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Research papers

Early liver metastases in resectable periampullary cancer: Incidence and risk factors

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ABSTRACT

Purpose: The aim of the present study was to estimate the incidence of very early hepatic metastases (HMs) (< 6 months) and their imaging patterns after cephalic duodenopancreatectomy (CDP) for periampullary carcinoma (excluding duodenal carcinoma) and to identify their associated risk factors.

Methods: From January 2003 to June 2016, all patients who underwent surgical treatment for periampullary carcinoma by CDP at our institution and with adequate pre- and postoperative CT scans were included. Univariate and multivariate logistic regressions were performed to determine factors associated with very early HM and recurrence.

Results: Of the 132 patients included retrospectively, 27 (20.5%) patients developed HMs. The mean time to diagnosis of HM was 103.9 ± 55.2 days. HMs were multiple in 81.4% of cases and bilobar in 59.3% of cases; their mean maximum size was 16.7 ± 12.7 mm.

In univariate logistic analysis, lymphovascular emboli were significantly associated with HM (p = 0.02). No independent risk factors for HM were found in multivariate analysis. In multivariate logistic analysis, two independent risk factors were identified for the occurrence of early recurrence: tumor size > 23 mm on preoperative CT scan (OR: 3.3; 95% CI: [1.2–9.3]; p = 0.02) and tumor differentiation (poor vs. good: OR 15.5; 95 CI [1.5–158.3]; moderate vs. good: OR: 17.1; 95% CI: [1.9–154.4]; p = 0.04).

Conclusions: Nearly one in five patients developed HM after CDP within 6 months with a highly consistent pattern. A thorough preoperative assessment, combining CT scan and MRI with a delay of less than three weeks before surgery, appears essential. A routine systematic postoperative CT scan at 8 weeks is also required prior to initiating adjuvant chemotherapy.

The type of surgical intervention does not seem to be a risk factor, although the risk of HM occurrence appears to be related to the lymphovascular invasion of the tumor and maybe its degree of differentiation, elements not assessable by imaging.

1. Introduction

In 2017, pancreatic head cancer is the fourth leading cause of cancer death in Europe [1]. Its prognosis is poor, with a 5-year survival, regardless of stage, ranging from 2 to 9% depending on the study [2]. Only 20% of patients undergo potentially curative resection [3]. Even after cephalic duodenopancreatectomy (CDP), the 5-year survival is estimated to be between 10 and 27% [4]. This number is largely influenced by the rate of early recurrences, defined as occurring within 12 months after surgery. The reported frequency of early recurrence in the literature varies between 20 and 61% [5–8]. Unlike late recurrences, early recurrences more often occur in the form of distant metastases, particularly in the liver (68.8%), as opposed to local recurrence (31.2%) [9], and have a more pejorative prognosis, with a 5-year survival of 9.4

Abbreviations: CDP, cephalic duodenopancreatectomy; HM, hepatic metastasis; PC, pancreatic or ductal adenocarcinoma; PVC, papilla of Vater carcinoma; BDC, primary bile duct cancer; IPMN, intraductal papillary mucinous neoplasm; DC, duodenal cancer; LNR, lymph node ratio; ASCO, American Society of Clinical Oncology

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vs. 42.4% [7].

There are very few data regarding the exact incidence of very early (< 6 months) hepatic metastases (HMs) discovered during the post-operative recovery window and at the initiation of chemotherapy for periampullary tumors. The presence of these metastases suggests the possibility of preoperative liver micrometastases, thus requiring improvement in preoperative staging.

The main objective of the present study was to estimate the incidence of very early HM (< 6 months) and recurrence in patients who had undergone CDP for carcinoma with a pancreaticobiliary phenotype and to identify possible clinical, radiological, pathological and surgical risk factors.

The secondary objective was to compare the above occurrence rate with that of a control group consisting of duodenal adenocarcinomas treated by CDP.

2. Materials and methods

2.1. Study design

This retrospective, observational single-center study was conducted at the Regional University Medical Centre *(Centre Hospitalier Régional Universitaire, CHRU)* in Nancy.

2.2. Ethical and regulatory aspects

In accordance with Article 22-2 of the modified French Data Protection Act, this study was entered into the registry of the Data Protection Office of the CHRU of Nancy under the number R2016-49. The data were anonymized during their extraction.

2.3. Sampling

The inclusion criteria were as follows: adult patient who had undergone surgical treatment by CDP for pancreatic or ductal adenocarcinoma (PC), papilla of Vater carcinoma (PVC), primary bile duct cancer (BDC) or malignant intraductal papillary mucinous neoplasm (malignant IPMN) with pathological confirmation and who had undergone thoracic-abdominal-pelvic CT less than 6 weeks prior to surgery and postoperative CT 6 months or later in the absence of recurrence or within 6 months in the event of recurrence.

Patients operated for neuroendocrine tumors or arterial borderline tumors were excluded.

A control group consisting of duodenal cancers (DCs) also treated by CDP was established.

2.4. Data collection

The data were collected over the period spanning from January 2003 to June 2016 using several search programs: imaging archives (Picture Archiving and Communication System (PACS)), pathology archives (DIAMIC© database, Infologic-Santé, Valence, Rhône-Alpes, France) and archives of the Department of Digestive Surgery (using the CCAM coding of the classification of diseases (ICD.10)).

2.4.1. Clinical data and preoperative staging

General data such as gender, age at diagnosis (considered as the date of preoperative CT scan) and BMI were recorded.

Preoperative thoracic-abdominal-pelvic CT scans were performed using a 64-detector CT scanner (GE Healthcare) and a standard multiphasic protocol consisting of the following:

- Abdominal-pelvic acquisition without injection (section thickness: 1.25 mm).
- Injection of 1.5 mL/kg of iodinated contrast agent with a flow rate of 3 mL/s.
- Supramesocolic arterial acquisition at 35 s after the initiation of the injection (section thickness: 1 mm).
- Abdominal-pelvic portal or venous acquisition at 80 s after the initiation of the injection (section thickness: 1 mm).
- Late supramesocolic acquisition at 180 s after the initiation of the injection (section thickness: 1 mm).

The scans were jointly reviewed by two radiologists with 5 and 15 years of experience.

The following data were collected on preoperative imaging: delay time between CT and surgery, tumor size (mm) and tumor resectability according to the MD Anderson criteria [10].

In instances where preoperative hepatic MRI was performed, the absence of HM was verified.

2.4.2. Treatments

Regarding surgery, the following information was collected after a review of the surgical reports by a senior surgeon: the performance of a venous resection, type of lymphadenectomy, i.e., standard or extensive [11], including celiac trunk lymphadenectomy and decompression of the celiac trunk.

The performance of adjuvant chemotherapy beginning within eight weeks after surgery was noted.

2.4.3. Histological data

From the histopathological reports established for each surgical specimen, the following prognostic factors were obtained: tumor histological type, tumor differentiation, tumor size, T and N stages according to the TNM classification, perinervous sheathings, lymphovascular invasion and quality of R0/R1 surgical resection according to the Royal College of Pathologists [12].

The numbers of studied and invaded lymph nodes, as well as the lymph node ratio (LNR), were collected.

2.4.4. Patient follow-up

The appearance of HM was defined by the occurrence of focal hepatic lesions within a delay of less than 6 months after surgery. These lesions were confirmed by MRI, transparietal biopsy or CT follow-up. The date of the HM diagnosis corresponded to the date of the post-operative CT scan that revealed the abnormalities. The following HM characteristics were specified: number, maximum size and uni- or bilobar distribution. Other types of recurrence were noted on post-operative CT: appearance of local recurrence, pulmonary metastases and peritoneal carcinosis.

2.5. Statistical analysis

Characteristics of the study sample are described according to the usual parameters: percentages for categorical variables and mean and standard deviation, median, quartiles and min/max for continuous variables.

For the comparative analysis of variables between groups, Chi-2 or Fisher's exact test was used for qualitative variables and Student's or the Wilcoxon test for quantitative variables.

To identify factors associated with early liver recurrences or metastases, bivariate logistic regression (selection of candidate variables at the $p < 0.1$ threshold) and multivariate logistic regression models were used ($p < 0.1$). The association strength was estimated by odds ratios (ORs) and their 95% confidence intervals (95% CIs).

The threshold for statistical significance was set at 5%.

Analysis of the statistical data was carried out using the SAS v9.4 software package (SAS Institute Inc., Cary, NC; 25513) with the support of the PARC CHRU de Nancy.