Evidence-based guideline on management of colorectal liver metastases in the Netherlands

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ABSTRACT

A Dutch national evidence-based guideline on the diagnosis and treatment of patients with colorectal liver metastases has been developed. The most important recommendations are as follows. For synchronous liver metastases, spiral computed tomography (CT) or magnetic resonance imaging (MRI) should be used as imaging. For evaluation of lung metastases, imaging can be limited to chest radiography. For detection of metachronous liver metastases, ultrasonography could be performed as initial modality if the entire liver is adequately visualised. In doubtful cases or potential candidates for surgery, CT or MRI should be performed as additional imaging. For evaluation of extrahepatic disease, abdominal and chest CT could be performed. Fluorodeoxyglucose positron emission tomography could be valuable in patients selected for surgery based on CT (liver/abdomen/chest), for identifying additional extrahepatic disease. Surgical resection is the treatment of choice with a five-year survival of 30 to 40%. Variation in selection criteria for surgery is caused by inconclusive data in the literature concerning surgical margins <10 mm, presence of extrhepatic disease and the role of (neo)adjuvant therapy. To minimise variation in selection criteria, selection should be performed according to this guideline and preferably in qualified centres. If resection is not possible due to extensive disease, palliative chemotherapy is recommended. Systemic chemotherapy with fluoropyrimidine first-line chemotherapy (5-FU/Leucovorin) combined with irinotecan or oxaliplatin should be considered as standard regimens. Radiofrequency ablation, isolated hepatic perfusion, portal vein embolisation, and intra-arterial chemotherapy are considered experimental and should only be performed as part of a clinical research protocol.

KEYWORDS
Guideline, liver metastases, diagnosis, treatment, colorectal neoplasms

INTRODUCTION

Colorectal cancer is the second leading cause of cancer-related deaths in the Netherlands with an incidence of 9900 and 4400 deaths in 2003 according to the Association of Comprehensive Cancer Centres.1 Approximately 50 to 60% of patients with colorectal cancer eventually develop liver metastases. As there are variations in the therapeutic strategies for these patients, the optimal therapy should be determined on an individual basis. A Dutch survey on the diagnostic and therapeutic work-up of patients with colorectal liver metastases performed in 2004 showed substantial variation between different centres in both diagnostic work-up and treatment. The most important points of concern according to the responders of this survey were the absence of a national guideline for diagnosis and treatment of patients with colorectal liver metastases and the absence of a registration system.2

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METHODS

To develop a national evidence-based guideline, a working group was established representing the disciplines involved in this field, including surgeons, medical oncologists, radiologists, gastroenterologists and nuclear medicine specialists. All specialists were mandated by their respective health professional organisations. A list of the members of the working group is presented in appendix 1.

We performed literature searches in the Cochrane, Medline, CANCERLIT, EMBASE, CINAHL and Web of Science databases from 1992 to 2005 for different questions. The search strategies are described in table 1. Literature searches were performed for:

1. Diagnostic accuracy of computed tomography (CT), magnetic resonance imaging (MRI), 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in the detection of liver metastases and for detection of extrahepatic lesions; no search was performed for the diagnostic accuracy of ultrasonography (US), as this modality has a low accuracy;

2. The diagnostic accuracy of diagnostic laparoscopy in the detection of liver metastases and for detection of extrahepatic lesions;
3. The selection criteria on which surgery is based;
4. The effectiveness of (neo)adjuvant chemotherapy;
5. The role and effectiveness of the experimental therapeutic options such as portal vein embolisation, ablation techniques and isolated hepatic perfusion; the effectiveness of the different chemotherapeutic regimens used;
6. The role of follow-up after treatment of colorectal liver metastases.

All evidence was collected, discussed and categorised by the working group according to general systems used in evidence-based medicine (table 2). Based on the relevant evidence and taking into account factors such as experience and availability, recommendations were formulated for daily practice. These recommendations with corresponding evidence were sent to all the disciplines involved for comments, remarks and approval; all disciplines responded with minor comments, remarks and suggestions and approved the final draft of the

Table 1. Search strategies

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<th>DIAGNOSIS</th>
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<tr>
<td>MEDLINE</td>
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<tr>
<td>Colorectal Neoplasms [MESH] AND (Liver neoplasms [MESH]) AND ((Laparoscopy [MESH] OR Tomography, Emission-Computed [MESH]) OR (magnetic resonance imaging [MESH]) OR (Tomography, X-Ray Computed [MESH]) OR (ULTRASONOGRAPHY [MESH]) OR (sensitivity and specificity [MESH]) OR (specificity [WORD]) OR (false negative [WORD]) OR (diagnosis [SH]) OR (diagnostic use [SH]) OR (detection [WORD]) OR (accuracy [WORD])))</td>
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<td>Colorectal Neoplasms [MESH] AND (Liver Neoplasms [MESH]) AND ((surgery [MESH]) OR (Hepatectomy [MESH]) OR (PERIOPERATIVE CARE [MESH]) OR (Catheter Ablation [MESH]) OR (Cryosurgery [MESH]) OR (Hypothermia, Induced [MESH]) OR (Palliative Care [MESH]) OR (Drug therapy [MESH]) OR (Antineoplastic Agents [MESH]) OR (Infusions, Intra-Arterial [MESH]) OR (Perfusion, Regional [MESH]) OR (Radiotherapy [MESH]) AND ((Treatment outcome [MESH]) OR (Survival analysis [MESH]) OR (Survival [MESH]) OR (Mortality [MESH]) OR (Morbidity [MESH])])</td>
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Table 2. Levels of evidence based on the categories of literature

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Categories of literature

A1: Systematic reviews of category A2 studies with consistent findings

A2: D: accuracy study (index test compared with reference test) of a high quality (prospectively performed with blinded interpretation of index test and reference test and large number of consecutive patients undergoing complete verification)
T: Randomised controlled trials of high quality (randomised, blinded, complete follow-up, similar baseline characteristics, intention-to-treat analysis)

B1: Systematic reviews of category B2 studies with consistent findings

B2: D: accuracy study (index test compared with reference test) with poor quality (missing the above mentioned characteristics)
T: Randomised controlled trial of low quality or other comparative studies such as nonrandomised, cohort and case-control studies

C: D: Noncomparative study (index test not compared with reference test)
T: Nonrandomised, cohort and case-control studies with poor quality or descriptive studies (non-comparative studies)

D: Opinion from expert committee or clinical experience

D = diagnosis; T = treatment

During follow-up and to determine resectability
1. For the detection of metachronous liver metastases, an additional FDG-PET could be helpful, because in patients with a long interval between CT and FDG-PET or patients selected for additional FDG-PET, FDG-PET seems to be sensitive for the detection of liver metastases and determining the resectability is limited. From a practical point of view, during the CT of the liver, additional CT of the abdomen could be performed; however, chest CT provides a high sensitivity, but it should be noted that chest CT also gives more false-positives. In addition, in patients with negative chest radiography, the additional value of CT is limited. (Level of evidence: 3)

2. If the liver cannot be evaluated properly by US, or the CEA elevation cannot be explained or the irresectability cannot be determined based on US, an additional spiral CT or MRI should be performed. MRI with gadolinium (Gd) or superparamagnetic iron oxide (SPIO) contrast medium and spiral CT with ≥45 g iodine have a comparable sensitivity for the detection of liver metastases. (Level of evidence: 1) The choice between spiral CT with >45 g iodine or MRI with contrast agent (Gd or SPIO) should, therefore, be mainly based on the local infrastructure (costs, availability and expertise).

3. The role of FDG-PET for the detection of liver metastases and determining the resectability is limited and should therefore not be performed routinely. In case of doubt concerning lesion characterisation on CT and MRI examination, an additional FDG-PET could be helpful, because in patients with a long interval between CT and FDG-PET or patients selected for additional FDG-PET, FDG-PET seems to be sensitive for the detection of liver metastases and is therefore also used as additional modality in daily practice. (Level of evidence: 1)

4. The prevalence of extrahepatic disease (lung metastases and lymph node metastases) in patients selected for surgery based on extensive imaging is low. From a practical point of view, during the CT of the liver, additional CT of the abdomen could be performed for evaluation of the abdomen. There are no studies evaluating the additional role of abdominal CT for detection of extrahepatic disease.

For the evaluation of the lungs, a chest CT could also be performed; however, chest CT provides a high number of false-positives and the additional value in patients with negative chest radiography seems to be low. (Level of evidence: 3) Taking into account the low prevalence of lung metastases and the limited additional value of chest CT for evaluation of the lungs, imaging can be limited to plain chest radiography.

5. In patients selected for surgery after chest, liver and abdominal CT, an additional FDG-PET can be considered. FDG-PET seems to be sensitive for the detection of extrahepatic disease. (Level of evidence: 1)
Moreover, the preliminary results of the POLEM study (randomised study: half of the patients selected for surgery based on abdominal, chest and liver CT underwent FDG-PET) showed that unnecessary laparotomy can be prevented in significantly more patients in the FDG-PET group. In the non-FDG-PET group 29% (14/49) underwent unnecessary laparotomy, while in FDG-PET group only 11% (5/48) underwent unnecessary laparotomy (p=0.02); in the FDG-PET group, surgery was cancelled in four patients after FDG-PET. However, these data are based on preliminary nine-month follow-up of 97 patients, while 150 patients are included in this study. (Report POLEM study, the Netherlands Organisation for Health Research and Development (ZonMw) grant 945-11-017).

PET-CT

Hybrid PET-CT can be used for detection of liver metastases and extrahepatic disease when equipment and sufficient expertise is available. Studies have shown that accuracy rates of up to 98% can be achieved for the detection of liver metastases, extrahepatic disease and local recurrence in patients who have been treated for colorectal tumour.17-19 (Level of evidence: 3)

DIAGNOSTIC LAPAROSCOPY

There is no role for diagnostic laparoscopy in routine daily practice, due to its invasiveness, low prevalence of small subcapsular lesions and extrahepatic disease and absence of clinical consequences of small liver metastases, as these can generally be resected. The additional value of diagnostic laparoscopy in patients after extensive imaging also seems to be limited.30-31 (Level of evidence: 3)

ADDITIONAL EXAMINATION

1. If liver metastases seem to be resectable based on imaging examination, additional examination of the cardiopulmonary system should be performed to study the clinical condition of the patient. In general no cytological/ histological biopsies are performed.

2. If liver metastases based on imaging examination and the clinical condition of the patient seem to be irresectable, no cytological/histological biopsies should be performed to verify the diagnosis because of the increased risk of developing needle tract metastases.32 Biopsies should only be performed if histopathology will have clinical consequences.

SURGERY

Approximately 20% of patients with liver metastases are considered candidates for surgery, with a five-year survival of 30 to 40%.33-36 Selection criteria for surgery are a residual liver volume of ≥30% after resection, the feasibility of an R0 resection (clear resection margin), limited or no presence of extrathoracic disease and adequate clinical condition of the patient. However, there is some variation in the prognostic factors such as the presence of extrathoracic disease, surgical margins <10 mm and the timing of the resection of synchronous liver metastases.37 Neoadjuvant and adjuvant chemotherapy are usually administrated to increase the effectiveness of surgery.37-38 The effectiveness of (neo)adjuvant chemotherapy is also unknown.

Recommendations based on the evidence found in the literature:

1. In patients with a normal functioning liver, at least 30% of the liver parenchyma should remain after surgery. Up to 70% of the liver volume can be removed in these patients with a normal functioning liver without risks of postoperative failure.39-41 (Level of evidence: 3)

2. As there are no uniform results in the literature concerning a margin of <10 mm,42-44 (Level of evidence: 3) and due to the fact that the surgical margin cannot be accurately determined preoperatively, a surgical margin of ≥10 mm is recommended. Depending on the anatomic location, a margin of <10 mm is acceptable as long as a radical resection can be obtained.

3. Attention should be paid to the preoperative evaluation of extrathoracic disease, as patients with extrathoracic disease have a significantly worse prognosis compared with patients without extrathoracic disease.45-48 (Level of evidence: 3)

However, there is some controversial data on the consequences of the involvement of lymph nodes located near the liver hilum. Several papers report that this should not be considered an absolute contraindication for resection and an extended lymphadenectomy should be performed,49-51 while in a systematic review only few five-year survivors after liver resection with involvement of hilum lymph nodes were reported.41 In summary, there is no uniform evidence concerning the resection of lymph nodes in the hilum of the liver.

4. The presence of a limited number of lung metastases, without mediastinal lymph node involvement, is not considered an absolute contraindication for resection of liver metastases, as resection of a limited number of lung metastases can prolong long-term survival.44-46 (Level of evidence: 3) Therefore, after radical surgery of the liver, subsequent lung surgery could be considered when only a limited number of lung metastases are found.


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5. High age in a patient with good cardiopulmonary condition should not be a contraindication for liver resection for colorectal cancer metastases. In patients >70 years a median survival of up to 33 months and a five-year survival of up to 22% can be achieved.67-69 (Level of evidence: 3)

6. Although patients with solitary metachronous liver metastases have a better survival compared with patients with synchronous metastases, the presence of synchronous liver metastases should not be a contraindication for surgery, as five-year survival of up to 31% can be obtained by resection of synchronous metastases.70-72 (Level of evidence: 3)

7. Even though survival after simultaneous resection of colorectal cancer and liver metastases and resection of liver metastases after an interval of two to three months are comparable,73,74 simultaneous resection should be avoided, due to the high complication rate. In addition, in two-thirds of patients major hepatic surgery is avoided, because of the detection of an increased number of hepatic or distant metastases after an interval of two to three months.75 (Level of evidence: 3)

8. Repeat hepatectomy is advised in patients with new liver metastases after previous liver surgery for colorectal metastases, if the patient fulfils all criteria for resectability. Repeat liver resection for colorectal liver metastases is safe and in well-selected patients can provide prolonged survival after recurrence of colorectal liver metastases with limited mortality and morbidity rate.76-78 (Level of evidence: 3)

9. Data on the effectiveness of (neo)adjuvant chemotherapy are controversial and we therefore recommend the use of (neo)adjuvant chemotherapy only in clinical research protocols. In a selected patient population, neo/adjuvant chemotherapy with the more effective regimens (combination of 5-FU/LV with irinotecan or oxaliplatin) can induce response, making curative resection of previously irresectable liver metastases possible.79,80-83 (Level of evidence: 3)

The role of adjuvant chemotherapy after curative surgery is unclear and not advised routinely.84-87 (Level of evidence: 2)

As there is a substantial variation in prognostic factors (see above), the working group recommends that:

1. Liver resection should be performed in centres with high experience level, where appropriate equipment is available and with enough experience in intensive care, anaesthesiology and interventional radiology. Administration of (neo)adjuvant chemotherapy should be limited to trials.

2. Registration of patients should be performed, also outside trials. Registration systems are important tools in evaluating indications for resection and results of resections.

EXPERIMENTAL THERAPY

As most of the patients with liver metastases are not considered suitable for surgery, other treatment modalities such as ablative therapy, portal vein embolisation and isolated hepatic perfusion have been developed during the last decades.88-90 However, there is no information available on the effectiveness of these modalities and the criteria for their application in the Netherlands.91 The recommendations of the working group are given for each experimental therapy.

PORTAL VEIN EMBOLISATION

Some patients not considered candidates for surgery due to insufficient remnant liver volume with increased risk of postoperative liver failure can undergo portal vein embolisation (PVE) of the liver parts to be resected. Portal vein embolisation results in atrophy of the embolised parts and hypertrophy of the remnant liver, reducing the risk of hepatic failure after extended hepatectomy. So far, only retrospective studies with long-term results or prospective studies with short-term results in terms of success rate and complications have been reported with, in general, favourable results/findings. (Level of evidence: 3) Moreover, small numbers of patients have been included in these studies. Due to the lack of data on long-term results, PVE should only be performed in trials, in centres with high experience and where clear-cut indications are defined.

ABLATIVE THERAPY

Another treatment modality developed during the last decades for patients with liver malignancies is local ablation therapy. The principle of ablation is based on tumour destruction by applying heat (RFA or interstitial laser therapy) or cold (cryotherapy) or by chemical tumour destruction (ethanol injection).

1. No recommendations could be made on the role of laser ablation, due to the small number of studies evaluating long-term results of laser therapy.89-92 (Level of evidence: 3)

2. The number of studies with long-term results on cryotherapy is limited. In comparison with RFA, cryotherapy has a higher complication rate (bleeding and infection) and more recurrence.93,94 (Level of evidence: 3)

3. The use of ethanol injection for colorectal liver metastases is not advised, due to the small number of studies and the low response rate obtained.95-97 (Level of evidence: 3)
4. RFA is the most promising technique for ablation purposes.\textsuperscript{95-98} (Level of evidence: 3) This technique is highly effective for tumour destruction. However, it is not known whether RFA will prolong the survival of patients with extensive disease. In an ongoing randomised phase III study (CLOCC trial), the role of local treatment by RFA in patients with irresectable colorectal liver metastases is being studied. In this study one arm receives RFA combined with chemotherapy while the second arm receives only chemotherapy. Current evidence on the safety and efficacy of RFA for colorectal cancer liver metastases does not appear adequate and this experimental therapy should therefore only be performed as part of a clinical research protocol.

**ISOLATED HEPATIC PERFUSION**

In patients with extensive nonresectable liver metastases, isolated hepatic perfusion (IHP) can be considered. IHP involves intraoperative perfusion of the isolated liver with extremely high-dose chemotherapy. The results of recent studies show that high response rates and considerable survival benefit can be achieved by IHP with different treatment strategies, including IHP with melphalan alone and melphalan combined with TNF-\(\alpha\) or followed by monthly hepatic intra-arterial infusion of fluorodeoxyuridine (FUDR) and leucovorin. In these studies, IHP for colorectal liver metastases showed response rates of up to 74\%, a median time to progression of up to 14.5 months and a median survival of up to 27 months.\textsuperscript{73-99} (Level of evidence: 3) IHP was first clinically applied over 40 years ago, but its technical complexity, the potential morbidity, toxicity rate and the lack of documented efficacy have probably prevented widespread use. Patient selection is important to ensure good results with minimal morbidity and mortality. Work to define the appropriate clinical groups is ongoing in the Leiden University Medical Centre and the Erasmus Medical Centre Rotterdam and therefore it is necessary to wait for the results of these studies.

**CHEMOTHERAPY**

Most patients with extensive and nonresectable metastases are only eligible for systemic chemotherapy. The following recommendations for systematic chemotherapy can be made:

1. For systemic chemotherapy fluoropyrimidine first-line chemotherapy (either oral or systemic 5-FU/leucovorin) combined with irinotecan or oxaliplatin should be considered as standard regimens; however, the optimal regimens with either irinotecan or oxaliplatin are unknown. The effect of oral 5-FU prodrug monotherapy is comparable with intravenous bolus 5-FU regimens.\textsuperscript{99-103} (Level of evidence: 1) Irinotecan or oxaliplatin combined with 5-FU/leucovorin increases the response and disease-free-survival compared with 5-FU/leucovorin alone.\textsuperscript{104-106} (Level of evidence: 2)

2. In the absence of contraindications, bevacizumab could be added to the first-line chemotherapy. This has additional therapeutic value if bevacizumab is added to a fluoropyrimidine first-line chemotherapy regimen (higher response rate, disease-free and total survival).\textsuperscript{107,108} (Level of evidence: 2)

3. An improvement in the field of chemotherapy is the development of regional (intra-arterial) chemotherapy.\textsuperscript{109-111} With regional chemotherapy higher doses can be administrated and therefore higher tumour response rates could be achieved; however, the effectiveness in terms of disease-free survival and overall survival are yet unknown.\textsuperscript{112} (Level of evidence: 1) Therefore, regional chemotherapy at this stage has no role in the routine management.

**FOLLOW-UP AFTER TREATMENT OF COLORECTAL LIVER METASTASES**

When possible, surgical resection is the treatment of choice for hepatic colorectal metastases, with five-year survival rates of up to 30 to 40\%. However, in most of the reported series, disease recurs in up to 80\% of patients after hepatectomy. The recurrence usually involves the liver and is confined to the liver in approximately half of these cases. As with initial hepatectomy, the feasibility of repeat resection depends not only on the disease being confined to the liver but also on the distribution of hepatic disease permitting curative resection. Overall, only 23 to 33\% of hepatic recurrences are resectable.\textsuperscript{59} Repeat hepatectomy is associated with five-year survival rates equivalent to those reported for first hepatectomy\textsuperscript{55} and therefore detecting hepatic recurrence at a resectable stage would significantly improve prognosis for this selected group of patients. The aim of follow-up, therefore, is to select patients who are candidates for repeat resection. This has also been shown in a recently published review.\textsuperscript{113} However, there is no evidence available on the timing, frequency and the programme of follow-up. Based on the results of the studies included in the review, a follow-up visit every three months is recommended for two years, thereafter every six months until five years. Each visit is accompanied by clinical examination, CEA measurements, and CT of the chest and abdomen.

**REGISTRATION SYSTEM**

Based on the survey/recommendations from the field, the working group also advocates the development of a national registration system for the diagnosis and treatment of colorectal cancer liver metastases.
patients with colorectal liver metastases. Registration systems are important tools in evaluating patient management. The collaboration between medical specialists and consulting specialists of the Association of Comprehensive Cancer Centres provides the possibility of a national registration.

IMPLEMENTATION OF THE GUIDELINES

For all practitioners involved in the management of patients with colorectal liver metastases in the Netherlands, the guideline is available on www.oncoline.nl or www.vikc.nl. Although we are aware that passive dissemination of a guideline may be unlikely to lead to change, whereas the combination of several active meetings is more likely to lead to success, we firstly choose to disseminate the guideline by internet. This is because in general, guidelines for oncological diseases reported by these sites are easily implemented in daily practice. In addition, a compact and transparent summary of the guideline has been written which will be sent to all the chairmen of oncology committees in each hospital, in which referral is made to the complete guideline. Also, the working group has presented this guideline during meetings of the several disciplines involved in the management of patients with colorectal liver metastases. There is ongoing research both on diagnosis (POLEM study) and treatment (CLOCC trial and experimental IHP, PVE). The results of these studies will most likely change the management of this patient group. Therefore this guideline should be updated, when the results of these and other relevant studies will be available.

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REFERENCES


A P P E N D I X 1

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