



Original Article

Morphological aspects of the hepatic response to neoadjuvant therapy



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ABSTRACT

Introduction: Therapy of metastatic colorectal carcinoma has greatly evolved in recent years. Surgery is still the best curative option and can improve survival in stage IV disease. Neoadjuvant chemotherapy (NAC) has emerged as a widely used therapeutic option before surgery. Pathologists have developed several systems to grade response, mainly adapting the grading systems used for the response in primary esophageal or rectal tumors. There are many reports confirming the prognostic utility of these grading systems. However, there have been fewer references to the potential significance of the pattern of histological response. The objective of the present study is to describe the histopathological lesions found in the tumor bed after NAC and their potential significance in terms of prognosis.

Material and methods: We reviewed the files of patients with colorectal carcinoma that developed hepatic metastasis during follow-up and received NAC before surgical resection of metastasis. We gathered demographic, analytical and morphological data of the cases, and also reviewed the hepatic resection samples to measure the pathological response to chemotherapy according to Blazer's criteria, and to define the predominant patterns of response (mucin pools, fibrosis or necrosis). We also determined the presence of satellitosis, measured the thickness of the tumor-normal interface (TNI) as proposed by Maru et al., and searched for vascular and bile duct invasion. All these pieces of information were collected in an Excel database and analyzed with SPSS 20.0 for Windows statistical package. The outcome measures were disease-free survival and overall survival in months since the first surgery to resect metastatic disease.

Results: Fifty patients fulfilled the inclusion criteria for the present study. All of them had received a chemotherapeutic regimen mainly based on platinum, associated or not with targeted drugs (18% received anti-EGFR drugs and 24% anti-VEGFR drugs). Of the primaries, 66% were of sigmoid-rectal origin, and 32% of the cases showed a major histopathological response to therapy (including 3 cases with a complete response). In 76% of the tumors, the predominant histological pattern was necrosis, followed by fibrosis (57.4%). Mucin pools were the predominant feature in 23.4% of the tumors. We found satellitosis (microscopic tumor nodules separated by more than 1 mm from the principal tumor) in 53.2% of the cases. A prominent inflammatory reaction was found in 19% of the cases, and it was mainly composed of lymphocytes and histiocytes (70% of the cases). Vessel invasion was seen in 30% of the cases, and perineural invasion was only found in 4%. We found no case of bile duct invasion by the tumor. The thickness of the TNI measured less than 2.5 mm in 60% of the present series. Statistical analysis of the series revealed that thickness of the tumor-liver interface was significantly associated with recurrence and overall survival. We found a significant association between response and thickness of the tumor-normal liver interface. In our series, the presence of satellitosis tended to predict a shorter DFS. The comparison of Kaplan–Meier curves with the log-rank test showed a significant association between overall survival and the presence of mucin pools and fibrosis in the tumor bed. The other histopathological factors did not predict differences in prognosis. These differences were independent of the use of targeted drugs.

Abbreviations: NAC, neoadjuvant chemotherapy; TNI, tumor-normal interface; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

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Discussion: The pathological reports of hepatic metastasis from colorectal carcinoma resected after NAC usually indicate only the number, the size and the response of the tumor cells to therapy, apart from the distance to the resection margin of the specimen. Few reports have analyzed the possible prognostic significance of the different kinds of histopathological responses. The results of the present study indicate that those tumors with extensive pools of mucin show a significantly worse prognosis as compared to tumors with less mucin secretion. Fibrosis indicates a better prognosis, except when desmoplasia is present. Our study further supports the prognostic significance of the thickness of the tumor-hepatic interface. We conclude that pathology reports should specify the kind of histopathological response to therapy, besides grading it, because this might add significant prognostic information.

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1. Introduction

Colorectal carcinoma is one of the most frequent human malignancies, largely in developed countries [1]. Despite recent advances in therapy, mainly after the introduction of targeted drugs against EGFR and VEGFR [2], mortality remains high for advanced stages, especially for metastatic disease. The best therapeutic option for metastasis amenable to resection is surgery [3], but neoadjuvant chemotherapy (NAC) is being increasingly used as a therapeutic alternative for patients with metastatic disease before resection [4], and it can achieve 40–60% survival at 5 years, similar to stage III disease. Several schemes have been developed to grade histopathological response of the metastatic tumor to NAC [5] and this factor is very important to help predict the outcome of the patients [6]. At present, pathological reports usually report only on the number of metastatic nodules, their size, the distance to the resection margin and the grade of response, but the pattern of response can vary widely between patients, and there might be some pathological aspects that increase the prognostic significance of the pathological reports. The aim of the present study is to analyze some morphological aspects of hepatic metastasis that are not usually considered in the pathological report, and to determine their possible prognostic influence.

2. Material and methods

We retrospectively reviewed the electronic files of the patients with colorectal carcinoma treated at the Fundación Jiménez Díaz Hospital in Madrid (Spain). From these, we included in the study those with initially resectable hepatic metastasis that received NAC and were subsequently operated on with disease free margins. After surgery, they received standard adjuvant therapy. For the objectives of the present study, we only included the specimen of the first resection (some patients were operated on several times after local recurrences of the hepatic lesions), and in case of multiple nodules, we calculated a mean value for the quantitative data and estimated the predominant pattern as an average value for all the nodules together. In our hospital, the metastasis resection specimens are completely embedded in paraffin. In cases with complete response, we performed serial sections and mucin stains, but we did not perform immunohistochemistry to search for cytokeratin-positive cells.

We collected general demographic and clinical data and also data from the primary tumor (location, differentiation grade, vascular invasion, inflammatory response, TNM staging). Besides, we reviewed the stained slides of the metastatic hepatic nodules to describe the morphological response to therapy according to Blazer criteria [6], but also other morphological features, such as vessel invasion, bile duct invasion, hepatic parenchyma invasion, presence of satellitosis (defined as a metastatic nodule separated more than 1 mm from the main nodule), differentiation grade of the metastatic nodule, inflammatory reaction within the nodule and kind of inflammatory response. We also measured the thickness

of the tumor at the tumor-normal interface (TNI), as proposed by Maru et al. [7] Prognosis of the patients was measured with the time to recurrence (disease free survival; DFS) and with the time to death secondary to the tumor (overall survival; OS), both expressed in months. All histopathological features were reviewed by two independent pathologists (MJFA and LE) blinded to the outcome of the patients. In case of discordance, the cases were reviewed together by the two pathologists to reach consensus. Concordance rate ranged between 75% and 80%.

Data were analyzed with SPSS for Windows 20.0 statistical package (IBM corporation). Univariate association between pathological and outcome variables was evaluated by chi-squared (or Fisher's exact) test. For survival analysis, we compared the Kaplan–Meier curves with the log-rank test. Due to the small sample size, no multivariate regression model was adjusted. The level of statistical significance was defined as a *p* value less than 0.05, as usual.

Permission for this study was obtained from the Ethical Committee on Scientific Investigation of our hospital. This study is in accordance with the national Spanish regulations concerning personal data protection.

3. Results

Inclusion criteria were fulfilled by 50 patients for the present study. The median follow-up time in this series was 55 months (range: 14–140). Table 1 summarizes the general characteristics of the series. Table 2 summarizes the histopathological features found in the metastatic nodule (Figs. 1–3). For the purpose of this study, we constructed an operator–receiver curve to determine the best cut-off point for the quantitative values and used the calculated

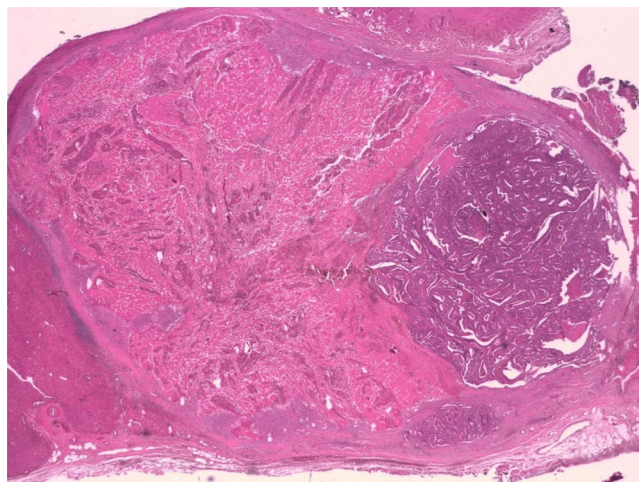


Fig. 1. Hepatic metastasis showing major response to NAC (H&E stained slide, ×40). Note the presence of tumor in less than 50% of the tumor bed and the extensive areas of necrosis.

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