



Liver Metastasis Resection Histopathology Reporting Guide

Family/Last name		Date of birth	DD – MM – YYYY
Given name(s)			
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

Preoperative neoadjuvant therapy

☐ Information not provided

☐ No

☐ Yes (select all that apply)

☐ Interventional radiology treatment

☐ Preoperative chemotherapy, specify

☐ Other, specify

Liver segments (select all that apply)

☐ 1

☐ 5

☐ 2

☐ 6

☐ 3

☐ 7

☐ 4

☐ 8

Other clinical information, specify

OPERATIVE PROCEDURE (Note 2)

☐ Not specified

☐ Hemihepatectomy

☐ Left

☐ Right

☐ Segmental resection, specify segment involved

☐ Non-anatomic (wedge) resection, specify segment involved

☐ Other, specify

SPECIMEN WEIGHT^a

 g

^a Report for each separate specimen.

SPECIMEN DIMENSIONS^a

 mm x mm x mm

NUMBER OF TUMOURS (Note 3)

☐ Not specified

MAXIMUM TUMOUR DIMENSION^b (Note 4)

Lesion 1

Maximum tumour dimension mm

Lesion 2

Maximum tumour dimension mm

Lesion 3

Maximum tumour dimension mm

Lesion 4

Maximum tumour dimension mm

Lesion 5

Maximum tumour dimension mm

☐ Cannot be assessed, specify

Comment

^b 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)

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

- ☐ Not known
☐ Colon
☐ Rectum
☐ Lung
☐ Pancreas
☐ Ovary
☐ Stomach
☐ Kidney
☐ Other, *specify*

HISTOLOGICAL TUMOUR TYPE (Note 7)**Colorectal cancer**

(Value list based on the World Health Organization
Classification of Digestive System Tumours, 6th Edition (2026))

- ☐ No evidence of residual tumour
☐ Adenocarcinoma, not otherwise specified (NOS)
☐ Mucinous adenocarcinoma
☐ Serrated adenocarcinoma
☐ Micropapillary adenocarcinoma
☐ Medullary carcinoma
☐ Adenoma-like adenocarcinoma
☐ Signet-ring cell adenocarcinoma
☐ Adenosquamous carcinoma
☐ Squamous cell carcinoma
☐ Low grade tubuloglandular adenocarcinoma
☐ Lymphoglandular complex-like adenocarcinoma
☐ Undifferentiated carcinoma
☐ Carcinoma with mesenchymal differentiation
☐ Neuroendocrine neoplasms^c
☐ Neuroendocrine carcinoma, NOS
☐ Large cell
☐ Small cell
☐ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
☐ Other, *specify*

Other sites, *specify*

^c Neuroendocrine tumours are not covered in this dataset.

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
☐ Cannot be assessed, *specify*

Evaluation by a standardised regression grading system^d

- ☐ No
☐ Yes, *specify result*

^d Core for metastases from colorectal cancer; non-core for all other origins.

TUMOUR GROWTH PATTERNS (Note 10)

- ☐ Encapsulated tumour
☐ Non-encapsulated tumour

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

- ☐ Penetration/perforation of the liver capsule
☐ Extrahepatic extension
☐ Other, *specify*

BILIARY TRACT INVASION (Note 12)

- ☐ Not identified
☐ Present

LYMPHOVASCULAR INVASION (Note 13)

- ☐ Not identified
☐ Present (select all that apply)
☐ Lymphatic invasion
☐ Vascular invasion

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

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

NEUROENDOCRINE NEOPLASMS ONLY^c**Neuroendocrine markers**

☐ Not performed

☐ Performed (select at least two of the following core options)

☐ Synaptophysin

☐ Chromogranin-A

☐ INSM1

☐ Other, *specify*

Specify test(s) performed and result(s) if available

^c Neuroendocrine tumours are not covered in this dataset.

Ki-67 proliferation index

☐ Not performed

☐ Performed


 %
p53

☐ Not performed

☐ Performed



☐ Abnormal, *specify test(s) performed and result(s) if available*

☐ Wildtype pattern

Mismatch repair (MMR) immunohistochemistry^d

☐ Not performed

☐ Performed



☐ Not interpretable

☐ Proficient

☐ Deficient, *specify*

RB1

☐ Retained

☐ Deficient

Low molecular weight cytokeratin(s)

☐ Positive

☐ Negative

^d Core for metastases from colorectal cancer; non-core for all other origins.

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 evidence¹). 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.

 [Back](#)

Scope

The dataset has been developed for the pathological reporting of liver resection specimens. Primary diagnostic biopsies specimens are 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 (NETs), gastrointestinal stromal tumours (GISTs), breast, uveal and melanoma LM are increasingly treated by a surgical approach.

In development of this dataset, the DAC considered evidence up until July 2026.

The authors of this dataset can be accessed [here](#).

 **Back**

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

Clinical information should 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)

All previous malignancies (type, origin, stage) of the patient should be disclosed.

Preoperative neoadjuvant therapy (Core)

Details of previous (neoadjuvant) treatment for the liver metastases should be disclosed, since this might alter the morphology of the metastases and require regression scoring, as well as careful examination of the surrounding non-malignant liver tissue. Specifically, details of the type of therapy should be noted. These may include type of systemic regimens, 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. ‘Portal vein embolisation’ and ‘hepatic vein embolisation’ (to induce hyperplasia of the remaining liver segments) should be separately mentioned.

Liver segments (Core)

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. For this dataset we use Arabic numbers. 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}

The surgeon should provide information on the type of resection performed and/or the segments removed.

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.

The number of tumours expected based on preoperative imaging should be mentioned in the clinical data. It would be helpful if the preoperative imaging report is available at the time of specimen dissection (either via hospital intranet or alternatively as a diagram indicating the position of tumours in the submitted specimen).

 **Back**

Note 2 – Operative procedure (Core)

The operative procedure performed should be a standard part of any pathology report.

Types of hepatectomy procedures include:

- Total hepatectomy which removes all eight liver segments (segments 1-8)
- Right hepatectomy which removes segments 5-8
- Left hepatectomy which removes segments 2, 3 and 4
- Right trisegmentectomy which removes segments 4-8
- Left lateral segmentectomy which removes segments 2 and 3
- Left trisegmentectomy which removes segments 2, 3 and 4.

Macroscopic evaluation of the resected specimen

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. The DAC recommends that 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.

 [Back](#)

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.

 [Back](#)

Note 4 – Maximum tumour dimension (Core and Non-core)

Tumour size of LM of colorectal origin is a significant predictor of poor disease-free survival (DFS).^{6,7} The maximum dimension 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. Additional tumour nodules may be documented in a comment (non-core).

 [Back](#)

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.

 [Back](#)

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 (NEC) (most frequently from the digestive tract), and squamous cell carcinoma (especially lung and esophagus).

In colorectal adenocarcinoma, approximately 70% to 80% of cases with metastatic disease remain confined to the liver.⁹ Nearly 40% of patients diagnosed with colorectal cancer (CRC) will develop LM, with 15% to 25% of these cases presenting with synchronous disease, the rest metachronous.⁹

 [Back](#)

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, 6th edition, 2026 (Table 1).¹⁰ Please refer to the corresponding ICCR datasets of the primary sites.¹¹

Table 1: 6th edition of the World Health Organization Classification of Digestive System Tumours.¹⁰

Descriptor	ICD-O codes ^a
Adenocarcinoma, metastatic, not otherwise specified (NOS)	81400/6
Carcinoma, metastatic, NOS	80100/6

^a These morphology codes are from the International Classification of Diseases for Oncology, fourth edition (ICD-O-4).¹² Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

© World Health Organization/International Agency for Research on Cancer. Reproduced with permission.

 **Back**

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, 6th edition, 2026.¹⁰ Please refer to the corresponding ICCR datasets of the primary sites.¹¹

‘Not applicable’ applies to the situation after pre-operative therapy in line with primary tumour grade assessment.

 **Back**

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.

The degree of pathological response has been shown to vary depending on the chemotherapy regimen used. In colorectal LM, pathological response is a prognostic factor that may influence subsequent treatment decisions.^{13,14}

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) system¹⁵ and a semiquantitative method based on the percentage vital tumour cells.^{16,17} Both scores have good interobserver agreement. It is core to report

whether response to preoperative neoadjuvant therapy has been evaluated using a standardised regression grading system for metastases from CRC; non-core for all other origins. Specifying the result of this evaluation is non-core. For assessment of response to immunotherapy a different method has been described,¹⁸ but not been validated for LM.

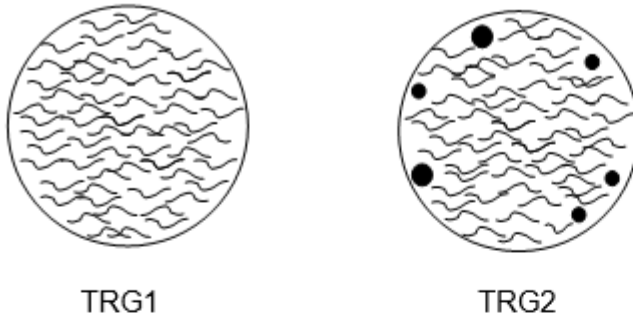
The TRG system for colorectal LM evaluates the ratio of residual viable tumour cells over fibrous tissue within the tumour (Table 2).¹⁵ It has the advantage of being an equivalent scoring system as the one used for primary colorectal tumours by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM^{19,20} allowing easy comparison of tumour response between the primary and the metastatic sites. The TRG system is recommended in the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for colorectal LM after preoperative chemotherapy.²¹ It consists of numerical values from 1 to 5.

Table 2: Five-tier Tumour Regression Grade (TRG) system for colorectal liver metastases.¹⁵

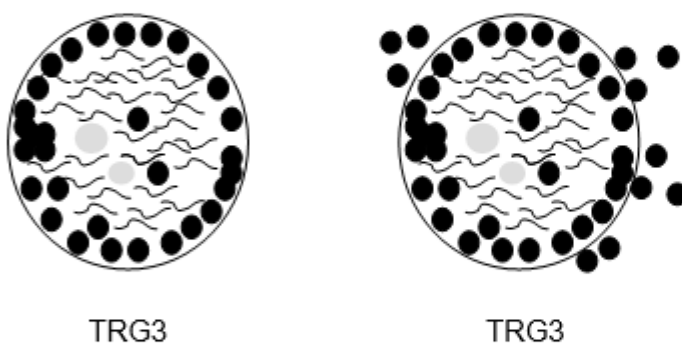
TRG5	Tumour shows no histological sign of regression in response to treatment and is composed of diffuse viable tumour cells, intermingled with dirty necrosis
TRG4	The tumour is composed primarily of viable tumour—however, areas of very mild fibrosis are also present
TRG3	The tumour consists of residual 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' (Figure 1).

Major pathological response



Partial pathological response



No pathological response

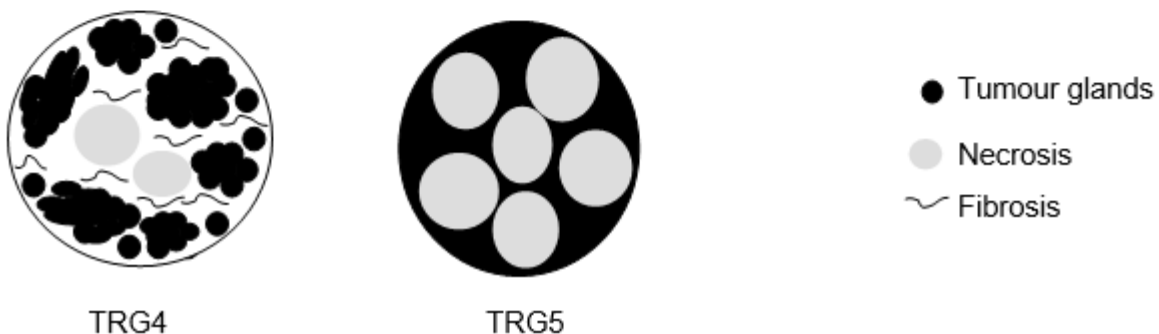


Figure 1: Schematic representation of the histologic patterns of the tumour regression grades for colorectal liver metastases. Adapted with permission from Rubbia-Brandt et al (2007). Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neoadjuvant chemotherapy followed by liver surgery. *Ann Oncol* 18(2):299-304.¹⁵

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 $\geq 50\%$ of viable cancer cells.^{16,17}

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.^{22,23}

'Not applicable' applies where preoperative neoadjuvant therapy has not been used.

 **Back**

Note 10 – Tumour growth patterns (Non-core)

The histopathological growth patterns are an independent prognostic factor in patients who underwent surgical resection of LM.^{21,24} Although the most convincing evidence comes from multivariate analyses in large cohorts of patients with LM of CRC,^{25,26} 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.^{24,27,28} The growth patterns also reflect vastly divergent biology concerning immune contexture, tumour differentiation and the origin of blood vessels and connective tissue stroma.^{29,30}

The two common growth patterns are the 'encapsulated' (formerly called 'desmoplastic') and the 'replacement' growth pattern (for histological pictures refer to the consensus guidelines^{24,31}). In this dataset, the latter is referred to as 'non-encapsulated', together with the more rarer growth patterns.

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) stained 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,³² but discussion is ongoing whether a continuous scoring system could offer more subtle prognostic information.³⁰ 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 percentage 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.²⁴

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).

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

 **Back**

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.

 **Back**

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 have 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.³³⁻³⁶

 **Back**

Note 13 – Lymphovascular 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.^{37,38} 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 invasion. In doubtful cases it is assessed 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 (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.

By pathologic examination, approximately 60% of hepatic vessels remained attached to or invaded by tumours, even after chemotherapy.³⁹ 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.

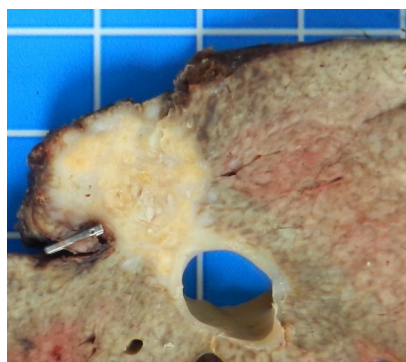


Figure 2: Perivascular invasion. *Permission courtesy of Professor Laura Rubbia-Brandt.*

↑ Back

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.^{35,37,40-43} Therefore, the DAC agreed to including this parameter in the histopathological report of CRC LM as non-core.

↑ Back

Note 15 – Margin status (Core)

The pathology report should clearly state the margin status and the distance of the tumour to the margin (in millimetres).

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.^{36,39,44-48}

R1 resections are classified according to the mode of margin involvement, either as vascular R1 (R1Vasc) or parenchymal R1 (R1Par).^{21,49-52} The latter refers to tumour at the resection margin, while R1Vasc refers to vascular invasion in the margin. The distinction between R1Vasc and R1Par is made by combining surgical and pathological data. The surgeon mainly classifies R1Vasc resections.

 [Back](#)

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.⁵³ While the ratio of metastatic to total number of resected perihepatic lymph nodes is an independent predictor of poor relapse free survival and overall survival after hepatectomy with lymphadenectomy,^{54,55} underlining the role of detailing the number of lymph nodes.

 [Back](#)

Note 17 – Coexistent pathology (Core)

The assessment of non-neoplastic liver tissue is important for further treatment decisions and should be 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 may grade and stage the inflammation and fibrosis, respectively, using the non-alcoholic fatty liver disease scoring system. This will depend on the aetiology.

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.

↑ Back

Note 18 – Ancillary studies (Core and 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 are also most likely to be performed on small core biopsies.

If a pure or mixed neuroendocrine neoplasm is suspected on morphology, positivity for at least two markers of neuroendocrine differentiation by immunohistochemistry is required (core) to confirm neuroendocrine differentiation, usually synaptophysin, chromogranin A and/or INSM1. As with other gastrointestinal tract and pancreatic neuroendocrine neoplasms, assessment of proliferation index by Ki-67 immunohistochemistry is a core component as it is fundamental to grading of the neuroendocrine component.¹⁰ For the differential diagnosis with grade 3 NET, p53 (core) and Rb1 (non-core) can be applied. Low molecular weight cytokeratins can be used (non-core). MMR stains should be used in liver metastases NECs (core). A Ki-67 proliferation index <55% is associated with better overall survival in NECs.⁵⁶ TP53 mutations are found in over 69% of NEC compared to 10-15% of NET grade 3 (G3),^{57,58} while RB1 loss is found in 40-60% of NEC and only very rarely in NET G3.⁵⁹

↑ Back

References

- 1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.
- 2 Newhook TE and Vauthey JN (2022). Colorectal liver metastases: state-of-the-art management and surgical approaches. *Langenbecks Arch Surg* 407(5):1765–1778.
- 3 Couinaud C (1957). The Liver: Anatomical and surgical studies. *Paris: Messon*:235–238.
- 4 Strasberg SM (2005). Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 12(5):351–355.
- 5 Strasberg SM and Phillips C (2013). Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. *Ann Surg* 257(3):377–382.
- 6 Viganò L, Capussotti L, Majno P, Toso C, Ferrero A, De Rosa G, Rubbia-Brandt L and Mentha G (2015). Liver resection in patients with eight or more colorectal liver metastases. *Br J Surg* 102(1):92–101.
- 7 Cheng KC and Yip AS (2022). Prognostic factors of survival and a new scoring system for liver resection of colorectal liver metastasis. *World J Hepatol* 14(1):209–223.
- 8 de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V and Nagtegaal I (2016). Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients. *Oncotarget* 7(34):55368–55376.
- 9 Hugén N, van de Velde CJH, de Wilt JHW and Nagtegaal ID (2014). Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. *Ann Oncol* 25(3):651–657.
- 10 WHO Classification of Tumours Editorial Board (ed) (2026). *WHO Classification of Tumours, Digestive System Tumours, 6th Edition*, IARC, Lyon.
- 11 International Collaboration on Cancer Reporting (2026). *ICCR Datasets*. Available at: <https://www.iccr-cancer.org/datasets/published-datasets/> (Accessed 21 September 2026).
- 12 International Agency for Research on Cancer (IARC) (2026). *International Classification of Diseases for Oncology, Fourth edition ICD-O-4*. Available from: tumourclassification.iarc.who.int/icd-o-4/ (Accessed 21 September 2026).
- 13 Tanaka H, Imai H, Matsushashi N, Higashi T, Kiyama S, Okumura N, Murase K, Takahashi T, Saigo C, Takeuchi T and Yoshida K (2022). The Prognostic Significance of a Histological Response to Preoperative Chemotherapy in Patients With Synchronous Colorectal Liver Metastases. *International Surgery* 106(1):5–17.
- 14 Baldo A, Akabane M, Elemosho A, Charalampous CM, Chatzipanagiotou OP, Kawashima J, Spolverato G, Ruzzenente A, Poultsides GA, Sasaki K, Endo I, Kitago M, Aucejo F, Popescu I, Hugh T, Weiss M, He J and Pawlik TM (2026). Anatomical and Histologic Response to Neoadjuvant Therapy: Recurrence Patterns Among Poor Responders. A Multi-institutional Observational Cohort Study. *Ann Surg* 284(4):680–688.

- 15 Rubbia-Brandt L, Giostra E, Brezault C, Roth AD, Andres A, Audard V, Sartoretti P, Dousset B, Majno PE, Soubrane O, Chaussade S, Mentha G and Terris B (2007). 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* 18(2):299–304.
- 16 Blazer DG, 3rd, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, Fogelman D, Eng C, Chang DZ, Wang H, Zorzi D, Ribero D, Ellis LM, Glover KY, Wolff RA, Curley SA, Abdalla EK and Vauthey JN (2008). Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 26(33):5344–5351.
- 17 Chang HH, Leeper WR, Chan G, Quan D and Driman DK (2012). Infarct-like necrosis: a distinct form of necrosis seen in colorectal carcinoma liver metastases treated with perioperative chemotherapy. *Am J Surg Pathol* 36(4):570–576.
- 18 Deutsch JS, Scolyer RA, Burton E, Busam KJ, Chen KY, Cimino-Mathews A, Cottrell TR, de Andrea CE, Fiset PO, Long GV, Messina J, Rawson RV, Salgado R, Schürch CM, Seethala RR, Sholl LM, Signoretti S, Topalian SL, van de Wiel BA, Xu X, Gershenwald JE, Tetzlaff MT and Taube JM (2026). Updated pan-tumor guidelines for neoadjuvant scoring of pathologic response: a joint SITC and INMC effort. *Ann Oncol* 37(2):141–154.
- 19 Brierley JD, Giuliani M, O'Sullivan B, Rous B and Van Eycken E (eds) (2025). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 9th Edition*, Wiley, USA.
- 20 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.
- 21 Bregni G, Adams R, Bale R, Bali MA, Bargellini I, Blomqvist L, Brown G, Cremolini C, Demetter P, Denecke T, Dohan A, Dopazo C, Elez E, Evrard S, Feakins R, Guckenberger M, Guren MG, Hawkins M, Hoorens A, Huguet E, Intven M, Koessler T, Kunz WG, Lordick F, Lucidi V, Mahnken AH, Malik H, Martinive P, Mauer M, Romero AM, Nagtegaal I, Orsi F, Oyen WJ, Pellerin O, Rengo M, Ricke J, Ricoeur A, Riddell A, Ronot M, Scorsetti M, Seligmann J, Sempoux C, Sheahan K, Stättner S, Svrcek M, Taieb J, West N, Wyrwicz L, Zech CJ, Moehler M and Scialfani F (2025). EORTC consensus recommendations on the optimal management of colorectal cancer liver metastases. *Cancer Treat Rev* 136:102926.
- 22 Maru DM, Kopetz S, Boonsirikamchai P, Agarwal A, Chun YS, Wang H, Abdalla EK, Kaur H, Charnsangavej C, Vauthey JN and Loyer EM (2010). Tumor thickness at the tumor-normal interface: a novel pathologic indicator of chemotherapy response in hepatic colorectal metastases. *Am J Surg Pathol* 34(9):1287–1294.
- 23 Mentha G, Terraz S, Morel P, Andres A, Giostra E, Roth A, Rubbia-Brandt L and Majno P (2009). Dangerous halo after neoadjuvant chemotherapy and two-step hepatectomy for colorectal liver metastases. *Br J Surg* 96(1):95–103.

- 24 Latacz E, Höppener D, Bohlok A, Leduc S, Tabariès S, Fernández Moro C, Lugassy C, Nyström H, Bozóky B, Floris G, Geyer N, Brodt P, Llado L, Van Mileghem L, De Schepper M, Majeed AW, Lazaris A, Dirix P, Zhang Q, Petrillo SK, Vankerckhove S, Joye I, Meyer Y, Gregorieff A, Roig NR, Vidal-Vanaclocha F, Denis L, Oliveira RC, Metrakos P, Grünhagen DJ, Nagtegaal ID, Mollevi DG, Jarnagin WR, D'Angelica MI, Reynolds AR, Doukas M, Desmedt C, Dirix L, Donckier V, Siegel PM, Barnhill R, Gerling M, Verhoef C and Vermeulen PB (2022). Histopathological growth patterns of liver metastasis: updated consensus guidelines for pattern scoring, perspectives and recent mechanistic insights. *Br J Cancer* 127(6):988–1013.
- 25 Höppener DJ, Galjart B, Nierop PMH, Buisman FE, van der Stok EP, Coebergh van den Braak RRJ, van Amerongen MJ, Balachandran VP, Jarnagin WR, Kingham TP, Doukas M, Shia J, Nagtegaal ID, Vermeulen PB, Koerkamp BG, Grünhagen DJ, de Wilt JHW, D'Angelica MI and Verhoef C (2021). Histopathological Growth Patterns and Survival After Resection of Colorectal Liver Metastasis: An External Validation Study. *JNCI Cancer Spectr* 5(3):pkab026.
- 26 Buisman FE, Giardiello D, Kemeny NE, Steyerberg EW, Höppener DJ, Galjart B, Nierop PMH, Balachandran VP, Cercek A, Drebin JA, Gönen M, Jarnagin WR, Kingham TP, Vermeulen PB, Wei AC, Grünhagen DJ, Verhoef C, D'Angelica MI and Koerkamp BG (2022). Predicting 10-year survival after resection of colorectal liver metastases; an international study including biomarkers and perioperative treatment. *Eur J Cancer* 168:25–33.
- 27 Leduc S, De Schepper M, Richard F, Maetens M, Pabba A, Borremans K, Jaekers J, Latacz E, Zels G, Bohlok A, Van Baelen K, Nguyen HL, Geukens T, Dirix L, Larsimont D, Vankerckhove S, Santos E, Oliveira RC, Dede K, Kulka J, Borbala S, Salamon F, Madaras L, Marcell Szasz A, Lucidi V, Meyer Y, Topal B, Verhoef C, Engstrand J, Moro CF, Gerling M, Bachir I, Biganzoli E, Donckier V, Floris G, Vermeulen P and Desmedt C (2023). Histopathological growth patterns and tumor-infiltrating lymphocytes in breast cancer liver metastases. *NPJ Breast Cancer* 9(1):100.
- 28 Barnhill R, van Dam PJ, Vermeulen P, Champenois G, Nicolas A, Rawson RV, Wilmott JS, Thompson JF, Long GV, Cassoux N, Roman-Roman S, Busam KJ, Scolyer RA, Lazar AJ and Lugassy C (2020). Replacement and desmoplastic histopathological growth patterns in cutaneous melanoma liver metastases: frequency, characteristics, and robust prognostic value. *J Pathol Clin Res* 6(3):195–206.
- 29 Latacz E, Verheul SML, Sillis Y, van Dam PJ, Doukas M, Grünhagen DJ, Nyström H, Dirix P, Dirix L, Van Laere S, Verhoef C and Vermeulen P (2024). Molecular characterization of the histopathological growth patterns of colorectal cancer liver metastases by RNA sequencing of targeted samples at the tumor-liver interface. *Clin Exp Metastasis* 42(1):1.
- 30 Fernández Moro C, Geyer N, Harrizi S, Hamidi Y, Söderqvist S, Kuznyecov D, Tidholm Qvist E, Salmonson Schaad M, Hermann L, Lindberg A, Heuchel RL, Martín-Bernabé A, Dhanjal S, Navis AC, Villard C, Del Valle AC, Bozóky L, Sparrelid E, Dirix L, Strell C, Östman A, Schmierer B, Vermeulen PB, Engstrand J, Bozóky B and Gerling M (2023). An idiosyncratic zonated stroma encapsulates desmoplastic liver metastases and originates from injured liver. *Nat Commun* 14(1):5024.
- 31 van Dam PJ, van der Stok EP, Teuwen LA, Van den Eynden GG, Illemann M, Frentzas S, Majeed AW, Eefsen RL, Coebergh van den Braak RRJ, Lazaris A, Fernandez MC, Galjart B, Laerum OD, Rayes R, Grünhagen DJ, Van de Paer M, Sucaet Y, Mudhar HS, Schvimer M, Nyström H, Kockx M, Bird NC, Vidal-Vanaclocha F, Metrakos P, Simoneau E, Verhoef C, Dirix LY, Van Laere S, Gao ZH, Brodt P, Reynolds AR and Vermeulen PB (2017). International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 117(10):1427–1441.

- 32 Höppener DJ, Nierop PMH, Herpel E, Rahbari NN, Doukas M, Vermeulen PB, Grünhagen DJ and Verhoef C (2019). Histopathological growth patterns of colorectal liver metastasis exhibit little heterogeneity and can be determined with a high diagnostic accuracy. *Clin Exp Metastasis* 36(4):311–319.
- 33 Latorre Fragua RA, Manuel Vazquez A, Rodrigues Figueira Y, Ramiro Pérez C, López Marcano AJ, de la Plaza Llamas R and Ramia Ángel JM (2019). Intrabiliary metastases in colorectal cancer: a systematic review. *J Hepatobiliary Pancreat Sci* 26(7):270–280.
- 34 Reijonen P, Nordin A, Savikko J, Poussa T, Arola J and Isoniemi H (2023). Histopathological Helsinki score of colorectal liver metastases predicts survival after liver resection. *Apmis* 131(6):249–261.
- 35 Stift J, Graf A, Schwarz C, Tamandl D, Starlinger P, Herac M, Beer A, Wrba F, Bodingbauer M, Kaczirek K and Stremitzner S (2018). Microscopic biliary and perineural invasion and clinical outcome after neoadjuvant bevacizumab-based chemotherapy and liver resection in patients with colorectal liver metastases. *Eur J Surg Oncol* 44(1):139–147.
- 36 Viganò L, Capussotti L, De Rosa G, De Saussure WO, Mentha G and Rubbia-Brandt L (2013). Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. *Ann Surg* 258(5):731–740; discussion 741–732.
- 37 de Ridder JA, Knijn N, Wiering B, de Wilt JH and Nagtegaal ID (2015). Lymphatic Invasion is an Independent Adverse Prognostic Factor in Patients with Colorectal Liver Metastasis. *Ann Surg Oncol* 22 Suppl 3:S638–645.
- 38 Knijn N, de Ridder JA, Punt CJ, de Wilt JH and Nagtegaal ID (2013). Histopathological evaluation of resected colorectal cancer liver metastases: what should be done? *Histopathology* 63(2):149–156.
- 39 Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M and Fukuda H (1999). Factors influencing survival of patients undergoing hepatectomy for colorectal metastases. *Br J Surg* 86(3):332–337.
- 40 Gomez D, Zaitoun AM, De Rosa A, Hossaini S, Beckingham IJ, Brooks A and Cameron IC (2014). Critical review of the prognostic significance of pathological variables in patients undergoing resection for colorectal liver metastases. *HPB (Oxford)* 16(9):836–844.
- 41 Reijonen P, Österlund P, Isoniemi H, Arola J and Nordin A (2019). Histologically Verified Biliary Invasion was Associated with Impaired Liver Recurrence-Free Survival in Resected Colorectal Cancer Liver Metastases. *Scand J Surg* 108(3):201–209.
- 42 Okano K, Yamamoto J, Moriya Y, Akasu T, Kosuge T, Sakamoto M and Hirohashi S (1999). Macroscopic intrabiliary growth of liver metastases from colorectal cancer. *Surgery* 126(5):829–834.
- 43 Yamamoto J, Sugihara K, Kosuge T, Takayama T, Shimada K, Yamasaki S, Sakamoto M and Hirohashi S (1995). Pathologic support for limited hepatectomy in the treatment of liver metastases from colorectal cancer. *Ann Surg* 221(1):74–78.
- 44 Holdhoff M, Schmidt K, Diehl F, Aggrawal N, Angenendt P, Romans K, Edelstein DL, Torbenson M, Kinzler KW, Vogelstein B, Choti MA and Diaz LA, Jr. (2011). Detection of tumor DNA at the margins of colorectal cancer liver metastasis. *Clin Cancer Res* 17(11):3551–3557.

- 45 Yokoyama N, Shirai Y, Ajioka Y, Nagakura S, Suda T and Hatakeyama K (2002). Immunohistochemically detected hepatic micrometastases predict a high risk of intrahepatic recurrence after resection of colorectal carcinoma liver metastases. *Cancer* 94(6):1642–1647.
- 46 Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, Sakamoto Y, Yamamoto J, Yamaguchi T, Muto T and Makuuchi M (2002). Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. *Arch Surg* 137(7):833–840.
- 47 Wakai T, Shirai Y, Sakata J, Valera VA, Korita PV, Akazawa K, Ajioka Y and Hatakeyama K (2008). Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. *Ann Surg Oncol* 15(9):2472–2481.
- 48 Wakai T, Shirai Y, Sakata J, Kameyama H, Nogami H, Iai T, Ajioka Y and Hatakeyama K (2012). Histologic evaluation of intrahepatic micrometastases in patients treated with or without neoadjuvant chemotherapy for colorectal carcinoma liver metastasis. *Int J Clin Exp Pathol* 5(4):308–314.
- 49 Iwaki K, Kaihara S, Kitamura K and Uryuhara K (2021). Resection strategy for colorectal liver metastasis focusing on intrahepatic vessels and resection margins. *Surg Today* 51(9):1440–1445.
- 50 Viganò L, Procopio F, Cimino MM, Donadon M, Gatti A, Costa G, Del Fabbro D and Torzilli G (2016). Is Tumor Detachment from Vascular Structures Equivalent to R0 Resection in Surgery for Colorectal Liver Metastases? An Observational Cohort. *Ann Surg Oncol* 23(4):1352–1360.
- 51 Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, Yanaga K, Maeda T, Kajiyama K and Sugimachi K (1997). Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. *Br J Surg* 84(8):1077–1080.
- 52 Torzilli G, Viganò L, Fontana A, Procopio F, Terrone A, Cimino MM, Donadon M and Del Fabbro D (2020). Oncological outcome of R1 vascular margin for mass-forming cholangiocarcinoma. A single center observational cohort analysis. *HPB (Oxford)* 22(4):570–577.
- 53 Okuno M, Goumard C, Mizuno T, Kopetz S, Omichi K, Tzeng CD, Chun YS, Lee JE, Vauthey JN and Conrad C (2018). Prognostic impact of perihepatic lymph node metastases in patients with resectable colorectal liver metastases. *Br J Surg* 105(9):1200–1209.
- 54 Christophi C, Nguyen L, Muralidharan V, Nikfarjam M and Banting J (2014). Lymphatics and colorectal liver metastases: the case for sentinel node mapping. *HPB (Oxford)* 16(2):124–130.
- 55 Oussoultzoglou E, Romain B, Panaro F, Rosso E, Pessaux P, Bachellier P and Jaeck D (2009). Long-term survival after liver resection for colorectal liver metastases in patients with hepatic pedicle lymph nodes involvement in the era of new chemotherapy regimens. *Ann Surg* 249(6):879–886.
- 56 Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, Pisa E, Barberis M, Vanoli A, Buzzoni R, Pusceddu S, Concas L, Sessa F, Solcia E, Capella C, Fazio N and La Rosa S (2017). The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories. *Neuroendocrinology* 104(1):85–93.

- 57 Venizelos A, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, Couvelard A, Hjortland GO, Sundlöv A, Svensson J, Garresori H, Kersten C, Hofslie E, Detlefsen S, Krogh M, Sorbye H and Knappskog S (2021). The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 29(1):1–14.
- 58 Sciarra A, Libera L, Destro A, Maragliano R, Furlan D, Guastafierro V, Marchiori D, Vanoli A, Gonzalez RS, Letovanec I, Lazzi S, La Rosa S and Uccella S (2026). Molecular Profiling of Digestive Grade 3 Neuroendocrine Tumors Reveals a Shared Molecular Framework with Lower-Grade Tumors, Marked Heterogeneity, and Therapeutic Opportunities. *Endocr Pathol* 37(1):23.
- 59 Chen R, Tihy M, Lacroix L, de Rycke O, Lacombe C, Just PA, Cazes A, Svrcek M, de Montpreville VT, Antoine M, Scoazec JY, de Mestier L, Couvelard A and Cros J (2025). Performance of Immunohistochemistry to Detect Rb/p53 Alterations in High-Grade Neuroendocrine Neoplasms: Staining Patterns and Comparison with Genetic Testing. *Endocr Pathol* 36(1):40.