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Liver Metastasis Resection Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided
◯ Information provided

Previous malignancy(s)

◯ Information not provided
◯ No
◯ Yes, *specify*

Neoadjuvant preoperative treatment
(select all that apply)

◯ Information not provided
☐ Interventional radiology treatment
☐ Preoperative chemotherapy, *specify*
☐ Other (e.g., immunotherapy), *specify*

Liver segments involved resected
(select all that apply)

☐ I ☐ V
☐ II ☐ VI
☐ III ☐ VII
☐ IV ☐ VIII

Other clinical information, *specify*

SPECIMEN TYPE (Note 2)

◯ Not specified
◯ Hemihepatectomy, left
◯ Hemihepatectomy, right
◯ Segmental resection, *specify segment involved*
◯ Non-anatomic (wedge) resection, *specify segment involved*
◯ Other, *specify*

SPECIMEN WEIGHT

g

SPECIMEN DIMENSIONS

mm x mm x mm

NUMBER OF TUMOURS (Note 3)

Number of tumours

◯ Cannot be assessed

MAXIMUM TUMOUR DIMENSION[a] (Note 4)

Lesion 1
Maximum tumour diameter mm

Lesion 2
Maximum tumour diameter mm

Lesion 3
Maximum tumour diameter mm

Lesion 4
Maximum tumour diameter mm

Lesion 5
Maximum tumour diameter mm

◯ Cannot be assessed, *specify*

[a] *Report for each lesion (up to 5).*

BLOCK IDENTIFICATION KEY (Note 5)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

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HISTOLOGICAL ORIGIN OF THE METASTASIS (Note 6) **(PRIMARY TUMOUR)**

- ◯ Not known
- ◯ Colon
- ◯ Rectum
- ◯ Lung
- ◯ Pancreas
- ◯ Ovary
- ◯ Stomach
- ◯ Kidneys
- ◯ Other, *specify*

HISTOLOGICAL TUMOUR TYPE (Note 7)

Colorectal cancer

(Value list based the World Health Organization (WHO) Classification of Tumours of the Digestive System (2019))

- ◯ Adenocarcinoma not otherwise specified (NOS)
- ◯ Mucinous adenocarcinoma
- ◯ Signet-ring cell adenocarcinoma
- ◯ Medullary carcinoma
- ◯ Serrated adenocarcinoma
- ◯ Micropapillary adenocarcinoma
- ◯ Adenoma-like adenocarcinoma
- ◯ Small cell neuroendocrine carcinoma
- ◯ Large cell neuroendocrine carcinoma
- ◯ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
- ◯ Other, *specify*

Other sites, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 8)

Colorectal cancer

- ◯ Not applicable
- ◯ Low grade
- ◯ High grade

Other sites, *specify*

RESPONSE TO PREOPERATIVE NEOADJUVANT THERAPY (Note 9)

- ◯ Not applicable
- ◯ Complete response
- ◯ Partial response
- ◯ No response

Evaluation by a standardised regression grading system[b]

- ◯ No
- ◯ Yes, *specify result*

[b] *Core for colorectal cancer; non-core for all other sites.*

TUMOUR GROWTH PATTERNS (Note 10)

- ◯ Encapsulated tumour
- ◯ Non-encapsulated tumour

EXTENT OF INVASION (select all that apply) (Note 11)

- ◯ Cannot be assessed
- ☐ Penetration/perforation of the liver capsule
- ☐ Extrahepatic extension
- ☐ Other, *specify*

BILIARY TRACT INVASION (Note 12)

- ◯ Not identified
- ◯ Present

VASCULAR INVASION (Note 13)

- ◯ Not identified
- ◯ Present

PERINEURAL INVASION (Note 14)

- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 15)

- ◯ Cannot be assessed
- ◯ Not involved

Distance from nearest hepatic resection margin ____ mm

Specify closest margin

- ◯ Involved
  - ◯ Vascular
  - ◯ Parenchyma

LYMPH NODE STATUS (Note 16)

- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved

  Number of lymph nodes with metastases

  - ◯ Number cannot be determined

COEXISTENT PATHOLOGY(select all that apply) (Note 17)

- ◯ None identified
- ☐ Steatosis
- ☐ Steatohepatitis
- ☐ Fibrosis
- ☐ Sinusoidal obstruction syndrome (SOS)
- ☐ Nodular regenerative hyperplasia (NRH)
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 18)

- ◯ Not performed
- ◯ Performed, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study.*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g. Pathological TNM staging, would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC.

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Scope

The dataset has been developed for the pathological reporting of liver resection specimens. Primary diagnostic biopsies specimens are here excluded.

The main origins of liver metastases (LM) are cancers of the colon, pancreas, ovary, rectum, stomach, lungs and kidneys. Liver resection is an option to treat colorectal metastases with a 5-year overall survival of approximately 70%.[2] There is a progressive trend to enlarge the indication of surgical approaches in hepatic metastases, notably due to the advance in tumour response to preoperative chemotherapy treatment, allowing the resection of tumours that initially exceeded the limits of resectability. Neuroendocrine tumours, gastrointestinal stromal tumours (GIST), breast, uveal and melanoma LM are increasingly treated by surgical approach.

NOTE: PRIOR TO PUBLICATION THE DATASET CONTENT WILL BE UPDATED TO REFLECT WHO 6TH EDITION.

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Note 1 – Clinical information (Core and Non-core)

Clinical information (Core)

Clinical information can be provided by the clinician on the pathology request form. Pathologists can search for additional information from possible previous pathology reports or clinical electronic files, when accessibility is available.

Previous malignancy(s) (Core)

It is important to considerer the patient's history of all previous malignancy, notably in situation of metachronous metastasis, referring to a cancer spread to the liver that occur after more than six months (often years) later after the initial diagnosis and treatment of colorectal cancer (CRC).

Neoadjuvant preoperative treatment of liver surgery (Core)

Given implications for interpretation by the pathologist in morphological features of the tumour and extent of response to any preoperative treatment and evaluation of hepatic non-tumoral liver tissue, it is important that details are provided to the pathologist regarding the application of any preoperative systemic or local procedures or treatment, and specifically details of such type therapy, notably type of chemotherapy regimens (core), duration and timing in relation to surgery, or local interventional radiology procedures such as radioembolisation, radiofrequency, trans arterial chemo-embolisation, or selective internal radiation therapy and should be mention 'portal vein embolisation', 'hepatic vein embolisation' (to induce hyperplasia of the remaining liver segments).

Liver segments involved resected (Core)

The type of operative procedure and, segments resected should be provided. The Couinaud classification of hepatic segments (French eponym) is the most widely and preferred classification used to describe liver anatomy and establish the basis of the various surgical options for liver resection.[3] It divides the liver into eight segments according to its own dual vascular arterial and venous inflow and biliary drainage rather than relying on the external appearance of the liver. The segments (II to VIII) are numbered in a clockwise fashion. In 2000, the Terminology Committee of the International Hepato-Pancreato-Biliary Association published a consensus hepatic nomenclature which is mostly adopted around the world.[4,5]

It is often not possible for pathologist to assign with certainty segmental location on resection specimens, and such information is thus best provided by the surgeon. Partial as more than one segments may be surgically resected.

Other clinical information (Non-core)

In the assessment of LM, a precise anatomical mapping is recommended in patients with multiple small metastases or when preoperative chemotherapy is performed because of the risk of vanishing metastases.

Number of tumours present based on preoperative imaging findings that should be present in the specimen should be mentioned. Wherever possible, the preoperative imaging report should be available to the pathologist at the time of specimen dissection (e.g., hospital intranet or alternatively or for any complex procedure, a diagram indicating the position of the tumour in the submitted specimen site could be provided.

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Note 2 – Specimen type (Core)

Specimen type

Total hepatectomy refers to resection of all the segments i.e., I-VIII, right hepatectomy procedure removes segments V-VIII, left hepatectomy is segments II-IV, right trisegmentectomy is segments IV-VIII, left lateral segmentectomy is segments II-III, and left trisegmentectomy is segments I-V5 and VIII. Pathologist records in the resections as wedge, partial (right or left lobe) resection as it is often not possible to assign segmental location, unless assisted by the surgeon

Macroscopic evaluation of the resected specimen

Macroscopic evaluation and sampling of LM is a crucial in the pathologic assessment in the diagnosis, prognosis, treatment decision, and follow-up of patient with LM and as an important role in quality control of the surgery. The surgical resection specimen should be examined accordingly.

The resection specimen should be macroscopically evaluated in sections of 5 millimetres (mm) thickness. This thin slicing can be performed on fresh state specimen when dissected for fixation, although thin slicing for macroscopic details is more accurate in the properly fixed hardened tissue. Transversal section in line with CT or magnetic resonance imaging (MRI) imaging is recommended.

The macroscopic aspect should then be carefully assessed, and each tumour described with respect to its dimension, and the closest to the distance from the surgical margin identified. The aspect of the border could be provided. One sample per centimetre, including both the centre and the periphery of the lesion, should be collected. In case of multiple nodules, samples from each of them could be recommended notably in the setting of a preoperative treatment to evaluated for a precise assessment of the degree of tumour response. In addition, sampling of closest to transection surgical margin, and the surrounding liver parenchyma (taken as far as possible from the lesion to avoid the mass-effect artefact) should be collected.

Liver resection specimens should be transferred as fast as possible to the Pathology department, preferably in unfixed state**.** Allocation of tissue samples for future molecular studies and for tissue biobank needs to be done in the Pathology department in the presence of a pathologist. All the decisions in this respect, whether possible to provide tumour or non-tumoral specimen (i.e., without compromising diagnostic and staging criteria) and from which area and the volume, need to be decided and recorded by the pathologists.

Photographing the specimens before dissection is also a useful practice.

Ink painting the resection margin may be performed.

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Note 3 – Number of tumours (Core)

The number of LM notably of colorectal origin is one of the most significant predictors of recurrence and overall survival.[6,7] It is thus important to report the total number of tumours within the hepatic resection in the pathology report and to be sure they correlate with the radiologic findings or the surgeon's operative report.

For the pathological assessment, a precise anatomical mapping is recommended notably in patients with multiple small metastases or when pre-operative chemotherapy has been performed because of the risk of

missing metastases and should be based ideally on the radiologic findings before preoperative chemotherapy.

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Note 4 – Maximum tumour dimension (Core)

Tumour size of LM of colorectal origin is a significant predictor of poor disease-free survival (DFS).[6,7] The maximum diameter can be measured in millimetres, both on the unfixed or fixed specimen (unfixed specimen avoids underestimation resulting from formalin fixation-induced shrinkage). For cases with multiple tumours, the DAC recommend that the size of at least the five largest tumour nodules should be provided.

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Note 5 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key to the tumour blocks. Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

A minimum of one block per tumour deposit is sufficient, although more may be taken in patients who have had neoadjuvant chemotherapy, especially if initial blocks show no viable tumour.

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Note 6 – Histological origin of the metastasis (primary tumour) (Core)

It is important to determine metastatic origin in both settings of known (notably in patients with multiple primary tumours) and unknown primary of tumours, at time of diagnosis, to offer best tailored therapies.

The liver is an ordinary site of metastasis for a large variety of primary tumours.[8] Most LM are carcinomas, followed by other far less common subtypes such as melanoma and sarcoma.

Adenocarcinomas are the most frequent subtype of carcinomas, most commonly from gastrointestinal tract (especially from colorectal or pancreatic) or breast origin, followed by small cell carcinoma of the lung, neuroendocrine carcinoma (most frequently from the digestive tract), and squamous cell carcinoma (especially lung and esophagus).

In colorectal adenocarcinoma, nearly 70% to 80% of cases with metastatic disease remain confined to the liver. Nearly 40% of patients diagnosed with CRC will develop LM, with 15% to 25% of these cases presenting with synchronous disease, the rest metachronous.

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Note 7 – Histological tumour type (Core)

Tumours should be histologically graded according to the World Health Organization (WHO) Classification of Tumours latest edition in each setting, notably for CRC the WHO Classification of Digestive System Tumours, 5th edition, 2019.[9] Please refer to the corresponding ICCR datasets of the primary sites.[10]

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Note 8 – Histological tumour grade (Core)

Tumours should be histologically graded according to the WHO Classification of Tumours latest edition in each setting, notably for CRC the WHO Classification of Digestive System Tumours, 5th edition, 2019.[9] Please refer to the corresponding ICCR datasets of the primary sites.[10]

'Not applicable' applies to when complete tumour regression (entirely necrotic or fibrotic nodule in response) in response to preoperative therapy is observed.

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Note 9 – Response to preoperative neoadjuvant therapy (Core and Non-core)

Downsizing of LM in response to preoperative chemotherapy is usually determined preoperatively by radiological imaging, but tumour cell response to chemotherapy can only be assessed with accuracy by pathology examination. In fact, even if a tumour appears to shrink radiologically in size, the number of viable tumour cells may not decrease proportionally.

More specifically, in colorectal LM, pathological response to preoperative chemotherapy has shown prognostic factor, and consequently may help guiding adjuvant treatment and is integrated as an endpoint in clinical trials. The degree of pathological response has been shown to vary depending on the chemotherapy regimen used .

Thus, assessing the tumour's response to the treatment is recommended in LM and essential in the pathology report for colorectal LM.

Two main histological scores have been retained to grade pathological response of colorectal LM to preoperative treatment: a Tumour Regression Grade (TRG) system,[11] and a semiquantitative method based on the percentage vital tumour cells. Both scores have good interobserver agreement.

The TRG system (refer to Table 1) evaluates the ratio of residual viable tumour cells over fibrous tissue within the tumour and has the advantage of being an equivalent scoring system as the one used for primary colorectal tumours by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM[12,13] allowing easy comparison of tumour response between the primary and the metastatic sites. This is recommended in the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for colorectal LM after preoperative chemotherapy.[14] It consists of numerical values from 1 to 5.

Table 1: Five-tier Tumour Regression Grade (TRG) system adapted for colorectal liver metastases. ***Adapted from Rubbia-Brandt 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 Feb;18(2):299-304.***[11]

TRG5	Tumour shows no histological sign of regression in response to treatment and is composed of diffuse viable tumour cells, intermingled with dirty necrosis
TRG4	The tumour is composed primarily of viable tumour—however, areas of very mild fibrosis are also present
TRG3	The tumour consists of residual viable tumour cells intermingled in predominant fibrosis reaction
TRG2	Only rare viable tumour cells within a largely predominates fibrosis
TRG1	The tumour shows a completely fibrotic treatment response and no residual viable tumour cells are observed.

The clinical significance can be summarised in three-tiers as follows: TRG 1-2 Major tumour response, TRG3 partial tumour response, and TRG4-5 no tumour response (refer to Figure 1).

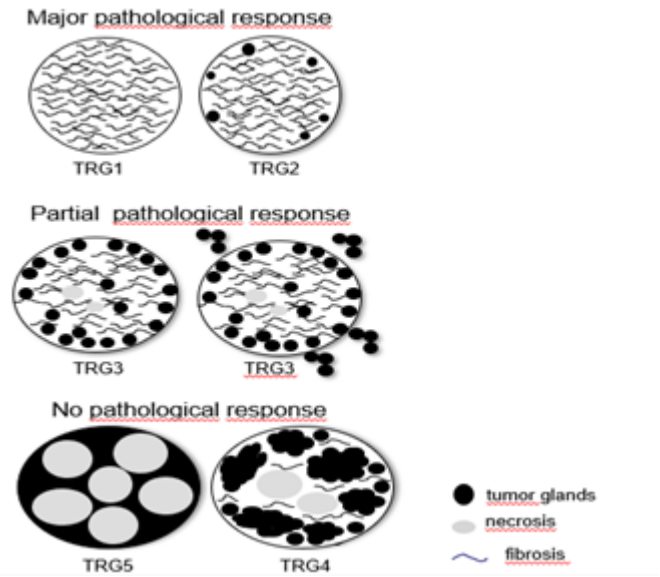

Figure 1: Schematic representation of the histologic patterns of the tumour regression grades for colorectal liver metastases. ***Adapted from Rubbia-Brandt et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neoadjuvant chemotherapy followed by liver surgery. Ann Oncol 2007 Feb;18(2):299-304.***[11]

The second histological score relies on the percentage of residual viable tumour cells, where complete response corresponds to 0% of residual viable cells, major response between 1% and 49% of residual cancer cells, and minor ≥50% of viable cancer cells.[15,16]

Of significance, residual viable cells after incomplete tumour regression are preferentially located at the periphery of the LM, producing a 'dangerous halo', which emphasise the need for enough surgical margin despite tumour downsizing.[17,18]

'Not applicable' applies to where you have not used preoperative neoadjuvant therapy.

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Note 10 – Tumour growth patterns (Non-core)

The histopathological growth patterns are an independent prognostic factor in patients who underwent surgical resection of LM.[14,19] Although the most convincing evidence comes from multivariate analyses in large cohorts of patients with LM of CRC,[20,21] the strong and independent prognostic value of the LM growth patterns also applies to other primary tumour types such as, for example, breast cancer and melanoma.[19,22,23] The growth patterns also reflect vastly divergent biology concerning immune contexture, tumour differentiation and the origin of blood vessels and connective tissue stroma.[24,25]

The two common growth patterns are the 'encapsulated' (formerly called 'desmoplastic') and the 'replacement' growth pattern (for histological pictures we refer to the consensus guidelines[19,26]).

In LM with an encapsulated growth pattern, the tumour cells are separated from the liver by a fibrous capsule of varying thickness. There is no contact of tumour cells and hepatocytes. A proliferation of bile ducts can often be observed in the capsule. Usually, this type of metastases is surrounded by a dense mononuclear inflammatory cell infiltrate.

In contrast, in LM with a replacement growth pattern, tumour cells are in contact with the hepatocytes, they replace the hepatocytes, and, in the process, they co-opt the sinusoidal blood vessels of the liver. As a result, the tissue architecture of the metastases with this growth pattern mimics the tissue architecture of the liver, such that the metastatic tumour cell arrangement recapitulates 'hepatic cell plates' in between co-opted hepatic sinusoidal blood vessels. Typically, but influenced by pre-surgery systemic treatment, only very few immune cells are present at the tumour-liver interface and in the tumour centre of replacement-type metastases.

The growth patterns are assessed on haematoxylin-eosin (H&E) sections of formalin-fixed and paraffin-embedded tissue of resection specimens of LM. Care should be taken to embed the interface between liver tissue and tumour tissue, preferably of the complete interface of the largest cross section of each of the resected LM. The centre of the metastasis does not contribute to the classification of a growth pattern. All the H&E sections of every resected metastasis should be analysed when scoring the growth patterns.

For CRC LM, the reproducibility of a two-tiered scoring system has been demonstrated to be high,[27] but discussion is ongoing whether a continuous scoring system could offer more subtle prognostic information.[25] In the two-tiered system, whenever replacement growth is observed, prognosis is worse than when only encapsulated growth is present, independent of the proportion of the tumour-liver interface with replacement growth. So, patients belong to the 'Encapsulated' group or to the 'Non-encapsulated' group (or 'Any % of replacement' group) when this system is applied. Alternatively, a continuous scoring system can be adopted. In this system, the mean of the scores of all available H&E sections is reported. For example, 85% encapsulated growth and 15% replacement growth. The greater the proportion of replacement growth, the less favorable is the prognosis. In case of multiple metastases, each metastases should be separately scored.[19]

There are some caveats when assessing the growth patterns of LM. Portal tracts at the tumour-liver interface and growth near the liver capsule (facing the peritoneal surface or soft tissue without intermediate liver parenchyma) should not be considered as part of the tumour-liver interface.

In case of severe inflammation and associated tissue changes it may be difficult to identify the growth patterns. The presence of co-opted hepatocytes and tumour cell-hepatocyte contact in the periphery of the metastasis are indicative of the replacement growth pattern.

Metastatic growth inside portal tracts or biliary ducts should not be regarded as desmoplastic growth (but can be reported separately) as micrometastases.

For further information, please refer to: https://www.livermetastasisgrowthpatterns.org.

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Note 11 – Extent of invasion (Non-core)

Spontaneous rupture of a metastatic liver tumour is rarely documented in the literature when compared to hepatocellular carcinoma. The incidental intraoperative discovery of extrahepatic disease remains a contraindication to hepatic resection.

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Note 12 – Biliary tract invasion (Non-core)

Biliary invasion is defined as the presence of tumoral cells within the lumen of a biliary duct, as identified by H&E stain and reported in around 10% of the specimens. Immunohistochemistry against cytokeratin-7 (a marker of biliary duct epithelium) and/or markers of CRC (e.g., CDX2, SATB2) may be useful in distinguishing biliary invasion from primitive biliary neoplasia.

Several studies found that biliary invasion is significantly correlated with shorter recurrence-free and occasionally with overall survival in patients with CRC LM who are receiving bevacizumab as preoperative treatment.[28-31]

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Note 13 – Vascular invasion (Core)

In LM, clinical relevance of intrahepatic vascular invasion detection is still unclear. Several studies on colorectal LM, have reported hepatic and portal vein invasion to have poor prognostic significance, while other studies have not identified this association.[32,33] However, given its prognostic significance in primary CRC and the fact that venous invasion represents a route of metastatic spread inside and outside the liver, the DAC recommend this as a core element.

Endovascular invasion is characterised by presence of tumour cells within a lumen lined by endothelial cells. Tumour invasion is most observed in intrahepatic portal or hepatic veins. Small vessels may represent lymphatic; in doubtful cases it is assessed by using immunohistochemistry against endothelial markers, lymphatics and venules may be distinguished by D2-40 immunohistochemistry, which only stains lymphatic endothelial cells.

Aggressive growth phase of LM can be accompanied by cancer cells being present within sinusoidal capillary vessels.

Perivascular invasion (refer to Figure 2) is defined as an attachment of tumour cells to the vascular wall notably the muscular wall or elastic lamina of larger blood vessels.

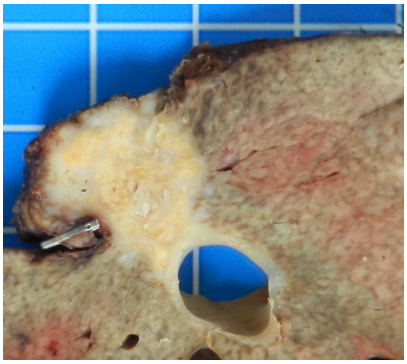

Figure 2: Perivascular invasion. *Permission courtesy of Professor Laura Rubbia-Brandt.*

By pathologic examination, approximately 60% of hepatic vessels remained attached to or invaded by tumours, even after chemotherapy.[34] Thus, attachment to or invasion of major intrahepatic vessels by liver metastasis is difficult to eradicate, even with otherwise effective chemotherapy and as an impact in evaluation of positive or negative margins.

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Note 14 – Perineural invasion (Non-core)

Perineural invasion can be assessed by using H&E stain or S100 immunohistochemistry. The prognostic relevance of perineural invasion in LM from CRC has been evaluated in few studies only.[30,32,35-38] Therefore, the DAC agreed to including this parameter in the histopathological report of CRC LM as non-core.

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Note 15 – Margin status (Core)

Pathology report should clearly state the margin status and the distance of the tumour to the margin (in mm).

In patients who undergo a large vessel resection, the vascular margin should be examined and reported separately from the parenchymal margin.

On pathological examination, a margin >1 mm is currently classified as R0 resection, whereas a margin ≤1 mm as R1 resection. Patients with resections of multiple LM are classified as R1 if at least one tumour has a margin <1 mm.

In larger resection specimens, such as from a segmentectomy or lobectomy, the margin status of large portal tracts and large vessels is also important to assess, since LM can cause biliary spread and large venous invasion.

Tumour margins for resection can be difficult to define after preoperative therapy. In cases of incomplete tumour regression residual viable cells are preferentially located at the periphery of the metastasis ('dangerous halo') which emphasise the need for sufficient margins despite tumour downsizing. Tumour-specific DNA has also been detected up to 4 mm beyond the visible tumour margin.[31,34,39-43]

R1 resections are classified as follows:[14,44-47]

- Vascular R1 (R1Vasc): is considered when the tumour is detached from a vascular structure, either first/second-order glissonean pedicles or from hepatic veins within their last 40 mm before confluence into the inferior vena cava. The tumour was exposed exclusively along the vessel. The R1v was defined that tumour exposed exclusively along the vessel. R1p was defined that tumour exposed along the transection plane
- Parenchymal R1 (R1Par): the tumour was exposed along the transection plane.

The distinction between R1Vasc and R1Par is made by combining surgical and pathological data. The surgeon is the one who mainly classified R1Vasc resections.

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Note 16 – Lymph node status (Core)

The regional perihepatic lymph nodes include hilar, hepatoduodenal ligament, inferior phrenic, common hepatic artery, coeliac trunk in the aortocaval space, and portal vein lymph nodes. The site of the submitted node cannot be defined with certainty by the pathologist, unless stipulated by the surgeon.

Perihepatic lymph node metastases are thought to result from metastatic spread of the LMs themselves through perihepatic lymphatic channels.

In colorectal LM, lymph nodes metastases are recognised as a poor prognostic factor, related to the number of involved nodes,[48] while the ratio of metastatic to total number of resected perihepatic LNs is an independent predictor of poor relapse free survival and overall survival after hepatectomy with lymphadenectomy,[49,50] underlining the role of detailing the number of lymph nodes.

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Note 17 – Coexistent pathology (Core)

The assessment of non-neoplastic liver tissue is important for further treatment decisions and should performed on a sample ideally 15 mm away from the tumour to avoid possible mass effect.

Two types of liver pathology should be distinguished: chemotherapy associated liver injuries (CALI) and tumour-independent pathology as follows:

1. **CALI:** This can result in higher postoperative morbidity or long term liver impairment. Liver injury may occur with chemotherapy regimens comprising irinotecan, which may cause steatohepatitis, and oxaliplatin, which may cause sinusoidal obstruction syndrome (previously known as venoocclusive disease) occasionally associated with development of perisinusoidal fibrosis or nodular regenerative hyperplasia (NRH).

   If steatohepatitis is identified in the resection specimen (whether from irinotecan or other risk factors), the pathologist should grade and stage the inflammation and fibrosis, respectively, using the non-alcoholic fatty liver disease scoring system.

If a patient has received FOLFOX and the background liver shows sinusoidal dilatation, congestion, NRH changes, and/or venous obstruction, a diagnosis of chemotherapy-induced sinusoidal injury and/or sinusoidal obstruction syndrome should be diagnosed.

2. **Tumour-independent pathology:** this includes any kind of relevant liver pathology according to the guidelines and recommendation relevant to the disease(s) in question.

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Note 18 – Ancillary studies (Non-core)

Allocation of tissue samples for future molecular studies and for tissue biobank needs to be done in the Pathology department in the presence of a pathologist. All the decisions in this respect, whether possible to provide tumour or non-tumoral specimen (i.e., without compromising diagnostic and staging criteria) and from which area and the volume, need to be decided and recorded by the pathologists.

Immunohistochemistry is not systematically required for these metastatic tumour resections because the diagnosis is usually established on core biopsy of the primary site prior to resection, and thus rarely needs to be repeated. Prognostic and predictive testing such as mismatch repair (MMR) and HER2 for CRC again are also most likely to be performed on small core biopsies.

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References

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