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Clinical outcome after biliary drainage for metastatic colorectal cancer: Survival analysis and prognostic factors

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ABSTRACT

Introduction: Biliary obstruction secondary to colorectal cancer liver metastases is associated with a poor prognosis especially when chemotherapy cannot be re-started. The aim of this study was to determine the survival after biliary drainage and the associated prognostic factors.
Methods: Patients from two French centers were included retrospectively after first biliary endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography drainage for biliary obstruction secondary to liver metastases of colorectal cancer, occurring during chemotherapy.
Results: The final analysis included 69 patients. Overall median survival was 115 days. In univariate analysis, a previous liver surgery, technical and functional success of drainage and restarted chemotherapy were significantly associated with an improved survival. Chemotherapy was restarted after a median of 27 days. When drainage was efficient, survival improved from 33 to 262 days ($p < 0.001$). In multivariate analysis, significant protective factors for survival included previous a hepatectomy (HR 0.41) and functional success of the drainage (HR 0.29). Predictive factors for death included increased lines of chemotherapy (HR 1.68) and fever before drainage (HR 2.97).
Conclusions: This is the first study concerning the benefits of biliary drainage for malignant biliary obstruction during the course of chemotherapy for colorectal cancer. A successful biliary drainage leads to improved survival and allows achievement of chemotherapy for 70% of patients.

1. Introduction

Colorectal cancer (CRC) is the third most frequent cancer in men worldwide and the second in women, rates being higher in developed countries. Its incidence is about 1.4 million cases and causes nearly 700,000 annual deaths worldwide [1]. Overall and progression-free survivals have improved since the introduction of biotherapies in first line chemotherapy for metastatic CRC (mCRC), whether in association with 5-fluorouracil [2], 5-fluorouracil-irinotecan [3], capecitabine alone [4,5] or oxaliplatin plus fluoropyrimidine [6]. The CRC related 5-year survival rate approaches 60% [7], and almost 50% of patients will develop metastases, with the most frequent location being the liver. One of the major complications of metastatic evolution is the onset of obstructive jaundice that can be due to intrahepatic and/or extrahepatic obstruction. Jaundice is associated with a poor prognosis, worsens quality of life and makes it impossible to receive some chemotherapeutic agents, such as irinotecan [8]. In 2008, patients who received only supportive care survived a median of 28 days [9] after the onset of jaundice, whether it was an obstructive jaundice or related to liver metastases.

There has been significant improvement in bile duct drainage techniques over the past ten years, combining percutaneous transhepatic cholangiography (PTC) drainage and endoscopic drainage by cholangiopancreatography (ERCP) and/or endoscopic ultrasonography (EUS) [10] (hepaticogastrostomy, choledochoduodenostomy, "rendez-vous" technique). These procedures are

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essential for the relief of symptoms caused by obstructive jaundice in gastrointestinal cancer [11].

2. Background

Most reports demonstrate the feasibility of biliary drainage. However, little information is known about the clinical benefits for patients and about some predictive variables for survival and efficacy of such endoscopical and radiological interventions. Multidisciplinary advice, taking into account patient's performance status, oncologic treatment strategy and expected benefits, is needed before undergoing an invasive procedure during the end stages of a patients' life. It is essential that the oncologist responsible for referring a patient for biliary drainage can perform a risk/benefit assessment.

The main aim of this study was to assess the survival outcomes for patients under chemotherapy for mCRC after biliary drainage. Secondary aims were to look for predictive factors that may guide better patient selection.

3. Materials and methods

This retrospective study analyzed patients from two expert French oncologic and tertiary endoscopic centers (University Timone hospital, Marseille and Paoli-Calmettes Institute, Marseille) between January 2005 and December 2014. Eighty-four patients were included after first biliary drainage for biliary obstruction secondary to liver metastases of CRC occurring during chemotherapy. All of the patients had histologically confirmed colorectal adenocarcinoma with liver metastases. They presented chemotherapy contraindications because of obstructive jaundice or cholestasis (intrahepatic obstruction due to hepatic metastasis or extrahepatic obstruction due to lymph nodes or peritoneal carcinomatosis) with or without cholangitis, treated by ERCP, EUS or PTC. Patients in a palliative situation without any possible oncologic treatment were excluded. Demographical, biochemical, procedure details, radiographical reports and outcome data were registered. All of the patients underwent, before drainage, an abdominal ultrasound (18 patients), and/or computed tomography (CT) (43 patients) and/or magnetic resonance cholangiography (MRC) (8 patients), which provided mapping of the biliary tree and revealed the site of the obstruction (common hepatic duct, hilum, or involving secondary bile ducts). When bile ducts were not dilated or dilated in non-communicating sectors, patients were not included.

All procedures were performed under general anesthesia and tracheal intubation in dorsal decubitus. ERCP were performed with therapeutic duodenoscope (ED-530XT8, FUJINON™, Japon ou ED34-i10T, PENTAX-HITACHI™, Hambourg, Germany depending on the center). Sphincterotomy was performed after a hydrophilic guide wire had been inserted in the biliary duct and cholangiography. For the PTC procedures, we punctured a peripheral bile duct under ultrasound monitoring or fluoroscopic guidance. In case of failure or impossibility of reaching the common biliary duct, EUS drainage was performed with therapeutic echoendoscope (EG 3870UTKPENTAX-HITACHI™, Hambourg, Germany). Hepaticogastrostomy was made by puncturing the intrahepatic biliary duct using a 19-gauge needle, which was exchanged over a guidewire for a 6.5-Fr diathermic cystotome and used to enlarge the channel. Insertion of biliary stents was performed under fluoroscopic guidance. One or two uncovered metal expandable stents and/or one or two plastic stents were positioned; their numbers and length depended on the stricture. A partially covered metal expandable stent was used for hepaticogastrostomy.

Technical success was defined as the ability to achieve the procedure of all biliary strictures, including the drainage of all opacified sectors and pneumobilia visualization. Partial technical success was defined by the persistence of dilated undrained areas. If the initial procedure failed or was considered incomplete, a second procedure by the same technique or by a combined approach (rendez-vous technique) was performed.

Functional success was defined as a decrease in bilirubin level to less than 50% of the pre-treatment value and/or healing sepsis within the first 15 days.

Adverse events and their severity were defined according to the 1991 consensus guidelines [12]. Perforation was obvious during the procedure or demonstrated by early CT. Immediate post sphincterotomy bleeding consisted of endoscopic evidence of venous oozing that required local hemostasis by injection of epinephrine or clips. Delayed bleeding was defined as clinical evidence of hemorrhage with a decrease in hemoglobin greater than 2 g/dL and the need for endoscopic treatment and/or blood transfusion up to 30 days post procedure. Procedure induced pancreatitis was defined as the onset of pancreatic pain and <3-fold elevation of serum lipase levels within 24 h post procedure, requiring at least one night of hospitalization. Cholangitis was defined as a temperature of more than 38.5 °C without evidence of other concomitant infections. Procedure related mortality was analyzed. The necessity of replacing a new stent for signs of inadequate bile drainage within 30 days was analyzed. Median survival time was defined as the time from the procedure until the time of death.

3.1. Statistical analysis

The continuous variables were described by their means, standard deviation, minimum and maximum value and first and third quartile. The categorical variables were described by their size and percentage.

The categorical variables were compared with the outcome of (1) functional success and (2) biliary stenosis using chi-squared tests or Fisher's exact test, according to the conditions of application. The non-parametric Wilcoxon signed-rank test was used for continuous variables. The results were considered statistically significant with a p value of $p \leq 0.05$.

Prognostic factors for the binary variable "death" were studied by the Kaplan–Meier method. The logrank test was used to compare the estimated distributions.

Cox models were used to perform univariate and multivariate survival analysis to calculate hazard ratios.

Statistical analysis was performed using the software program R (version 3.1.0).

4. Results

4.1. Patient characteristics

Of the 84 patients, 69 who had biliary obstruction secondary to colorectal cancer liver metastases responsible for jaundice or cholangitis after first biliary drainage were included. Fifteen patients could not be included because of unavailable data. Only one patient was alive at the time of analysis.

The median age was 71 years (range 31–93 years) and were mostly men (69.6%). Baseline clinical data are provided in Table 1. The median time from the CRC diagnosis and the development of biliary obstruction was 31.1 months (16.13–61.1). Six patients (8.7%) had not started chemotherapy, 15 (21.7%) were on first-line therapy, 13 (18.8%) were on second-line therapy and 35 (50.7%) were on third-line or more therapy. Sixty-five patients (94.2%) had jaundice before drainage, of which 11 had a documented fever. The remaining four had fever without jaundice. All of these symptoms contraindicated chemotherapy. Biliary stenosis was situated

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