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# Factors Predicting Response to Neoadjuvant Therapy of Hepatic Metastasis from Colorectal Carcinoma

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**Summary**

**Introduction:** Neoadjuvant chemotherapy (NAC) is a widely used therapeutic option for patients with resectable hepatic metastasis from colorectal carcinoma. In this setting, the intent of NAC is to reduce metastatic size and make surgery easier and/or less extensive, mostly in patients that are amenable to surgery. Several studies confirm that response to neoadjuvant therapy is indicative of a better prognosis for such patients and several methods have been proposed and validated to measure both radiological and histopathological response. However, surgery remains the only curative option for these patients and patients should be operated on after chemotherapy regardless of response. Knowing this, it would be beneficial to predict which patients are likely to respond to therapy, for a lack of response could make resection of hepatic metastatic disease more difficult or even impossible and result in a delay in efficient therapy with negative consequences for the patient. Very few studies have analyzed this issue to date. The objective of the present study is to determine the factors that can predict response to NAC of hepatic metastasis from colorectal primary turmors.

**Material and Methods:** We reviewed the files of patients with colorectal carcinoma that developed hepatic metastasis and who received neoadjuvant chemotherapy before surgical resection of metastasis. We also gathered demographic, analytical and morphological data of the cases and reviewed the hepatic resection samples to measure the pathological response to chemotherapy according to Rubbia-Brandt et al. criteria. A statistical analysis was done to define which factors can help predict response to therapy.

**Results:** 50 patients fulfilled inclusion criteria for the present study. All of them had received a chemotherapeutic regimen mainly based on platinum, associated with or without targeted drugs (18% received anti-EGFR drugs and 24% anti-VEGFR drugs). Sixty-six% of the primaries were of sigmoid-rectal origin and 32% of the cases showed a good histopathological response to therapy (including 3 cases with a complete response). As for the factors predicting response to therapy, we performed a logistic regression analysis and found that only the histological differentiation of the primaries and the CEA levels prior to NAC, were statistically significant in association with histopathological response.

**Discussion:** At this moment it is not yet possible to predict precisely whether patients are going to respond or not to neoadyuvant therapy for hepatic metastasis from colorectal primaries. Overall, there is not a well established correlation between RECIST criteria of response and histopathological response, although morphological criteria rather than size shrinkage could potentially change this situation. Lack of response to neoadjuvant therapy could result in a delay in surgery, that could influence the prognosis of these patients and it is reasonable to predict which patients are more likely to respond to therapy. In our study, well differentiated primaries and also lower CEA levels prior to NAC predicted poor response. Nevertheless, larger studies are necessary to better resolve this question.

**Keywords**

Hepatic metastasis, Colorectal carcinoma, Neoadjuvant therapy, Prognosis, Histopathological response

## Introduction

Colorectal carcinoma is one of the most frequent human malignancies, primarily in developed countries [1]. Despite recent advances in therapy, particularly 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 and R0 resection is one of the most important prognostic factors in these patients [3]. Neoadjuvant chemotherapy (NAC) has been proposed as a therapeutic alternative for patients with metastatic disease in whom surgery is technically difficult [4]. In this sense, the objective of therapy is not to completely kill tumor cells, but rather to reduce tumor size and allow surgery [5]. However, some patients do not respond to NAC and some tumors may even progress during it. This can result in a delay in surgery or even make it impossible. For this reason it would be beneficial to know which patients are more likely to respond to therapy in this setting, a fact that has not been widely analyzed in the literature to date.

## 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 have 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. We have collected general demographic and clinical data and also data from the primary tumor (location, differentiation grade, vascular

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invasion, inflammatory response, TNM staging). We collected the CEA values before NAC. We also reviewed the stained slides of the metastatic hepatic nodules to describe the morphological response to therapy according to Rubbia-Brandt criteria [6]. We did not analyze radiological data of response, due to being inadequately reported in the clinical records of many patients.

We designed a data base in Excel and performed statistical analysis of the results with SPSS 20 for Windows statistical software (IBM corporation). We performed a descriptive analysis and a logistic regression model to find which factors can help predict response to therapy.

The permission for this study has been obtained from the Ethical Committee on Scientific Investigation of our hospital. This study is in accordance to national regulations regarding personal data protection.

**Table 1:** General characteristics of the 50 patients meeting inclusion criteria

| | Percentage |
|---|---|
| Gender | Male: 54%<br>Female: 46% |
| Age | 62.3 (11.3) |
| Comorbidities | No: 70%<br>Yes: 30% |
| Family history of cancer | No: 74%<br>Yes: 26% |
| Personal history of cancer | No: 82%<br>Yes: 18% |
| Location of primary tumor | Rectosigmoid: 66%<br>Other: 44% |
| T stage of primary | T1: 2%<br>T2: 10%<br>T3: 80%<br>T4: 8% |
| N stage of primary | N0: 50%<br>N1: 30%<br>N2: 20% |
| Data are expressed either as percentages or mean (SD), as indicated | |

## Results

Inclusion criteria for the present study were met by 50 patients. Table 1 summarizes the general characteristics of the series. Table 2 summarizes the histopathological features of the primary colon tumors, according to their response. In our series, 3 patients showed a complete response (6%), 33 showed a minor response (66%) and 14 (28%) showed a major response.

The statistical analysis of the factors influencing response was made considering both patients with complete and major response. We compared the mean values of the quantitative variables with Student's T test and estimated the association between qualitative variables with Chi-Square test. We only found significant differences in the mean values of CEA ($p = 0.01$), which were significantly higher in minor responders. For subsequent analysis we classified the patients in those with CEA values 5 ng/ml or less and those with CEA higher than 5 ng/ml, table 3 summarizes the data from this analysis.

Lastly, we performed a logistic regression model considering all the demographic and histopathological data that could influence response and found that only CEA preoperative levels ($p = 0.02$) significantly influenced response of the hepatic metastasis to NAC and histological differentiation of the tumor showed a trend toward significance ($p = 0.07$). Well differentiated tumors tended to respond less to NAC than poorly differentiated ones.

## Discussion

NAC has emerged in recent times as a useful therapeutic approach to the management of hepatic metastasis from colorectal malignant

**Table 3:** Univariate analysis: statistically significant associations

| | **Major responders** | **Minor responders** | **p value** |
|---|---|---|---|
| CEA level | <= 5 6 (80%)<br>> 5 2 (20%) | <= 5 1 (5%)<br>> 5 20 (95%) | 0.001 |
| Differentiation | Low grade 4 (31%)<br>High grade 9 (69%) | Low grade 29 (85%)<br>High grade 5 (15%) | 0.001 |

**Table 2:** Histopathological features of the primary tumors

| | Complete response (n = 3)* | Major response (n = 10) | Minor response (n = 34)* |
|---|---|---|---|
| Differentiation | Low grade 1 (50%)<br>High grade 1 (50%) | Low grade 3 (30%)<br>High grade 7 (70%) | Low grade 27 (84.5%)<br>High grade 5 (15.5%) |
| Location | Colon 0<br>Sigmoid-rectum 3 (100%) | Colon 3 (30%)<br>Sigmoid-rectum 7 (70%) | Colon 13 (38%)<br>Sigmoid-rectum 21 (62%) |
| Lymph vessel invasion | Present 0<br>Absent 2 (100%) | Present 1 (10%)<br>Absent 9 (90%) | Present 8 (25%)<br>Absent 24 (75%) |
| Lymphohistiocytic Inflammatory reaction | Absent 1 (50%)<br>Scarce 1 (50%)<br>Intense 0 | Absent 5 (50%)<br>Scarce 3 (30%)<br>Intense 2 (20%) | Absent 17 (53%)<br>Scarce 6 (19%)<br>Intense 9 (28%) |
| Leading front | Pushing 0<br>Infiltrative 2 (100%) | Pushing 3 (30%)<br>Infiltrative 7 (70%) | Pushing 9 (28%)<br>Infiltrative 23 (72%) |
| Desmoplasia | Absent 2 (100%)<br>Present 0 | Absent 7 (70%)<br>Present 3 (30%) | Absent 28 (87.5%)<br>Present 4 (12.5%) |
| Mucin production | Absent 2 (100%)<br>Present 0 | Absent 10 (10%)<br>Present 0 | Absent 27 (84.4%)<br>Present 5 (15.6%) |
| pT stage | T1 0<br>T2 1 (33%)<br>T3 2 (64%)<br>T4 0 | T1 1 (10%)<br>T2 1 (10%)<br>T3 7 (70%)<br>T4 1 (10%) | T1 0<br>T2 2 (6%)<br>T3 29 (85%)<br>T4 3 (9%) |
| pN stage | N0 3 (100%)<br>N1 0<br>N2 0 | N0 4 (40%)<br>N1 2 (20%)<br>N2 4 (40%) | N0 15 (44%)<br>N1 13 (38%)<br>N2 6 (8%) |
| *Histopathological data of the primaries were missing in one patient from the complete response group and two from the minor response group | | | |

tumors. It is well known that almost 50% of the patients with colon carcinoma will develop metastasis during follow-up and to improve survival it is essential to design aggressive therapeutic schemes that try to reduce the burden of disease and enhance response to adjuvant chemotherapy and also to targeted drugs [2]. Surgery of the metastasis is the best therapeutic alternative [3], but at times it may be difficult to achieve complete resection or surgery may be technically complex leading to some groups advocating the use of NAC to make resection more manageable.

NAC is usually based on oxaliplatin or irinotecan associated to fluoropyrimidines. Some schemes also employ targeted drugs (namely, anti-EGF and anti-VEGF drugs) in this setting. The response to therapy is usually followed with serial CT scans during NAC, for progression of disease could even make surgical resection impossible or recommend NAC cessation. However, it is rather clear than the RECIST criteria relying on size reduction are not well correlated to the histopathological response [7] and also that this criteria does not precisely predict prognosis after resection. In this sense radiologists have developed the so called morphological criteria [8,9], which seem to correlate better with histopathology and not only takes into account the shrinkage of the tumor, but rather also the changes in the radiological features of the metastatic nodules in the CT scan.

NAC combined with radiotherapy (NACRT) is a frequent therapeutic scheme for rectal tumours [10]. Pathological response to NACRT is one of the most important prognostic factors according to the literature in these patients. Schemes to evaluate response are varied [11], but most recent reports use the one recommended by the American College of Pathologists [12]. Over the years histopathological response to NAC of hepatic metastasis has also been evaluated with varying criteria. However, in 2008 Rubbia-Brandt proposed a new system to classify response creating three groups (complete, major and minor response), which showed good correlation with prognosis [6] and has been widely adopted. Rubbia-Brandt's criteria showed good correlation with morphological data of response in radiological follow-up and this is important for clinicians' decision making.

Besides, there are many reports trying to predict response of rectal carcinomas to therapy, for therapy is not devoid of adverse effects and it would be important to define patients that can benefit more from NAC [13]. Despite the many reports about the prognostic significance of histopathological response of metastasis, we have only found one previous report trying to predict response of the hepatic metastasis, as we intend to do in the present study [14]. In this report, Blazer et al. established that histopathological response of hepatic metastasis to NAC influenced prognosis (33% of patients with minor response were alive at 5 years follow-up as opposed to 75% of patients with major response), but also tried to determine which factors could influence response. In a multivariate analysis on 305 patients undergoing hepatic resection after NAC they concluded that CEA preoperative levels, tumor size and use of bevacizumab were significantly associated to histopathological major response. After this report, there have been no further ones specifically analyzing this issue. In our small series of 50 patients we have also tried to define which factors can significantly influence response to NAC. In the univariate analysis both CEA preoperative levels and differentiation of the primary tumor were significantly associated to major response, but in the multivariate logistic regression model, only CEA levels showed independent predictive value of response. Blazer's report does not mention the differentiation grade of the tumor in his analysis. Tumor size was not adequately reported in the clinical records of our patients and bevacizumab in our series was only administered in 11 patients (22%) not permitting conclusions to be obtained from these two factors.

Some reports have tried to determine the recurrence risk of patients with resected metastasis from colon carcinoma, even establishing predictive algorithms [15,16]. It would be beneficial to design similar algorithms for prediction of response to therapy with hopes to improve selection of the best candidates for this therapy as it is done in rectal carcinoma. In the near future molecular factors will probably gain interest in this area, as in many other oncologic fields [17].

The present study has several drawbacks, which deserve to be mentioned. The most important one is the small number of cases, although the results are similar to those obtained by Blazer [13] who had a much larger number of cases. Also, the retrospective nature has made it impossible to retrieve information regarding image data, mainly morphological changes in the nodules, which have become an interesting factor to predict response. It seems clear, however that prospective adequately powered studies are necessary to settle this matter and avoid NAC in patients less likely to respond, therefore reducing toxicity and allowing an earlier resection of the lesions if possible.

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