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Recommendations of a group of experts for the pathological assessment of tumour regression of liver metastases of colorectal cancer and damage of non-tumour liver tissue after neoadjuvant therapy

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Abstract Colorectal cancer (CRC) incidence has increased during the past decades in Spain, being the first malignant tumour in incidence. Observed mortality for CRC is mainly due to liver and lung metastases. The only curative treatment is surgery; new surgical techniques and neoadjuvant treatments have increased the number of surgery candidate patients. Patients should be managed with a multidisciplinary approach that includes imaging techniques, chemotherapy, surgery and pathological assessment. As an answer to this approach, a group of pathology experts interested on CRC liver metastases aimed to review the diagnosis and prognosis of liver mestastases and developed practical recommendations for its assessment. The expert group revised the current literature and prepared questions to be discussed based on available evidence and on their clinical practise. As a result, recommendations for the assessment of tumour regression of liver metastases are

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proposed, which could be implemented in oncology centres allowing assessment standardisation for these patients. Prospective multi-center studies to evaluate these recommendations validity will further contribute to improve the standard care of CRC liver metastases patients.

Keywords Recommendation · Colorectal cancer · Liver metastases · Pathological response · Tumour regression grade

Introduction

Colorectal cancer (CRC) is one of the most common cancers in the western world. In the US, it is the third most common and fatal cancer in both men (after prostate and lung cancers) and women (after breast and lung cancers) [1].

In Europe, it ranks second among all malignant tumours [2]. In Spain, in contrast with other countries, the incidence of CRC has increased in the last few decades [3]. According to the Spanish Society of Medical Oncology (SEOM), when considering men and women together, CRC is the tumour with the highest incidence rate in the country, estimated at 30,628 people with CRC in 2006 and 33,801 in 2012 [4]. Also, it is the second most common in terms of mortality (12,877 deaths in 2006 and 13,204 in 2012) [4] (Fig. 1).

The high mortality rate of CRC is due to the presence of metastases at the time of diagnosis (synchronous metastases) or during the course of the disease. The most

Fig. 1 Global incidence (**a**) and mortality (**b**) in 2006 and 2012 (in thousands of people) of the five most important cancers

common location for metastases is the liver, followed by the lung [5].

CRC liver metastases

Fifteen percent to 25 % of all CRC patients present with liver metastases at diagnosis and up to 50 % will develop liver metastases during the course of the disease, primarily in the first 3 years [6]. In approximately 30 % of patients with liver metastases, the disease is limited to the liver [7]. Only 10–25 % of these patients are considered as candidates for surgical resection according to classic resectability criteria [6, 8, 9]. The non-resectability of CRCLM is the reason for a 5-year survival rate of only 20 % [10]; in contrast, the 5-year survival rate is more than 50 % for patients undergoing surgical resection with curative intent [11]. Since surgical resection is the only potentially curative option, there is considerable interest in increasing the number of surgical candidates through the development of new surgical techniques, pre-operative systemic treatments (neoadjuvant therapy), and the application of different resectability criteria [12, 13].

Neoadjuvant systemic therapy

In patients with non-resectable CRCLM, the use of new chemotherapy and biological agents has reduced the tumour size and increased the possibility of surgery with curative intent, improving these patients' survival [5, 7, 14].

In the last few years, oxaliplatin and irinotecan have been added to classic chemotherapy regimens based on 5-fluorouracil (5-FU). When used in different combinations as neoadjuvant therapy, these regimens obtained resectability rates of up to 37.5 % [9]. However, the addition of these drugs has been associated with morphological lesions affecting the liver's microvascular structure, such as sinusoidal dilatation, perisinusoidal fibrosis or veno-occlusive lesions, especially related to oxaliplatin [15], and steatohepatitis, more closely linked to irinotecan and 5-FU [16]. Recently, the introduction of biological agents, such as bevacizumab or cetuximab has further increased the therapeutic possibilities in this field [17–19]. Although, there is a little information about the hepatotoxic potential of these drugs, it has been reported that bevacizumab in combination with cytotoxic drugs is associated with less sinusoidal damage [18].

Neoadjuvant systemic therapy, therefore, causes significant histopathological alterations, on the positive side, it induces tumour pathological regression; on the negative side, it affects the non-tumour parenchyma. In both cases, the pathologist's participation is important to assess these changes since they have important diagnostic and prognostic value.
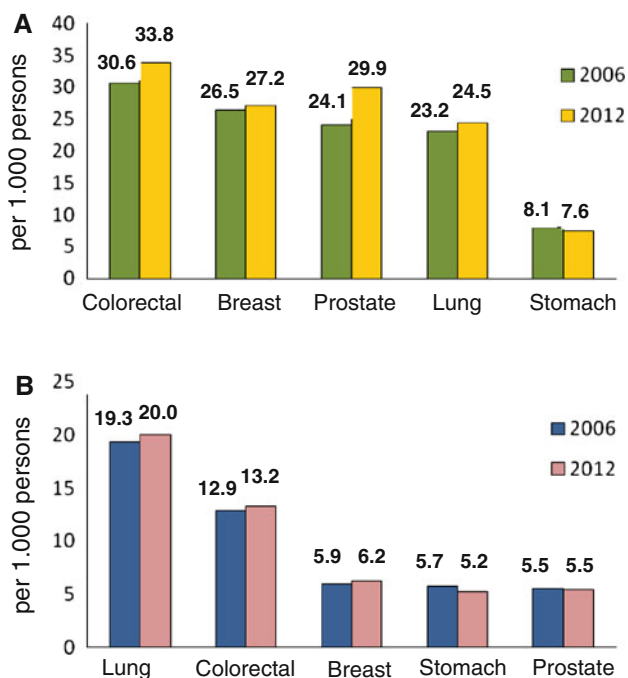
Resectability criteria

Until a few years ago, resectability of any tumour depended on the number of metastases, lesion size and the possibility of maintaining a 1 cm tumour-free surgical margin. Resectability criteria have now been extended to include patients in whom all tumour tissue can be removed with a negative margin and with adequate hepatic volume or reserve [12]. Also, it has been observed that the response of metastasis to pre-operative (neoadjuvant) chemotherapy is a better predictor of long-term survival than the number of metastases [20]. However, the metastasis size is not always indicative of a tumour's aggressiveness (but possibly of the time it has taken to be diagnosed). Studies aimed to assess tumour size as a prognostic factor have rendered contradictory results, so, tumour size should not be considered when deciding on tumour removal [12]. Likewise, the distance from the tumour to the surgical margin is not considered to be a survival predictor, being only required a completely negative margin (R0 or total absence of tumour cells) [21]. It has even been suggested that an R1 resection could be acceptable if we consider the efficacy of new systemic treatment options [22].

The definition of surgical resectability of liver metastases has changed as new chemotherapy [23] and biological agents have become available, and as diagnostic and surgical techniques have evolved [12]. Compared with the previous concept of resectability, which considered number, size and tumour-free margin, the following criteria are now considered [11, 12, 24, 25]:

- Good overall status and absence of surgical contraindications
- Curative intent of surgery, with complete resection of all tumour lesions and a microscopically negative margin (a resection margin of less than 1 cm does not contraindicate resection).
- Prediction that post-resection functional liver reserve will be adequate, preserving at least two adjacent hepatic segments, with good vascularisation and biliary drainage.
- Resectable extra-hepatic disease (the presence of extra-hepatic disease should not be classified as an absolute contraindication for hepatic resection).

According to this new approach, the number of patients with resectable disease could increase if the hepatic reserve is enlarged (by portal vein embolisation or two-stage hepatectomy) and resection is combined with ablation or a decrease in tumour size by pre-operative systemic treatment [12].

The management of patients with advanced CRC must be done from a multidisciplinary perspective [12] including: imaging techniques (important for assessing resectability and response criteria), systemic treatment before (aimed at converting non-resectable patients into resectable) and after surgery, surgery itself, and the histological study of the resected product (important for diagnostic and prognostic value). An integrated approach that includes radiologists, oncologists, surgeons and pathologists is therefore required.

The role of the pathologist

In the multidisciplinary team, the pathologist plays a key role in assessing tumour response and the post-treatment status of non-tumour liver parenchyma. Moreover, the histopathological diagnosis has significant prognostic value.

Pathological response: degree of tumour regression

In an attempt to standardise the assessment of the response of solid cancers to treatment, various non-pathological criteria have been suggested over the years [24–29], largely based on technological progress in diagnostic methods [30].

The purpose of radiological criteria is to homogenise diagnoses, so they can be interpreted similarly in different settings; however, there is not always a correlation between the degree of response according to radiological imaging and histopathological findings. This became clear when biological agents with different mechanisms of action were added to cancer therapy; radiological criteria based on the decrease of tumour volume after cytotoxic therapy (such as RECIST) may not be appropriate when interpreting the morphological changes caused by cytostatic treatment [31]. Klinger et al. [18] recently found that the effect of a biological drug, such as bevacizumab, on the tumour was not reflected in the response according to RECIST criteria, so, the use of such criteria with patients treated with bevacizumab would be of no use for predicting clinical benefit.

In addition to the different markers that predict recurrence in patients who have undergone CRCLM surgery [positive lymph nodes in primary tumour, carcinoembryonic antigen (CEA) >200 ng/ml, tumour size >5 cm, etc.], pathological response or degree of tumour regression, defined as the amount of residual tumour cells in resected tissue, is now classified as an important prognostic factor in patients treated with pre-operative chemotherapy [32, 33]. Rubbia-Brandt et al. [34] showed a correlation between histological response to chemotherapy and overall survival in patients treated with an oxaliplatin-based regimen. Mandard's tumour regression grade system was validated for CRC in this study [35]. Moreover, Ribero et al. [17] found that adding bevacizumab to a regimen with oxaliplatin and fluoropyrimidines significantly improved the pathological response of patients with CRCLM. Blazer

et al. [34] considered three degrees of pathological response and concluded that the pathological response predicted survival in patients with CRCLM treated with pre-operative chemotherapy and undergoing hepatic resection. Factors associated with a greater pathological response were CEA ≤5 ng/ml, tumour size ≤3 cm and oxaliplatin plus bevacizumab as neoadjuvant therapy. More recently, Klinger et al. [19], in a retrospective analysis of two prospective clinical trials, confirmed a positive association between addition of bevacizumab to the neoadjuvant regimen, degree of tumour response and patient survival. Chan et al. [36] also showed the prognostic potential of pathological response using 3 levels that could be divided into two: strong response and weak response. In this study (similar to the Rubbia-Brand classification), the authors realised the need to grade response and not only considered complete response (total absence of viable cells) as a good prognostic factor for survival or cure.

There is reasonable evidence to suggest that pathological response is a predictor of survival in patients subject to resection of liver metastases. In view of these results, the addition of biological agents to pre-operative treatment, specifically bevacizumab, has been shown to obtain better pathological response and survival rates [35].

However, as Table 1 shows, each study used different parameters to classify pathological response, and none of them compared the different methods, so it is difficult to estimate their relative value. There is a clear need to unify pathological response criteria as much as possible.

After showing the importance of assessing pathological response grade according to the proportion of tumour cells, it was found that most residual tumour cells are found in the peripheral area of metastasis; this is, in the tumour-normal tissue interface (TNTI) of the surgical specimen. The measurement of this TNTI is correlated with

radiological and pathological response and recurrence-free survival, as shown by Maru et al. [37]. Therefore, tumour thickness measured in TNTI is a potential predictor of response to treatment and survival in patients with resection of CRCLM [39]. The inclusion in the pathological report of this parameter together with pathological response and surgical margin could, therefore, help to make decisions regarding subsequent treatments [38].

Non-tumour liver tissue involvement following neoadjuvant therapy

There is a clear association between pre-operative chemotherapy and potential hepatic toxicity. Regimens containing oxaliplatin and irinotecan appear to involve a greater risk of post-operative morbidity. 5-FU has been associated with the onset of steatosis, irinotecan with steatosis and steatohepatitis and oxaliplatin with endothelial (or sinusoidal) injury. In all cases, liver involvement may increase post-operative morbidity considerably [39]. Although there is less information about biological treatments, their addition to chemotherapy regimens does not appear to increase their potential toxicity [40]. In this regard, bevacizumab has been described as protecting against the toxic sinusoidal effect of oxaliplatin [41, 42]. Ribero et al. [17] identified a significantly lower incidence of sinusoidal dilatation (of any grade) in patients treated with bevacizumab than in untreated patients. Also, Zalinski et al. [43] found that the administration of bevacizumab do not interfere with hepatic regeneration after portal embolisation.

In addition to its anti-tumour effect, neoadjuvant treatment also has side effects on the non-tumoral liver which can be detected by the histological analysis. Hence the importance of determining not only the tumour regression data but also the liver damage due to systemic treatment.

Table 1 Grades of pathological response used by different authors in the reviewed studies

	Grades of pathological response						
	Mandard 1994	Rubbia-Brandt 2007	Klinger 2010	Blazer 2008		Chan 2010	
Absence of tumour cells replaced by fibrosis	TRG1	TRG1	MjHR	Complete response	Absence of tumour cells	Strong response (in all lesions)	PRG 3 = absence of viable cells
Few tumour cells spread in abundant fibrosis	TRG2	TRG2		Major response	1–49 % tumour cells		PRG 2 ≤ 10 % viable cells
Visible tumour cells even with predominant fibrosis	TRG3	TRG3	PHR			Weak response (in at least 1 lesion)	PRG 1 ≥ 10 % viable cells
Abundant tumour cells predominant over fibrosis	TRG4	TRG4	NHR	Minor response	≥50 % tumour cells		
Abundant tumour cells without fibrosis	TRG5	TRG5					

TRG tumour regression grade, *MjHR* major histological tumour response, *PHR* partial histological tumour response, *NHR* no histological tumour response, *PRG* pathological response grade

Need for homogeneous criteria

As mentioned before, there is a considerable variability with regard to the methodology and the diagnostic response criteria which makes it difficult to compare the results of different clinical studies, and to take therapeutic decisions based on heterogeneous information. It should be recalled that the studies mentioned above refer to retrospective studies, which also hinders the homogeneity of the macroscopic study as they refer to samples included from surgical specimens from the past.

As a result, the recommendations of the present manuscript are based on the work of pathologists from different Spanish centres, in collaboration with a medical oncology specialist, who share the same concern: to establish reliable protocols that will allow the study of samples from CRCLM patients based on standardised criteria to provide complete and homogeneous histopathological reports that facilitate subsequent clinical decisions.

Methodology

These recommendations are the result of a three-stage process. After a literature review and analysis of the current situation, participant guidelines were designed with the issues to be discussed. The expert group met twice. During the first meeting, the experts discussed the following questions: What should the histopathological report contain? How should tumour regression grade be assessed? How should the involvement of non-tumour liver tissue after neoadjuvant therapy be assessed? What discrepancies are there in the evaluation of tumour response and non-tumour parenchyma? On the second meeting, the group reached an agreement on the protocol to be followed in the histopathological diagnosis of tumour regression in CRCLM and of the involvement of non-tumour liver tissue after neoadjuvant therapy.

The participants drafted these recommendations based on a realistic, practical and reproducible agreement.

Recommendations

Surgical specimen handling[1]

Regular procedure for the macroscopic study

- Weigh and measure the specimen.
- Stain surgical border with India ink.

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[1] Surgical specimens must reach the laboratory untouched for macroscopic assessment and in order to prepare the sections with a comprehensive view of the sample.

- Cut into sections.

  - Fix sections and wait 24 h to cut thinner slices.
  - Thickness of the slices once fixed should be around 5 mm.
  - Sections should be cut in parallel, and following the perpendicular axis to the surgical margin.

- Take macroscopic pictures and/or make a diagram from each section with samples included.
- Number of blocks.

  - All nodules with a diameter of up to 2 cm should be included entirely.
  - For nodules between 2 and 5 cm, at least one complete section of each nodule (panoramic) should be included along with its inclusion diagram (Fig. 2).
  - For nodules >5 cm, add at least one more block which should be included for each centimetre above 5 cm.
  - For large nodules, it is important to sample the tumour's heterogeneity and include samples from both centre and periphery.
  - Non-tumour liver distant from the nodule should be included. It is advisable to leave at least 2 cm between the non-tumour liver sample and the nodule. When this is not possible, samples will be taken from the area most distant to the nodule.

Macroscopic report

The macroscopic report should include the following results:

- *Number of nodules and satellites nodules* Report the number of nodules found macroscopically (even though the number may not be the same as for the microscopic report). Satellite nodules are defined as being located less than 1 cm from the primary nodule. If the distance is greater than 1 cm, these nodules will be classified as other metastases.
- *Nodule size* Report at least the greatest diameter of each nodule, although, the diameter of the 3 dimensions is recommended.
- *Free border study* Should be specified in millimetres, measured macroscopically or with an optical microscope, it should specify the shortest distance between the tumour and the border stained with India ink. If the tumour is in contact with the margin or the margin is thermocoagulated, report "contact with margin".

Histochemical staining of histological samples

- Standard hematoxylin–eosin staining
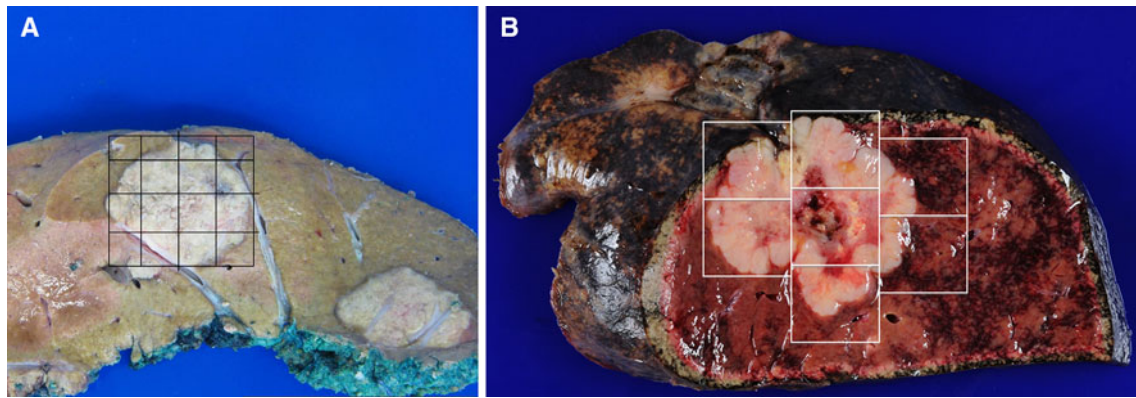
Fig. 2 a Sampling with squared grid to define the included sections. Normal liver tissue macroscopically. **b** Sampling with squared grid for the panoramic section of 45 × 48 mm metastases.

- Staining of non-tumour liver with at least

  - Masson's trichrome
  - Reticulin
  - And, if possible, also with
  - Periodic-acid Schiff (PAS).
  - Perl's iron stain.

Microscopic report

It should include the number of nodules, size, distance to margin in mm, tumour regression grade and the lesions observed in the non-tumour liver parenchyma.

Measure of tumour regression grade (pathological response)

- It is advisable to report the pathological response grade in each of the nodules.
- Pathological response should be measured according to the proportion of viable tumour cells in all the studied sections, defined as the percentage of the total tumour nodule (including tumour necrosis, coagulative necrosis, fibrosis and mucous).

  - Pathological response grades: presence of viable cells will be estimated in all studied sections. We recommend to evaluate response as percentages, including the following intervals:

    - 0 % = complete pathological response (CPR): absence of viable cells in all studied sections following this protocol[2]

Macroscopically, the liver parenchyma shows heterogeneous reddish coloration indicative of congestive lesions due to a severe SOS

  - 1–10 % = isolated tumour cells or small groups of cancer cells.
  - 11–50 % = significant reduction in tumour cells, which represent less than half of the initial tumour volume.
  - >50 % = minimal response, extensive residual tumour.

The choice of these cut-off points is based on the analyses of the series presented by Chan [38], Blazer [34], and Poultsides [43], among others, which shows the prognostic value of the regression grade between these cut-off points. Their interpretation is based on the recommendations of the College of American Pathologists (CAP) for the evaluation of tumour regression.

Other measures

- With the presence or absence of viable tumour cells, it is advisable to report on the presence or absence of:

  - Fibrosis
  - Necrosis, specifying whether it is of the normal or infarct-type
  - Mucous
  - Predominance of any of these features over the others, as some recent studies have pointed to the prognostic value of type of non-tumour tissue [44, 45].

- Due to its prognostic value, it is also advisable to report on the presence or absence of

  - Pseudo-capsule
  - Growth pattern of the tumour margin: expansive versus infiltrating.
  - Invasion:

    - vascular

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[2] If CPR is found after following this protocol, additional macro, micro or immunohistochemical analyses are not necessary for confirmation of CPR, although the final decision should be made according to the pathologist criteria.

- peri-neural
- bile duct
- sinusoidal

Post-treatment liver damage

Presence and severity of steatosis, steatohepatitis and lesions related to the sinusoidal obstruction syndrome should be reported.

Steatosis and steatohepatitis

- *Steatosis* estimated as percentage of affected hepatocytes and categorised as:

  - 0: absent
  - 1: mild (0–33 %)
  - 2: moderate (33–66 %)
  - 3: severe (>66 %)

- *Steatohepatitis* (*Activity grade*) Categorised according to Brunt [45]

Lesions related to the sinusoidal obstruction syndrome (SOS) (categorised according to the classification by Rubia-Brant [44])

- *Sinusoidal dilatation* (Fig. 3) Assessed semi-quantitatively as:

  - 0: absent
  - 1: mild (centrilobular involvement in 1/3 of lobule)
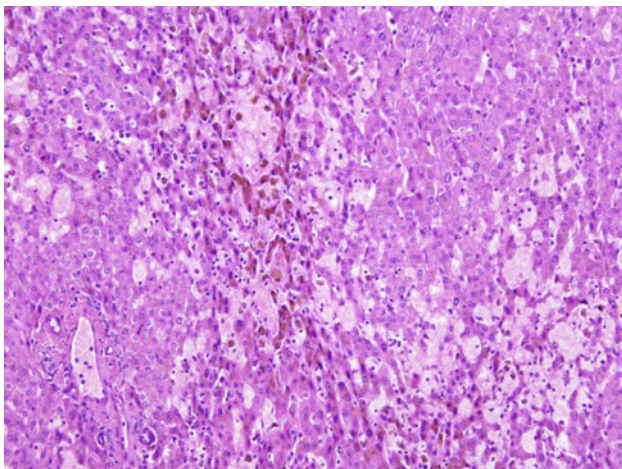 - 2: moderate (centrilobular involvement in 2/3 of lobule)

Fig. 3 Moderate sinusoidal dilatation with endothelial sinusoids disruption, congestion and hepatocellular atrophy (hematoxylin–eosin, ×100)

- 3: severe (whole lobule involvement or bridging congestion)

- *Central and perisinusoidal fibrosis* (Fig. 4) Report as present or absent. If possible, it should be graded as:

  - 0: absent
  - 1: mild (<50 % of veins and sinusoids, evaluated in 20 high-magnification fields)
  - 2: moderate (>50 % of veins and sinusoids, evaluated in 20 high-magnification fields)

- *Regenerative nodular hyperplasia* (Fig. 5). Report as present or absent. If possible, it should be graded as:

  - 0: absent
  - 1: mild (focal, evident with reticulin but not with HE staining)
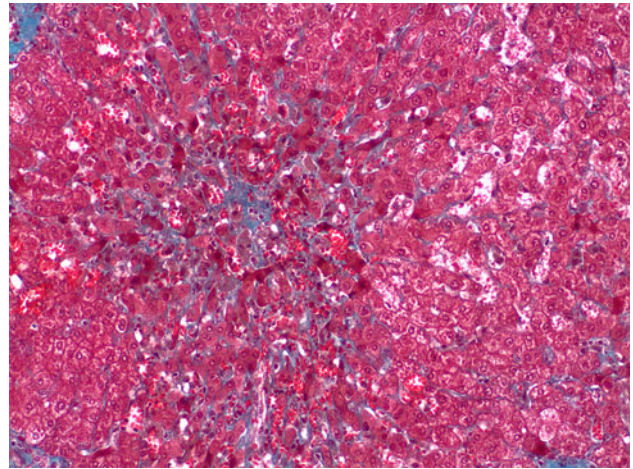

Fig. 4 Central lobular fibrosis. Sinusoidal dilatation, congestion and perisinusoidal fibrosis can be observed in the near surrounding of the vein (Masson's trichrome, ×200)
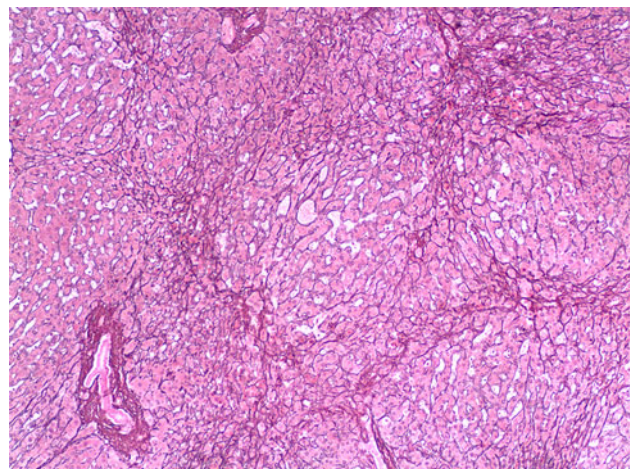

Fig. 5 Regenerative nodular hyperplasia (reticulin staining, ×100)

– 2: moderate (focal, evident with HE and highlighted with reticulin staining)
– 3: severe (diffuse, evident with HE and highlighted with reticulin staining)

- *Others* When other lesions that the pathologist classifies as significant, report on the presence of:

  – Hepatocyte necrosis
  – Peri-sinusoidal haemorrhage

- *SOS* Considered when sinusoidal dilatation of any grade with fibrosis and/or regenerative nodular hyperplasia is observed.

Conclusions

The assessment of the tumour response has changed lately based on the results exerted by the new chemotherapy and biologic agents. These new regimens induce a different response both in the tumour and non-tumour liver tissue. On the present manuscript, we provide recommendations on how to assess the tumour regression grade on liver metastases from CRC and how to assess the non-tumour tissue to help a standard assessment among different centres and to help to accurately decide on treatment options.

Also, a standard procedure on the tumour regression response will allow comparing the results between Pathology laboratories. Prospective multi-centric studies to validate our proposed recommendations will further contribute to establish the most effective method to assess liver metastasis and to understand the effects that new treatments have on the liver tissue.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277–300. http://onlinelibrary.wiley.com/doi/10.3322/caac.20073/pdf.
2. EuropaColon. Colorectal cancer statistics. http://www.europacolon.com/crcstatistics.php?Action=Crcstatistics. Accessed 9 August 2013.
3. Béjar L, Gili M, Díaz V, Ramírez G, López J, Cabanillas JL, et al. Incidence and mortality by colorectal cancer in Spain during 1951–2006 and its relationship with behavioural factors. Eur J Cancer Prev. 2009;18:436–44.
4. Sociedad Española de Oncología Médica. El cáncer en España 2012. Cifras de cáncer, estimaciones para el año. 2012. http://www.seom.org/en/prensa/el-cancer-en-espanyacom/103644-el-cancer-en-espana-2012?showall=1. Accessed 9 August 2013.
5. Redondo Capafons S, Planas Giner A, Garriga Biosca R, Pla Poblador R. Neoadjuvant chemotherapy used for colorectal liver and lung metastasis resections. Farm Hosp. 2011;35(5):255, e1–5.
6. Khatri VP, Chee KG, Petrelli NJ. Modern multimodality approach to hepatic colorectal metastases: solutions and controversies. Surg Oncol. 2007;16(1):71–83.
7. Gómez-Ramírez J, Martín-Pérez E, Amat CG, Sanz IG, Bermejo E, Rodríguez A, et al. Influence of pre-surgical chemotherapy on liver parenchyma and post-surgical outcome of patients subjected to hepatectomy due to colorectal carcinoma metastases. Cir Esp. 2010;88(6):404–12.
8. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol. 2005;23(9):2038–48.
9. Kemeny N. Presurgical chemotherapy in patients being considered for liver resection. Oncologist. 2007;12(7):825–39.
10. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol. 2009;27:1829–35.
11. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27(22):3677–83.
12. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008;13(1):51–64.
13. Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol. 2005;23:7125–34.
14. Díez-Fernández R, Salinas Hernández P, Girón-Duch C. Revisión del tratamiento quimioterápico del cáncer de colon metastásico. Farm Hosp. 2006;30:359–69.
15. Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol. 2004;15(3):460–6.
16. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006;24:2065–72.
17. Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer. 2007;110(12):2761–7.
18. Klinger M, Eipeldauer S, Hacker S, Herberger B, Tamandl D, Dorfmeister M, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. Eur J Surg Oncol. 2009;35(5):515–20.
19. Klinger M, Tamandl D, Eipeldauer S, Hacker S, Herberger B, Kaczirek K, et al. Bevacizumab improves pathological response of colorectal cancer liver metastases treated with XELOX/FOLFOX. Ann Surg Oncol. 2010;17(8):2059–65.
20. Pawlik TM, Abdalla EK, Ellis LM, Vauthey JN, Curley SA. Debunking dogma: surgery for four or more colorectal liver metastases is justified. J Gastrointest Surg. 2006;10:240–8.
21. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005;241(5):715–22.
22. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg. 2008;248(4):626–37.
23. Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol. 2005;23:7125–34.
24. Moertel CG, Hanley JA. The effect of measuring error on the results of therapeutic trials in advanced cancer. Cancer. 1976;38:388–94.
25. WHO handbook for reporting results of cancer treatment who offset publication no. 48. ISBN 92 4 170043 3. Geneva: World Health Organization; 1979. http://whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf.
26. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47:207–14.
27. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer. 1999;35(13):1773–82.
28. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000;92:205–16.
29. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

30. Fernández A, Duch J, Flotats A, Camacho V, Estorch M, Carrió I. CT–PET and evaluation of therapy response. Is the size really important? Rev Esp Med Nucl. 2010;29(4):184–8.

31. Chun YS, Vauthey JN, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA. 2009;302(21):2338–44.

32. Blazer DG 3rd, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol. 2008;26(33):5344–51.

33. Gruenberger T, Arnold D, Rubbia-Brandt L. Pathologic response to bevacizumab-containing chemotherapy in patients with colorectal liver metastases and its correlation with survival. Surg Oncol. 2012;21(4):309–15.

34. Rubbia-Brandt L, Giostra E, Brezault C, Roth AD, Andres A, Audard V, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Oncol. 2007;18(2):299–304.

35. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73(11):2680–6.

36. Chan G, Hassanain M, Chaudhury P, Vrochides D, Neville A, Cesari M, et al. Pathological response grade of colorectal liver metastases treated with neoadjuvant chemotherapy. HPB (Oxford). 2010;12(4):277–84.

37. Maru DM, Kopetz S, Boonsirikamchai P, Agarwal A, Chun YS, Wang H, et al. Tumor thickness at the tumor-normal interface: a novel pathologic indicator of chemotherapy response in hepatic colorectal metastases. Am J Surg Pathol. 2010;34(9):1287–94.

38. Abengózar M, Fernández-Aceñero MJ, Chaves S, Celdrán A. Prognostic utility of tumor thickness at the tumor-normal interface in chemotherapy-treated hepatic colorectal metastasis. Pathol Res Pract. 2012;208(4):235–9.

39. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010;17(11):2870–6.

40. Cleary JM, Tanabe KT, Lauwers GY, Zhu AX. Hepatic toxicities associated with the use of preoperative systemic therapy in patients with metastatic colorectal adenocarcinoma to the liver. Oncologist. 2009;14(11):1095–105.

41. Zalinski S, Bigourdan JM, Vauthey JN. Does bevacizumab have a protective effect on hepatotoxicity induced by chemotherapy? (Article in French). J Chir (Paris). 2010;147(Suppl 1):S18–24.

42. Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology. 2010;56(4):430–9.

43. Poultsides GA, Bao F, Servais EL, Hernandez-Boussard T, Dematteo RP, Allen PJ, et al. Pathologic response to preoperative chemotherapy in colorectal liver metastases: fibrosis, not necrosis, predicts outcome. Ann Surg Oncol 2012;19(9):2797–804 (Epub 2012 Apr 3).

44. Chang HH, Leeper WR, Chan G, Quan D, Driman DK. Infarct-like necrosis: a distinct form of necrosis seen in colorectal carcinoma liver metastases treated with perioperative chemotherapy. Am J Surg Pathol. 2012;36(4):570–6.

45. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol. 1999;94(9):2467–74.