remission of jaundice at the end of intraluminal brachytherapy.

The nine patients who completed the protocol had a similar survival (10 months) to the surgical group (5 patients, 10.5 months), but higher than the other groups treated with brachytherapy plus biliary decompression (7 patients, 6 months) and metallic stenting alone (5 patients, 2.75 months).

The average hospital stay was 15 days (range 8-17 days) for the multimodality treatment group and 20 days (range 15-30 days) for the surgical group due to a higher morbidity rate.

**Discussion**

Hilar CLCA is an uncommon tumor recognized as a distinct clinical entity after the first study of 13 patients in 1965 (4). Resection with negative margins is the only curative treatment and this often necessitates major hepatectomy. Unfortunately, radical surgery is applicable in about 20% of cases, the remaining patients being candidates for palliative therapies.

The aims of palliation in patients with unresectable hilar CLCA would be relief from obstructive jaundice, pruritis, cholangitis, pain and quality of life improvement (13, 14).

The palliative options for the treatment of unresectable hilar CLCA are represented by surgical, endoscopic and percutaneous palliation.

Patients undergoing surgical bypass are reported to have a longer survival and a superior quality of life compared to those palliated by other means. However, these results need to be interpreted with caution because the patient population between the two groups was dissimilar, with lower risk patients undergoing surgical palliation and those with advanced disease or co-morbidity being referred for percutaneous biliary drainage (13).

At present, the current use of self-expandable metallic stents, placed by percutaneous or endoscopic approach, is becoming the first choice in palliative treatment for patients affected by advanced disease, with low procedure-related complications and mortality and a satisfactory long-term patency.

Recently, radiotherapeutic treatments have shown promising results in controlling biliary obstruction as direct antitablastic therapy (8, 10, 12, 15), especially with a combination of external beam radiotherapy (EBRT) and brachytherapy (16). The rationale for the use of this association is the delivery of single large dose of radiation administered to an area with high risk of complications, such as upper gastrointestinal bleeding or stenosis, cholangitis and ascites.

The combination of radiotherapy and chemotherapy is another therapeutic approach for the management of unresectable cholangiocarcinoma, with the aim to achieve locoregional and systemic tumor control. The initial studies
regarding the use of 5-fluorouracil associated with radiotherapy report a beneficial effect with significant improvement in the quality of life in responders (14, 17-19).

Therefore, we decided to use a combined radio-chemotherapy treatment (intraluminal brachytherapy and external radiotherapy plus systemic chemotherapy) with percutaneous intervention in patients with unresectable hilar CLCA, obtaining a better outcome (low incidence of intercurrent diseases and no mortality) and cost/benefit ratio (average hospital stay of 15 vs. 20 days with surgery) compared to surgical palliation (20, 21).

Our results are promising, since no complications occurred in the nine patients who completed the protocol, with an average survival of 10 months, similar to the outcome after surgical biliary decompression (10.5 months) in control group. These results are comparable with other reports in recent published series (16, 22). This is particularly satisfactory since all patients in our study had a neoplastic stenotic extension at cholangiography >3 cm, an independent negative prognostic factor for the outcome of patients with hilar CLCA.

An accurate evaluation of the diagnostic findings is mandatory in order to select suitable unresectable patients, thus avoiding an explorative laparotomy, and to enrol these patients in alternative treatment.

In conclusion, in the absence of Randomized Controlled Trials comparing different palliative treatments, and based on our results, we believe that combined percutaneous and radio-chemotherapy approach represents a valid alternative to surgical palliation of unresectable hilar cholangiocarcinoma, improving patient survival, with lower morbidity, shorter hospital stay and subsequent lower cost/benefit ratio.

Figure 1. Type IV Klatskin tumor. (a) Transhepatic cholangiography shows severe neoplastic stenosis of the biliary ducts at the confluence, involving the hepatic ducts and proximal common bile duct, with a 3 cm global extension. (b) Placement of right and left transhepatic drainage (10 F), with efficient internal biliary system decompression. (c) Intraluminal brachytherapy simulation, performed by inserting two calibrated guidewires within the drainages, to measure the extension of the "target area". (d) After intraluminal brachytherapy, a double J right and left plastic endoprostheses were inserted, with decompression of the bile ducts. (e) Three months later, after transhepatic removal of the endoprostheses, an adequate restoration of biliary patency was obtained, as demonstrated at cholangiography. (f) In this case, after brachytherapy, a double metallic stent was definitively inserted to ensure biliary patency.
References


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