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Research paper

Diagnostic performance of contrast-enhanced CT-scan in sinusoidal obstruction syndrome induced by chemotherapy of colorectal liver metastases: Radio-pathological correlation

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ABSTRACT

Purpose: Sinusoidal obstruction syndrome (SOS) is a likely side effect of colorectal liver metastases (CRLM) chemotherapy. This study aimed to assess computed tomography scan (CT-scan) performance for SOS diagnosis for patients receiving neoadjuvant chemotherapy (NC) prior to CRLM surgery, comparing obtained results with pathological gold standard.

Methods: Preoperative CT-scans of 67 patients who had received a NC prior to liver resection for CRLM from 2011 to 2016 were retrospectively analysed. Positive diagnosis and severity of SOS were established after consensual review of the slides by three pathologists. Preoperative CT-scans were separately interpreted by two radiologists and evocative signs of SOS were sought, defined according to a literature review and operators experience. In order to identify SOS predictors, univariate analysis and multivariate logistic regression were used to study CT-scan signs and pathological results correlation.

Results: Twenty-nine patient (43%) had an SOS, 22 (33%) were low-grade and 7 (10%) were high-grade. All patient had received a median of 6 cures (3–27) containing Oxaliplatin for 53 (79%) of them. In univariate analysis, hepatic heterogeneity ($p < 0.001$), puddle-like or micronodular appearance ($p < 0.001$), peripheral distribution of heterogeneity ($p = 0.085$), clover-like sign ($p = 0.02$), splenomegaly ($p = 0.0026$), spleen volume increase ≥30% ($p = 0.04$) or splenic length increase ≥15% ($p = 0.04$), as well as the subjective impression of the observer ($P < 0.001$) were significantly associated with SOS diagnosis. In multivariate analysis, clover-like sign (OR 1.87, 95% CI 1.18–2.95, $p = 0.0081$), increase in spleen volume ≥30% (OR 1.29, 95% CI 1.01–1.64, $p = 0.04$), and the peripheral distribution of heterogeneity (OR 1.53, 95% CI 1.21–1.94, $p < 0.001$) were independent SOS predictors. The area under the ROC curve was 0.804. The inter-observer agreement for SOS diagnosis was moderate (Kappa = 0.546).

Conclusion: CT-scan can detect suggestive signs of SOS in patients receiving chemotherapy for CRLM. By integrating clinical and biological information into CT-scan data, it may be fruitful to create a positive diagnostic and severity score for chemotherapy-induced SOS.

Abbreviations: 5FU, 5-fluorouracil; CIFH, chemotherapy-induced focal hépatopathie; CLV, centrilobular vein; CRLM, colorectal liver metastases; CT-scan, computed tomography scan; EGFR, epidermal growth factor receptor; HSCT, hematopoietic stem cell transplantation; ICT, initial computed tomography scan; MHL, midclavicular hepatic length; MHV, middle hepatic vein; NC, neoadjuvant chemotherapy; NPV, negative predictive value; NRH, nodular regenerative hyperplasia; OR, Odds Ratio; OX, oxaliplatin; PA, pyrrozilidine alkaloids; PHT, portal hypertension; POCT, preoperative computed tomography scan; PPV, predictive positive value; ROC, receiver operating characteristic; SI, sinusoidal injury; SOS, sinusoidal obstruction syndrome; VEGF, vascular endothelial growth factor

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1. Introduction

Sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease, is a non-thrombotic hepatic microvascular injury caused by toxic aggression on sinusoidal endothelial cells [1,2]. This term includes a continuum of histological lesions ranging from simple sinusoidal dilation to severe lesions of peliosis or nodular regenerative hyperplasia (NRH) [1–3]. Several SOS risk factors are known, especially chemotherapies used in colorectal liver metastases (CRLM) [4–6]. Oxaliplatin (OX) is particularly incriminated [1,2,5,7], as well as 5-flurorouracil (5-FU) [2,8] to a lesser extent. The incidence of sinusoidal injuries (SI) induced by OX is estimated between 19 and 52% of hepatectomies [6,7,9]. Bevacizumab, a biotherapy combined with chemotherapy without RAS mutation, appears to have a protective role, restricting the onset and severity of SI [1,10].

Several studies have analysed the clinical consequences of SOS among patients undergoing liver resection for CRLM, with varying results. Most of these studies have shown that SOS increases the perioperative morbi-mortality along with post-operative liver failure [7,9], and might jeopardise the hepatic regeneration abilities. These lesions imply a bad postoperative prognostic, and can induce non-cirrhotic portal hypertension (PHT). Establishing SOS diagnosis remains challenging. It can be suspected clinically through PHT signs [11,12] and biologically through an increase in liver enzymes [3]. The gold standard diagnostic relies on pathological analysis. Liver biopsies fail to provide a reliable estimation of SI due to its irregular distribution [3,5]. Preoperative diagnostic of SOS would allow changing the treatment and therefore improving post-operative prognostic: adaptation of chemotherapy protocols, choice of the best timing to perform surgery [5,7]. It is currently agreed that the surgery must leave at least 30% of the liver in case of a sane liver, and 40% in case of chronic hepatopathy or preoperative chemotherapy, owing to a potential SOS [7].

Computed tomography scan (CT-scan) is the reference examination in the oncologic monitoring of patients treated by chemotherapy for CRLM. Alterations of the non-neoplastic liver or PHT signs possibly implying SOS have been spotted in our daily practice. As none of those alterations are specific or pathognomonic, interpreting them is tricky. SOS signs in medical imaging are still to be clearly established. Moreover, SOS lesions are hard to identify as they exhibit time-varying features and severity [3]. Magnetic Resonnance Imagning (MRI) can also detect SOS, with good predictive values. Notably, several authors reported the interest of enhanced-MRI using hepatospecific contrast agents [13,14].

The literature highlights the role of medical imaging, especially CT-scan, for SOS diagnostic. The relevance of each radiologic sign remains difficult to clarify. The main objective of our study was to assess CT-scan performance for SOS diagnosis among patients with neoadjuvant chemotherapy (NC) prior to CRLM surgery and compare obtained results with the pathological gold standard. The secondary objective was to study the inter-observer agreement of those signs.

2. Material and method

2.1. Patients inclusion

This monocentric retrospective observational study was approved by our institution's ethics committee. In accordance with French law, subjects were informed of the re-use of their data and their right to oppose it. The study was performed in agreement with the Helsinki Declaration of the World Medical Association. From october 2011 to april 2016, we retrospectively screened 170 patients who underwent hepatic resection for CRLM in the University Hospital of Tours. Of these 170 patients, according to/following our inclusion and exclusion criterias, 67 patients were included in our study (Fig. 1).

The inclusion criteria were: patient having undergone surgical hepatic resection for synchronous or metachronous CRLM; having received a NC; having had two preoperative contrast-enhanced CT-scans with a portal phase (an initial CT (ICT) before the NC and a preoperative CT (POCT)). The chemotherapeutic regimens were as follows: 5-Fluorouracil (5FU), Oxaliplatin (OX) and Leucovorin (FOLFOX); 5FU, Irinotecan and Leucovorin (FOLFIRI); 5FU, OX, Irinotecan and Leucovorin (FOLFOXIRI); Leucovorin and 5FU (LV5-FU2). Some patients had received several lines of chemotherapy. The targeted therapies were Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody; Cetuximab and Panitumumab, two anti-epidermal growth factor receptor (EGFR) monoclonal antibodies.

The exclusion criteria were: preoperative embolization or portal ligation, prior radiofrequency treatment (leading to perfusion abnormalities); chronic hepatopathy; small surgical specimen not permitting pathological analysis (non-tumorous liver margin < 2 cm); history of treatment with hepatotoxic chemotherapy for another cancer.

Table 1 summarizes the clinical characteristics of our population.

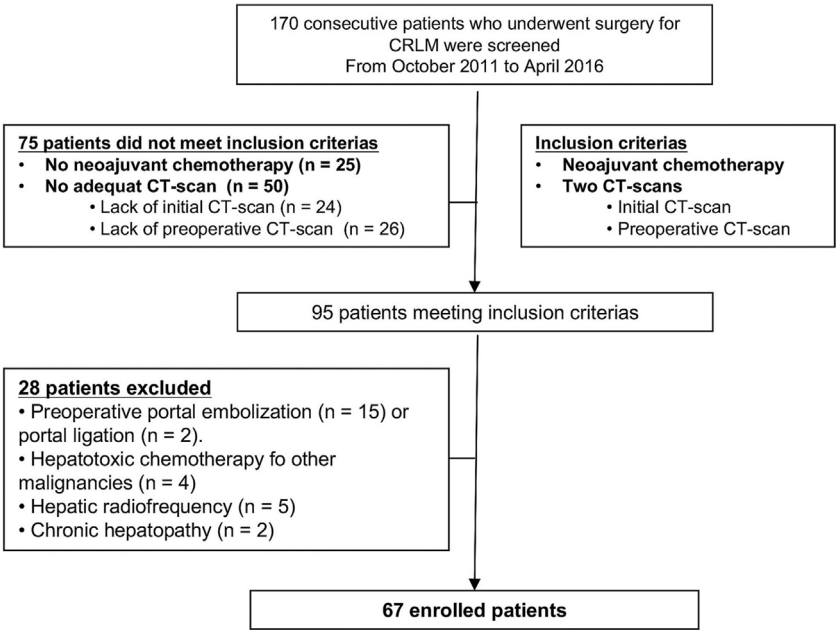

Fig. 1. Flowchart of patient selection, inclusion and exclusion. *CRLM, colorectal liver metastases; CT-Scan, Computed Tomography Scan.*