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Radio-Pathological Correlations in Patients with Liver Metastases for Colorectal Cancer

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Keywords
Colorectal liver metastases · Radiology in colorectal liver metastases · Pathological findings

Abstract
Background: Colorectal cancer (CRC) is the most frequent gastrointestinal cancer. The liver is the organ most commonly affected by CRC metastases. Synchronous CRC liver metastases (CRCLM) are present in 15–25% at diagnosis, and metastases are confined to the liver in 70–80% of these cases. The aim of the present study was to investigate the existence of significant correlations between the pathological features and computed tomography scan morpho-densitometric findings. ***Summary:*** A retrospective study of prospectively collected data has been performed; all patients underwent curative-intent hepatic resection from January 2004 to December 2012 and had histologically confirmed CRCLM. ***Key Messages:*** Thirty-four (57%) patients were males; the mean age was 64.4 (±10.2) years. Statistically significant differences have been found with the percentages of intra-tumoral fibrosis ($p = 0.038$) and necrosis ($p = 0.007$); the values of fibrosis are higher in the absence of a peri-lesional ring, while those of necrosis are higher in the presence of a peri-lesional ring.There was a correlation between the histopathological response to treatments and the global attenuation levels observed in the computed tomography scan of CRCLM. Furthermore, the presence of a radiologically evidenced peripheral ring was associated with the amount of viable tumor cells in the periphery of the tumor, and with responses predominated by necrosis. More studies are needed to clarify the radiological and histological correlation and to be able to better select patients who are going to undergo surgery.

Introduction

Colorectal cancer (CRC) is the most frequent gastrointestinal cancer, and one of the most common causes of cancer mortality worldwide: there were over 1.8 million new cases in 2018 [1]. The liver is most commonly affected by CRC metastases, being involved in 25% of cas-

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es at diagnosis and 50–75% of cases within 3 years after primary CRC resection; half of the distant CRC metastases involves exclusively to the liver [2]. Synchronous CRC liver metastases (CRCLM) are present in 15–25% at diagnosis, and metastases are confined to the liver in 70–80% of these cases. It has been demonstrated that the biological behavior of CRCLM is less aggressive than that of other common solid tumors; nevertheless, approximately two-thirds of deaths by CRC are due to CRCLM [3].

CRCLM, either synchronous or metachronous, can be resectable or unresectable. In this regard, radiological imaging of CRCLM is essential for the evaluation of their anatomic extension and, therefore, their clinical management. Computed tomography (CT) scans allow a precise definition of several morphological features, such as the number, diameter, presence of vascular pattern, involvement of the peritoneum, and presence of benign lesions, that can complicate surgery [4–9]. In addition, CT scan is useful in the assessment of responses to medical treatments, through evaluation of tumors' dimensional variations. Nevertheless, the advent of biological therapies (e.g., bevacizumab, a vascular epithelium growth factor inhibitor) made clear that dimensional criteria are not appropriate for the radiological follow-up of patients because these medications have a cytostatic rather than a cytotoxic effect, which causes the inhibition of angiogenesis and tumor growth without an evident reduction of its volume; in other words, the Response Evaluation Criteria in Solid Tumors (RECIST) are not always appropriate for the evaluation of CRCLM treatments, especially multidisciplinary ones. Treatment responses should be radiologically investigated on the basis of cellular viability and, thus, the presence of necrosis or fibrosis and the morphology of the interphase between the tumor and the healthy liver parenchyma. Although liver resection is the mainstay of CRCLM management with a 5-year overall survival up to 35%, radiological evaluation is more important to choose the best treatment and to better plan the steps.

The aim of the present study was to investigate the existence of significant correlations between the pathological features and the CT scan morpho-densitometric findings of CRCLM, in order to identify associations which could be applicable in the follow-up protocols of sufferers. This study was aimed at finding out whether CT scan findings correlate with histological patterns.

Materials and Methods

Patient Population

A retrospective study of data prospectively collected by the research group of the Hepatobiliopancreatic Surgery and Anatomic Pathology Units of the University Hospital Miguel Servet of Zaragoza has been conducted; all patients underwent curative-intent hepatic resection from January 2004 through December 2012 and had histologically confirmed synchronous or metachronous CRCLM. To be included, all cases should have had an abdominal CT scan evidencing the presence, extension, and morphological features of their CRCLM in the archives of the Radiology Service of the hospital. Furthermore, the pathological evaluation should have been performed by the same pathologist (CH) and been inclusive of all the pathological features to investigate.

The exclusion criteria were (1) cases without CT scan images or CT scans performed in other hospitals, or CT scans with digitally inaccessible images; (2) cases in whom contrast agent was not administered for iodine allergy or other reasons; (3) cases in which appropriate technical criteria were not respected (parameters and acquisition phase, rate of contrast injection, 5 mm collimation, and 2.5 mm slices); and (4) cases with incomplete clinical or pathological data, or deficient or inconclusive medical records regarding the variables studied. In all cases, signed informed consent was obtained for the use of the anonymous data of the patients for clinical research purposes.

Radiology Methods

All CT scans were performed at the Radiology Service of the Miguel Servet University Hospital, using multi-detector helicoidal acquisition groups of 4–64 rows, with collimation of 5 mm and a reconstruction algorithm at 2.5 mm. Imaging acquisition was performed with one of the following approaches: (a) multiphase liver protocol, with a contrast phase followed by the arterial (25 s), portal (70–75 s), and late (180 s) phases, and ingestion of 400–600 cm^3 of water before starting the study, and (b) single-phase protocol, with administration of the contrast medium and acquisition of the images in the portal phase (70–75 s). In both cases, the flow rate of the medium administered was 3–4 mL/s, and its total amount was calculated on the basis of the patient's weight: 2 mL/kg up to 120 mL (maximum iodine concentration of 320–350 mg/dL).

In cases with multiple lesions, the radiological evaluation was performed considering the greatest lesion, and in all cases included (1) the maximum diameter of the lesion, (2) its anatomical localization, (3) the mean attenuation value (region of interest [ROI], the density of the metastases, and the liver parenchyma before and after systemic therapy were analyzed by the ROI technique) in the portal phase (because it is known that in the arterial phase it does not vary before and after chemotherapy [CTh]), (4) the characteristics of its limits (regular or irregular), and (5) the presence of a peri-lesional ring (an enhanced ring in radiology correlates with tumor progression; the thicker and the more enhanced the ring is, the more the tumor component is supposed to be). The mean attenuation value in the lesion's area, given in Hounsfield units (HU), is calculated after 3 measures, which do not include the peripheral ring, if any. A circumferential area that occupied the entire lesion except for the tail ring was made. The study of these features was performed by 2 independent radiologists, dedicated to liver diseases assessment and without any notion of the pathological features of the lesions under investigation (Luis Sarría, Carlos Paradisi).

Histopathology Methods

As mentioned above, pathological examination of the specimens was performed by a single pathologist. The features evaluated and registered were as follows: number and maximum diameter of the metastases, resection margins, percentages of necrosis and fibrosis in the context of the lesions, histological subtype, characteristics of the tumor boundaries (infiltrating or expanding), presence of a fibrous pseudo-capsule surrounding the tumors, growth pattern in relation to the adjacent non-tumor parenchyma, vascular pattern (hypoxic or non-hypoxic), and presence of tumor-normal interface (TNI) of the metastases. Histological grade was not included.

Statistical Analysis

The variables under investigation were described with frequency tables in case of cumulative variables, while means, SDs, medians, 95% confidence intervals, and ranges were used for continuous variables. Pearson's χ^2 test with Yates correction, Fisher's exact test, Student's *t*-test, and Mann-Whitney nonparametric tests were used for qualitative variables, as appropriate. For qualitative variables with more than 2 categories, ANOVA for independent samples or the nonparametric test of Kruskal-Wallis was used, as appropriate. Statistical analyses were performed with software PASW Statistic v. 18.0.0 (SPSS Inc., Chicago, IL, USA).

Results

Among the 150 patients evaluated (183 resections), 90 satisfied at least one of the exclusion criteria and were therefore excluded. Thirty-four (57%) of the 60 remaining patients were males and 26 (43%) were females; the mean age (±SD) of the global 60 patients was 64.4 (±10.2) years. Table 1 summarizes the main demographic and clinical data of the patients.

Investigation of the radiological and histopathological evaluation results of both the dimensions and the maximum diameter of the lesions showed a good concordance. A weak negative association between ROI and tumor necrosis ($p = 0.059$) was evidenced, while no association was evidenced between ROI and intra-lesional fibrosis ($p = 0.0569$). Nevertheless, a significant statistical correlation was evidenced between ROI and the global histological response, defined as the sum of the intra-tumoral necrosis and fibrosis; the higher the histological response, the lower the attenuation of the lesion registered (Fig. 1). No correlations were found between ROI and the histological subtype of the CRCLM.

Also, the radiological contour of the metastases was investigated in relation to tumor necrosis ($p = 0.389$), fibrosis ($p = 1.000$), boundaries ($p = 0.144$), vascular pattern ($p = 0.356$), and fibrous pseudo-capsule ($p = 0.173$), but no statistically significant correlations were found. In other words, all the latter features can be present regardless of the radiological aspect of the CRCLM. The mean attenuation value in the area of the dominant metastasis was 65.49 HU, with a range of 34–124 HU and an SD of 19.86 HU (95% confidence interval 60.36–70.62 HU) (Fig. 2).

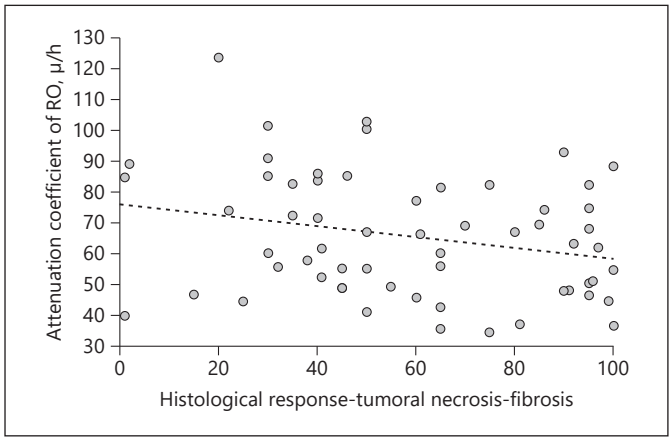

Fig. 1. Correlation between histopathological tumor response (fibrosis and necrosis) and CT attenuation levels.

Investigating the correlations between the presence of a peri-lesional ring and other pathological features, statistically significant differences were found with the percentages of intra-tumoral fibrosis ($p = 0.038$) and necrosis ($p = 0.007$); the values of fibrosis are higher in the absence of a peri-lesional ring (Fig. 3), while those of necrosis are higher in the presence of the peri-lesional ring (Fig. 3). The presence of the ring was not significantly associated with other features such as the vascular pattern ($p = 1.000$), the presence of a fibrous pseudo-capsule ($p = 0.720$), and tumor margin ($p = 0.301$).

Discussion

Evaluation of responses to oncological treatments is a main issue in the current clinical practice and can involve both the radiologists and the pathologists. Response rates of preoperative systemic treatments evaluated pathologically have been linked to survival in patients with solid tumors [10, 11]. For this reason, noninvasive imaging techniques have been employed with the aim of obtaining an anticipated objective estimation of the pathological response of the tumors to treatments, but the results of several techniques are somehow inconsistent, despite consistent advances in recent times.

Table 1. Main demographic, clinical, and pathological features of patients included in the study

Feature	Value
Male sex, *n* (%)	34 (57)
Age (mean ± SD), years	64.4±10.2
Radiological features	
Maximum diameter of the greatest lesion (mean ± SD, range), mm	35.6±25.9 (8–150)
Hepatic segment of radiologically evaluated lesions, *n* (%)	
1, *n* (%)	1 (1.6)
2, *n* (%)	3 (4.8)
3, *n* (%)	4 (6.4)
4, *n* (%)	8 (12.9)
5, *n* (%)	11 (17.8)
6, *n* (%)	14 (22.6)
7, *n* (%)	11 (17.8)
8, *n* (%)	10 (16.1)
Total	62 (100)
ROI (mean ± SD, range), HU	65.5±19.9 (34–124)
Lesion boundary	
Regular, *n* (%)	44 (73.3)
Irregular, *n* (%)	16 (26.7)
Peripheral ring	
Yes, *n* (%)	29 (48.4)
No, *n* (%)	31 (51.6)
Peripheral ring thickness (mean ± SD, range), mm	3.2±2 (1–10)
Pathological features	
Lesions resected per patient (mean ± SD, range)	2.75±2.6 (1–13)
Maximum diameter of the greatest lesion, (mean ± SD, range), mm	32.5±20.6 (5–100)
Resection margin (mean ± SD, range), mm	7.21±8.7 (0–40)
Percentage of tumor necrosis (mean ± SD, range)	40.8±31.3 (0–100)
Percentage of tumor fibrosis (mean ± SD, range)	18.1±22.4 (0–90)
Type of tumor margin	
Infiltrative, *n* (%)	30 (50%)
Expansive, *n* (%)	30 (50%)
Presence of fibrotic pseudo-capsule	
Yes, *n* (%)	7 (11.7)
No, *n* (%)	53 (88.3)
Histological type	
Conventional, *n* (%)	54 (90)
Mucinous, *n* (%)	5 (8.3)
Other, *n* (%)	1 (1.7)
Vascular pattern	
Hypoxic, *n* (%)	26 (43.3)
Non-hypoxic, *n* (%)	34 (56.7)
Peripheral tumor-normal interface, mm	2.36±2 (0–7)

In 2000, the European Association for the Study of the Liver (EASL) stated that the reduction of the volume of the tumor (areas with lower reaction levels on CT or magnetic resonance imaging) could be considered a valid method to judge responses to local treatments for hepatocellular cancer (HCC) [12]. Since then, most authors adopted this recommendation for the evaluation of the results of chemoembolization and other ablative methods used to treat HCC [13–15]. However, HCC is a primary liver tumor with a very different behavior from that of CCRLM. Nevertheless, subsequent studies demonstrated that this approach overestimates or underestimates responses to neoadjuvant CTh [16, 17], making the histological evaluation necessary. The latter is based on the percentage of intra-lesional fibrosis, necrosis, and viable cells and represents currently one of the most important

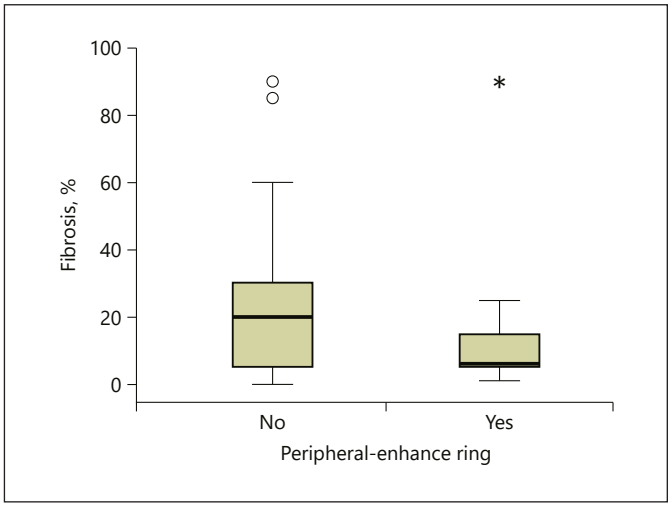

Fig. 2. Fibrosis levels in lesions with and without a peripheral ring at CT scan.

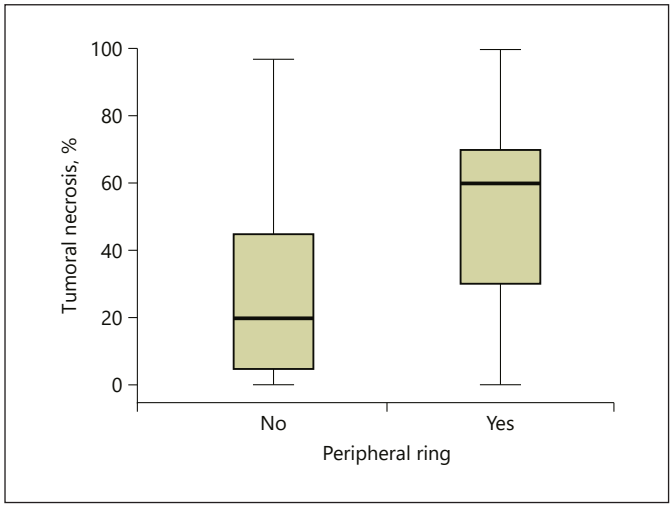

Fig. 3. Necrosis levels in lesions with and without a peripheral ring at CT scan.

prognostic factors in numerous solid cancers, such as mammary [17], esophageal [18], gastric [19], and rectal cancer [20, 21].

In 2012, Chung et al. [22] postulated that the attenuation value on CT scan of CRCLM shows a linear correlation with the concentration of the contrast agent and, thus, the vascularization of the tumor. In addition, Boonsirikamchai et al. [23] evidenced that CRCLM is an aggregate of variably attenuated tissues which form a heterogeneous mass, hypodense in comparison to the surrounding healthy liver, and the grade of attenuation changes in relation to the relative proportions of mucin, fibrosis, live cells, and dead cells. These observations led the hypothesis that the attenuation levels are related to several biological events involving tumors. Indeed, in our series, we evidenced that lesions with greater necrosis percentages showed lower attenuation values, as expected from the theoretical behavior of necrotic tissues, although the correlation was near the limit of statistical significance ($p = 0.059$) but not significant.

From a histological point of view, it has been postulated that intra-tumoral fibrosis is a better predictor of responses to treatments than necrosis because the latter can be spontaneously caused also by hypoxic events other than cell apoptosis directly produced by CTh [24–26]. Our study evidenced a nonsymmetric distribution of tumor fibrosis values, which can be interpreted as a result of a greater response in patients submitted to neoadjuvant therapy. Indeed, several authors have shown in the past that the percentage of fibrosis in the context of tumors is significantly higher in patients treated with neoadjuvant therapy than those without [24–27]. In any case, we did not find any differences in terms of attenuation between patients submitted to neoadjuvant therapy and those not submitted in our cohort. Furthermore, attenuation was not statistically correlated with fibrosis ($p = 0.569$) in our series.

On the contrary, histological response (intended as the sum of the necrosis and fibrosis of the tumors) was significantly correlated with radiological attenuation ($p = 0.05$); the correlation was negative (Spearman −0.256). Thus, the values of attenuation were reduced with the increase in the percentages of fibrosis and necrosis within the lesions. Similar findings have been published in the past, even with a stronger statistical tendency [22, 23]; the weak tendency found in our cohort may be due to the restricted number of cases. Similarly, the absence of any association between histological types, conventional or mucinous, and the attenuation levels may be due to the number of patients (only 5 patients with mucinous histology).

Maru et al. [28] were the first to introduce the concept of TNI in order to describe the fact that most of the viable cells in treated tumors are located peripherally. Also, Mentha et al. [29] and Rubbia-Brandt et al. [24] described a halo of live tumor cells which infiltrated the interface between the tumor and the healthy surrounding tissue in patients submitted to neoadjuvant CTh. Saudí Moro et al. [30] used the term tumor "Casquete" to describe this phenomenon, and defined it as the maximum thickness (in millimeters) of the area between the central necrosis of the lesion and its external borders.

In our study, we found that the values of tumor fibrosis were higher in cases of absence of a peripheral ring, while necrosis was higher when the ring was present, as observed by Riaz et al. [31]in patients submitted to radioembolization for HCC. To this regard, Rubbia-Brandt [24] observed that the histological response of CRCLM is characterized by fibrous replacement rather than necrosis, and Maru et al. [28] observed that the thickness of the TNI directly correlates with the presence of live tumor cells. We can state, therefore, that the absence of a peripheral ring is a sign of major fibrosis and, thus, a sign of a good response to CRCLM treatments before surgery, but this result needs further confirmation in future studies. On the other hand, the presence of a fibrous pseudo-capsule, which is a positive prognostic factor in patients with HCC [32–35], did not show any association with the presence of a peripheral ring. The results do not change the surgical criteria. These results show that the presence of a peripheral ring correlates with the persistence of tumor in the surgical specimen.

Regarding the histological evaluation of tumor border (infiltrating or expanding), Nagashima et al. [36] observed that the infiltrating pattern of the CRCLM acts as a negative prognostic factor and could be hypothesized as a correlation with the appearance of the contour of the lesions (regular or irregular). Nevertheless, such an association was not observed in our cohort, underlining the difficulties of macroscopic methods such as CT scan to evaluate accurately the tumor contours. Indeed, we did not find any association between the vascular pattern and the tumor contour, as well as between the type of tumor margin (infiltrating or expanding) and the presence of a peripheral ring. Finally, we did not evidence any statistical correlation between the tumor contour and the percentages of fibrosis or necrosis. This is not in accordance with some theoretical postulations stating that macroscopic transformation of the tumor border dictates a good response to treatment [10], and observations confirming that regular borders are associated with higher percentages of fibrosis and/or necrosis [17–21, 24, 25, 37, 38].

Our study has some limitations, mainly the retrospective approach, the long period of data collection (8 years), and the number of patients included. Furthermore, our hospital is a reference center for a wide geographical area and receives mostly complex cases not treated in smaller hospitals. The central hypodensity of the tumors did not allow us to differentiate between fibrosis and necrosis. Thus, our study did not discriminate between treated and untreated patients. However, our objective was to determine the relationship between the existence of the lesion ring and the histological component. Nevertheless, our study is one of the few studies to investigate the topic, with a single pathologist and two dedicated radiologists who worked blindly in defining the features under investigation.

Conclusions

Our study evidenced a correlation between histopathological responses to treatments, considered as the combination of fibrosis and necrosis percentages within the context of the lesions, and the global attenuation levels observed in the CT scan of CRCLM. Furthermore, the presence of a radiologically evidenced peripheral ring was associated with the amount of viable tumor cells in the periphery of the tumor and with responses predominated by necrosis; the absence of the ring was associated with responses predominated by fibrosis, which generally shows a better prognosis. More studies are needed to clarify the radiological and histological correlation and to be able to better select patients who are going to undergo surgery.

Statement of Ethics

Due to the retrospective and anonymized study design, informed consent of the patients was not required.

Disclosure Statement

The authors declare no conflicts of interest.

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The authors did not receive any funding.

Author Contributions

Alejandro Serrablo, Carlos Parisi, Carlos Hörndler, and Luis Sarria research and surgeon, radiologists and pathologist belonged to the research group. Panos Paliogiannis is a medical writer. Leyre Serrablo collected data. Luis Tejedor corrected the English of the article. Daniel Azoulay was an external reviewer and corrected and proofread the research paper.

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