Netherlands
The Journal of Medicine

REVIEW

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

S. Bipat[1*], M.S. van Leeuwen[2], J.N.M. IJzermans[3], E.F.I. Comans[4], A.S.Th. Planting[5], P.M.M. Bossuyt[6], J-W. Greve[7], J. Stoker[1]

[1]Department of Radiology, Academic Medical Centre, Amsterdam, [2]Department of Radiology, University Medical Centre Utrecht, [3]Department of Surgery, Erasmus Medical Centre, Rotterdam, [4]Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, [5]Department of Medical Oncology, Erasmus Medical Centre, Rotterdam, [6]Department of Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, [7]Department of Surgery, Maastricht University Hospital, [*]corresponding author S. Bipat, Department of Radiology, Academic Medical Centre, Amsterdam, the Netherlands, e-mail: s.bipat@amc.uva.nl

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 extrahepatic 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]

© 2007 Van Zuiden Communications B.V. All rights reserved.

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*

DIAGNOSIS

MEDLINE
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])) AND ((sensitivity and specificity [MESH]) OR (specificity [WORD]) OR (false negative [WORD]) OR (diagnosis [SH]) OR (diagnostic use [SH]) OR (detection [WORD]) OR (accuracy [WORD]))

EMBASE
(Colorectal Cancer [MESH]) AND (Liver metastasis [MESH])

CINAHL/SUMSEARCH
(Colorectal Neoplasm [MESH]) AND ((Liver Neoplasms [MESH]) OR (Neoplasm Metastasis [MESH]))

Web of Science/CANCERLIT/ COCHRANE
(Colorectal cancer) AND ((liver metastases) OR (hepatic metastasis))

TREAMENT

MEDLINE
(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 (Hyperthermia, 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]))

EMBASE
(Colorectal Cancer [MESH]) AND (Liver metastasis [MESH])

CINAHL/SUMSEARCH
(Colorectal Neoplasm [MESH]) AND ((Liver Neoplasms [MESH]) OR (Neoplasm Metastasis [MESH]))

Web of Science/CANCERLIT/ COCHRANE
(Colorectal cancer) AND ((liver metastases) OR (hepatic metastasis))

Table 2. *Levels of evidence based on the categories of literature*[*]

Level of evidence	
1	Systematic review (A1) or at least two independently performed studies of category A2
2	Systematic review (B1) or at least two independently performed studies of category B2
3	1 study of category A2, B2 or C
4	Expert opinion (category D)
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, intension-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

[*] **Sackett DL, Strauss SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone 2000.**

guideline. All comments and remarks were incorporated in the final version of the guideline.

In this paper, on behalf of the working group, we report the recommendations with the corresponding evidence (including the level of evidence) for the diagnosis, treatment and follow-up of patients with colorectal liver metastases in the Netherlands.

DIAGNOSIS

Beside medical history, physical examination and laboratory testing (e.g. carcinoembryonic antigen (CEA) measurements), imaging modalities such as transabdominal ultrasonography (US), CT, MRI and FDG-PET imaging play a major role in the selection of patients with liver metastases.[3-11] During the past ten years, improvements in the imaging modalities and changes in applications have been made.[6,7,10] Extensive research has been carried out on the diagnostic performance of US, CT, MRI, and FDG-PET for the detection of liver metastases. Another diagnostic technique playing a role in the evaluation of liver metastases is diagnostic laparoscopy. However, the optimal imaging staging strategy has not yet been defined.

Imaging plays a major role at the time of the diagnosis and treatment of the primary tumour (for detection of synchronous liver and lung metastases); during the follow-up after the treatment of the primary tumour (for detection of metachronous liver metastases) and for determining the resectability (detection of liver metastases and extrahepatic disease). The recommendations are described in the following paragraphs.

At the time of initial diagnosis and treatment

1. To study baseline characteristics, a spiral CT or MRI of the liver should be performed instead of US, due to the low accuracy of US. Baseline CT or MRI are important not only for the detection or characterisation of liver lesions, but also for determining whether patients need adjuvant therapy. In case of doubt about the presence and characterisation of lesions, the CT or MRI examination should be repeated after three months. (Level of evidence: 4)
2. For the evaluation of the lungs, imaging can be limited to plain chest radiography, due to the low prevalence of lung metastases. 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.[12,13] (Level of evidence: 3)

During follow-up and to determine resectability

1. For the detection of metachronous liver metastases, we recommend using CEA as marker if an elevated CEA level was measured at the time of detection of the primary colorectal tumour. For the evaluation of the liver, imaging may be limited to US if the entire liver is assessable. For follow-up no additional value of spiral CT or MRI to US has been demonstrated.[14] (Level of evidence 2) Because of its noninvasive character, low cost, and widespread availability, US is a valuable screening tool for the imaging of liver metastases. Moreover, US is highly efficient in helping to distinguish between two groups of patients with liver metastases: patients with diffuse metastases who are no longer eligible for curative treatment and patients with no or a limited number of metastases. In daily practice, therefore, US is often used as the initial imaging modality for the detection of metachronous liver metastases.[2]
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.[15] (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[2] 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.[12,13] (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.[16] (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.[20,21] (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.[22] 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%.[23-26] 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 extrahepatic disease and adequate clinical condition of the patient. However, there is some variation in the prognostic factors such as the presence of extrahepatic disease, surgical margins <10 mm and the timing of the resection of synchronous liver metastases.[2] Neoadjuvant and adjuvant chemotherapy are usually administrated to increase the effectiveness of surgery.[27,28] 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.[29-31] (Level of evidence: 3)
2. As there are no uniform results in the literature concerning a margin of <10 mm [32-36] (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 extrahepatic disease, as patients with extrahepatic disease have a significantly worse prognosis compared with patients without extrahepatic disease.[37,38] (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,[39,40] 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.[42-46] (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.

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.[47,48] (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.[49-51] (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,[51,52] 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.[52] (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.[53-59] (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, neoadjuvant 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.[27,60-65] (Level of evidence: 3)

   The role of adjuvant chemotherapy after curative surgery is unclear and not advised routinely.[66-71] (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.[72-82] However, there is no information available on the effectiveness of these modalities and the criteria for their application in the Netherlands.[2] 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[83,84] or prospective studies with short-term results in terms of success rate and complications[74,85-88] 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.[89,90] (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.[73,89,91] (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.[92-94] (Level of evidence: 3)

4. RFA is the most promising technique for ablation purposes.[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-α 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.[75,99] (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.[100-103] (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.[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).[107,108] (Level of evidence: 2)
3. An improvement in the field of chemotherapy is the development of regional (intra-arterial) chemotherapy.[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.[112] (Level of evidence: 1) Therefore, regional chemotherapy at this stage has no role in the routine management.

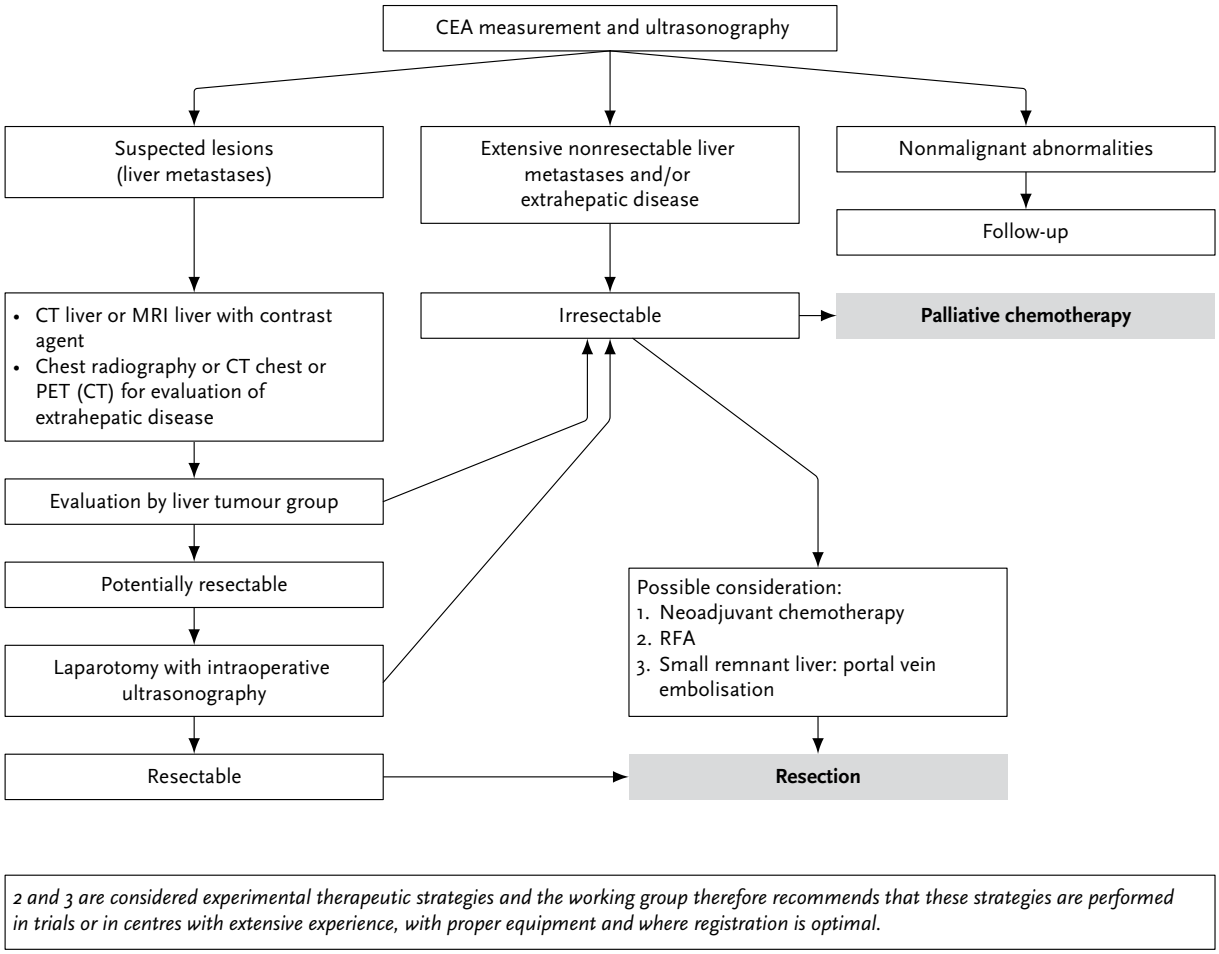
FOLLOW-UP AFTER TREATMENT OF COLORECTAL LIVER METASTASES

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.[59] Repeat hepatectomy is associated with five-year survival rates equivalent to those reported for first hepatectomy[53] 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.[56] 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

Figure 1. *Diagnostic and therapeutic strategy in the follow-up after primary colorectal tumour management*



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.

Supported by a grant from the Dutch Order of Medical Specialists.

REFERENCES

1. http://www.ikcnet.nl.
2. Bipat S, van Leeuwen MS, IJzermans JN, Bossuyt PM, Greve JW, Stoker J. Imaging and treatment of patients with colorectal liver metastases in the Netherlands: a survey. Neth J Med 2006;64:147-51.

3. Hagspiel KD, Neidl KF, Eichenberger AC, Weder W, Marincek B. Detection of liver metastases: comparison of superparamagnetic iron oxide-enhanced and unenhanced MR imaging at 1.5 T with dynamic CT, intraoperative US, and percutaneous US. Radiology 1995;196:471-8.

4. Hung GU, Shiau YC, Tsai SC, Chao TH, Ho YJ, Kao CH. Value of 18F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent colorectal cancer. Anticancer Res 2001;21:1375-8.

5. Ruers TJ, Langenhoff BS, Neeleman N, et al. Value of positron emission tomography with $^{F-18}$fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388-95.

6. Schmidt J, Strotzer M, Fraunhofer S, Boedeker H, Zirngibl H. Intraoperative ultrasonography versus helical computed tomography and computed tomography with arterioportography in diagnosing colorectal liver metastases: lesion-by-lesion analysis. World J Surg 2000;24:43-7.

7. Scott DJ, Guthrie JA, Arnold P, et al. Dual phase helical CT versus portal venous phase CT for the detection of colorectal liver metastases: correlation with intra-operative sonography, surgical and pathological findings. Clin Radiol 2001;56:235-42.

8. Valls C, Andia E, Sanchez A, et al. Hepatic metastases from colorectal cancer: preoperative detection and assessment of resectability with helical CT. Radiology 2001;218:55-60.

9. Vitola JV, Delbeke D, Sandler MP, et al. Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. Am J Surg 1996;171:21-6.

10. Ward J, Naik KS, Guthrie JA, Wilson D, Robinson PJ. Hepatic lesion detection: comparison of MR imaging after the administration of superparamagnetic iron oxide with dual-phase CT by using alternative-free response receiver operating characteristic analysis. Radiology 1999;210:459-66.

11. Whiteford MH, Whiteford HM, Yee L,F et al. Usefulness of FDG-PET scan in the assessment of suspected metastatic or recurrent adenocarcinoma of the colon and rectum. Dis Colon Rectum 2000;43:759-67.

12. Kronawitter U, Kemeny NE, Heelan R, Fata F, Fong Y. Evaluation of chest computed tomography in the staging of patients with potentially resectable liver metastases from colorectal carcinoma. Cancer 1999;86:229-35.

13. Povoski SP, Fong Y, Sgouros SC, Kemeny NE, Downey RJ, Blumgart LH. Role of chest CT in patients with negative chest x-rays referred for hepatic colorectal metastases. Ann Surg Oncol 1998;5:9-15.

14. Berman JM, Cheung RJ, Weinberg DS. Surveillance after colorectal cancer resection. Lancet 2000;355:395-9.

15. Bipat S, van Leeuwen MS, Comans EF, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology 2005;237:123-31.

16. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. Cancer 2005;104:2658-70.

17. Kamel IR, Cohade C, Neyman E, Fishman EK, Wahl RL. Incremental value of CT in PET/CT of patients with colorectal carcinoma. Abdom Imaging 2004;29:663-8.

18. Kim JH, Czernin J, len-Auerbach MS, et al. Comparison between 18F-FDG PET, in-line PET/CT, and software fusion for restaging of recurrent colorectal cancer. J Nucl Med 2005;46:587-95.

19. Selzner M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann Surg 2004;240:1027-34.

20. D'Angelica M, Fong Y, Weber S, et al. The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. Ann Surg Oncol 2003;10:183-9.

21. Jarnagin WR, Conlon K, Bodniewicz J, et al. A clinical scoring system predicts the yield of diagnostic laparoscopy in patients with potentially resectable hepatic colorectal metastases. Cancer 2001;91:1121-8.

22. Metcalfe MS, Bridgewater FH, Mullin EJ, Maddern GJ. Useless and dangerous--fine needle aspiration of hepatic colorectal metastases. BMJ 2004;328:507-8.

23. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-46.

24. Jatzko GR, Lisborg PH, Stettner HM, Klimpfinger MH. Hepatic resection for metastases from colorectal carcinoma--a survival analysis. Eur J Cancer 1995;31A:41-6.

25. Mutsaerts EL, van Ruth S, Zoetmulder FA, Rutgers EJ, Hart AA, van Coevorden F. Prognostic factors and evaluation of surgical management of hepatic metastases from colorectal origin: a 10-year single-institute experience. J Gastrointest Surg 2005;9:178-86.

26. Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S. Analysis of preoperative prognostic factors for long-term survival after hepatic resection of liver metastasis of colorectal carcinoma. J Gastrointest Surg 2005;9:374-80.

27. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-53.

28. Kemeny MM. Chemotherapy after hepatic resection of colorectal metastases. Cancer Treat Res 1994;69:121-8.

29. de Baere T, Roche A, Elias D, Lasser P, Lagrange C, Bousson V. Preoperative portal vein embolization for extension of hepatectomy indications. Hepatology 1996;24:1386-91.

30. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176-81.

31. Schneider PD. Preoperative assessment of liver function. Surg Clin North Am 2004;84:355-73.

32. Cady B, Jenkins RL, Steele GD Jr, et al. Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 1998;227:566-71.

33. Elias D, Cavalcanti A, Sabourin JC, Pignon JP, Ducreux M, Lasser P. Results of 136 curative hepatectomies with a safety margin of less than 10 mm for colorectal metastases. J Surg Oncol 1998;69:88-93.

34. Elias D, Cavalcanti A, Sabourin JC, et al. Resection of liver metastases from colorectal cancer: the real impact of the surgical margin. Eur J Surg Oncol 1998;24:174-9.

35. Kokudo N, Miki Y, Sugai S, et al. Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 2002;137:833-40.

36. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241:715-22.

37. Beckurts KT, Holscher AH, Thorban S, Bollschweiler E, Siewert JR. Significance of lymph node involvement at the hepatic hilum in the resection of colorectal liver metastases. Br J Surg 1997;84:1081-4.

38. Jamison RL, Donohue JH, Nagorney DM, Rosen CB, Harmsen WS, Ilstrup DM. Hepatic resection for metastatic colorectal cancer results in cure for some patients. Arch Surg 1997;132:505-10.

39. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg 2003;90:567-74.

40. Jaeck D. The significance of hepatic pedicle lymph nodes metastases in surgical management of colorectal liver metastases and of other liver malignancies. Ann Surg Oncol 2003;10:1007-11.

41. Rodgers MS, McCall JL. Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review. Br J Surg 2000;87:1142-55.

42. Ike H, Shimada H, Togo S, Yamaguchi S, Ichikawa Y, Tanaka K. Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer. Br J Surg 2002;89:1164-8.

43. Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. J Thorac Cardiovasc Surg 1999;118:1090-6.

44. Lehnert T, Knaebel HP, Duck M, Bulzebruck H, Herfarth C. Sequential hepatic and pulmonary resections for metastatic colorectal cancer. Br J Surg 1999;86:241-3.

45. Mineo TC, Ambrogi V, Tonini G, et al. Longterm results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. J Am Coll Surg 2003;197:386-91.

46. Regnard JF, Grunenwald D, Spaggiari L, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. Ann Thorac Surg 1998;66:214-8.

47. Brand MI, Saclarides TJ, Dobson HD, Millikan KW. Liver resection for colorectal cancer: liver metastases in the aged. Am Surg 2000;66:412-5.

48. Termuhlen PM, Kemeny MM. Surgery in the older patient. Oncology (Williston Park) 2002;16:183-9.

49. Fujita S, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. Jpn J Clin Oncol 2000;30:7-11.

50. Lyass S, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol 2001;78:17-21.

51. Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. World J Surg 1991;15:62-7.

52. Lambert LA, Colacchio TA, Barth RJ Jr. Interval hepatic resection of colorectal metastases improves patient selection. Arch Surg 2000;135:473-9.

53. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-60.

54. Fong Y, Blumgart LH, Cohen A, Fortner J, Brennan MF. Repeat hepatic resections for metastatic colorectal cancer. Ann Surg 1994;220:657-62.

55. Imamura H, Kawasaki S, Miyagawa S, Ikegami T, Kitamura H, Shimada R. Aggressive surgical approach to recurrent tumors after hepatectomy for metastatic spread of colorectal cancer to the liver. Surgery 2000;127:528-35.

56. Metcalfe MS, Mullin EJ, Maddern GJ. Choice of surveillance after hepatectomy for colorectal metastases. Arch Surg 2004;139:749-54.

57. Muratore A, Polastri R, Bouzari H, Vergara V, Ferrero A, Capussotti L. Repeat hepatectomy for colorectal liver metastases: A worthwhile operation? J Surg Oncol 2001;76:127-32.

58. Nagakura S, Shirai Y, Suda T, Hatakeyama K. Multiple repeat resections of intra- and extrahepatic recurrences in patients undergoing initial hepatectomy for colorectal carcinoma metastases. World J Surg 2002;26:141-7.

59. Nordlinger B, Vaillant JC, Guiguet M, et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. J Clin Oncol 1994;12:1491-6.

60. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57.

61. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 1999;10:663-9.

62. Meric F, Patt YZ, Curley SA, et al. Surgery after downstaging of unresectable hepatic tumors with intra-arterial chemotherapy. Ann Surg Oncol 2000;7:490-5.

63. Punt CJ. New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 2004;15:1453-9.

64. Rivoire M, De CF, Meeus P, Negrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283-92.

65. Wein A, Riedel C, Kockerling F, et al. Impact of surgery on survival in palliative patients with metastatic colorectal cancer after first line treatment with weekly 24-hour infusion of high-dose 5-fluorouracil and folinic acid. Ann Oncol 2001;12:1721-27.

66. Figueras J, Valls C, Rafecas A, Fabregat J, Ramos E, Jaurrieta E. Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. Br J Surg 2001;88:980-5.

67. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341:2039-48.

68. Kemeny N, Gonen M, Sullivan D, et al. Phase I study of hepatic arterial infusion of floxuridine and dexamethasone with systemic irinotecan for unresectable hepatic metastases from colorectal cancer. J Clin Oncol 2001;19:2687-95.

69. Lorenz M, Muller HH, Staib-Sebler E et al. Relevance of neoadjuvant and adjuvant treatment for patients with resectable liver metastases of colorectal carcinoma. Langenbecks Arch Surg 1999;384:328-38.

70. Ruers T, Bleichrodt RP. Treatment of liver metastases, an update on the possibilities and results. Eur J Cancer 2002;38:1023-33.

71. Tono T, Hasuike Y, Ohzato H, Takatsuka Y, Kikkawa N. Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases: A randomized study. Cancer 2000;88:1549-56.

72. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg 2001;88:165-75.

73. Adam R, Hagopian EJ, Linhares M, et al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. Arch Surg 2002;137:1332-9.

74. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480-6.

75. Bartlett DL, Libutti SK, Figg WD, Fraker DL, Alexander HR. Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. Surgery 2001;129:176-87.

76. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29:1099-105.

77. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 2003;97:3027-35.

78. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521-7.

79. Marinelli A, de Brauw LM, Beerman H, et al. Isolated liver perfusion with mitomycin C in the treatment of colorectal cancer metastases confined to the liver. Jpn J Clin Oncol 1996;26:341-50.

80. Pearson AS, Izzo F, Fleming RY, et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. Am J Surg 1999;178:592-9.

81. Rothbarth J, Pijl ME, Vahrmeijer AL, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of colorectal metastasis confined to the liver. Br J Surg 2003;90:1391-7.

82. Vahrmeijer AL, van Dierendonck JH, Keizer HJ, et al. Increased local cytostatic drug exposure by isolated hepatic perfusion: a phase I clinical and pharmacologic evaluation of treatment with high dose melphalan in patients with colorectal cancer confined to the liver. Br J Cancer 2000;82:1539-46.

83. Elias D, De Baere T, Roche A, Bonvallot S, Lasser P. Preoperative selective portal vein embolizations are an effective means of extending the indications of major hepatectomy in the normal and injured liver. Hepatogastroenterology 1998;45:170-7.

84. Elias D, Ouellet JF, de Baere T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: long-term results and impact on survival. Surgery 2002;131:294-9.

85. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29:1099-105.

86. Fujii Y, Shimada H, Endo I, et al. Changes in clinicopathological findings after portal vein embolization. Hepatogastroenterology 2000;47:1560-3.

87. Kodama Y, Shimizu T, Endo H, Miyamoto N, Miyasaka K. Complications of percutaneous transhepatic portal vein embolization. J Vasc Interv Radiol 2002;13:1233-7.

88. Fujii Y, Shimada H, Endo I, et al. Effects of portal vein embolization before major hepatectomy. Hepatogastroenterology 2003;50:438-42.

89. Christophi C, Nikfarjam M, Malcontenti-Wilson C, Muralidharan V. Long-term survival of patients with unresectable colorectal liver metastases treated by percutaneous interstitial laser thermotherapy. World J Surg 2004;28:987-94.

90. Mack MG, Straub R, Eichler K, et al. Percutaneous MR imaging-guided laser-induced thermotherapy of hepatic metastases. Abdom Imaging 2001;26:369-74.

91. Seifert JK, Morris DL. Prognostic factors after cryotherapy for hepatic metastases from colorectal cancer. Ann Surg 1998;228:201-8.

92. Giorgio A, Tarantino L, Mariniello N, et al. [Ultrasonography-guided percutaneous ethanol injection in large an/or multiple liver metastasis]. Radiol Med (Torino) 1998;96:238-42.

93. Giovannini M, Seitz JF. Ultrasound-guided percutaneous alcohol injection of small liver metastases. Results in 40 patients. Cancer 1994;73:294-7.

94. Livraghi T, Vettori C, Lazzaroni S. Liver metastases: results of percutaneous ethanol injection in 14 patients. Radiology 1991;179:709-12.

95. Gillams AR, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. Eur Radiol 2004;14:2261-7.

96. Solbiati L, Ierace T, Goldberg SN, et al. Percutaneous US-guided radio-frequency tissue ablation of liver metastases: treatment and follow-up in 16 patients. Radiology 1997;202:195-203.

97. Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 2001;221:159-66.

98. Solbiati L, Ierace T, Tonolini M. Long-term survival of patients treated with radiofrequency ablation for liver colorectal metastases: improved outcome with increasing experience. Radiology 2003S;229:411.

99. Alexander HR Jr, Bartlett DL, Libutti SK, Fraker DL, Moser T, Rosenberg SA. Isolated hepatic perfusion with tumor necrosis factor and melphalan for unresectable cancers confined to the liver. J Clin Oncol 1998;16:1479-89.

100. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3617-27.

101. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002;20:3605-16.

102. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282-92.

103. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097-106.

104. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-47.

105. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041-7.

106. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000;18:136-47.

107. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

108. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:3697-705.

109. Harmantas A, Rotstein LE, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. Cancer 1996;78:1639-45.

110. Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. Lancet 2003;361:368-73.

111. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. J Clin Oncol 2000;18:243-54.

112. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. Meta-Analysis Group in Cancer. J Natl Cancer Inst 1996;88:252-8.

APPENDIX 1

The working group

Chairman: J. Stoker, MD, PhD, radiologist, Academic Medical Centre, Amsterdam
Vice-chairman: J.W. Greve MD, PhD, surgeon, Maastricht University Hospital, Maastricht
Other members in alphabetic order:
S. Bipat MSc, researcher, Academic Medical Centre, Amsterdam
P.M.M. Bossuyt PhD, clinical epidemiologist, Academic Medical Centre, Amsterdam
A. Cats MD, PhD, gastroenterologist, Netherlands Cancer Institute, Amsterdam
E.F.I. Comans MD, PhD, nuclear medicine specialist, VU University Medical Centre, Amsterdam
T.M. van Gulik MD, PhD, surgeon, Academic Medical Centre, Amsterdam
R.L.H. Jansen MD, PhD, medical oncologist, Maastricht University Hospital, Maastricht
M.S. van Leeuwen MD, PhD, radiologist, University Medical Centre Utrecht, Utrecht
M.E.J. Pijl MD, PhD, radiologist, Martini Hospital, Groningen
A.S.Th. Planting MD, PhD, medical oncologist, Erasmus Medical Centre, Rotterdam,
R.A. Tollenaar MD, PhD, surgeon, Leiden University Medical Centre, Leiden
J.N.M. IJzermans MD, PhD, surgeon, Erasmus Medical Centre, Rotterdam