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Imaging and treatment of patients with colorectal liver metastases in the Netherlands: a survey

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ABSTRACT

Background: Clinical experience has highlighted the absence of a uniform approach to the management of patients with colorectal liver metastases in the Netherlands.

Methods: A written survey on the diagnosis and treatment of patients with colorectal liver metastases was sent to all 107 chairmen of oncology committees in each hospital. Questions were asked concerning: specialists involved in decision-making, availability and existence of guidelines and meetings, factors that needed to be improved, information regarding the diagnostic work-up of liver metastases, detailed techniques of ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), factors influencing resectability, types of surgery performed, the use of (neo)adjuvant chemotherapy, portal vein embolisation performance, considering isolated hepatic perfusion (IHP) or local ablation as treatment options, actual performance of local ablation and the use of systemic as well as regional chemotherapy.

Results: Response rate was 68% (73/107). Specialists involved in the management were mostly surgeons (70), medical oncologists (66) and radiologists (42). Factors that needed to be improved, as indicated by responders, were the absence of 1) guidelines; 2) registration of patients and 3) guidelines for radiofrequency ablation (RFA).

Diagnostic work-up of synchronous liver metastases occurred in 71 hospitals, (by US in 69 and by CT in 2). For the work-up of metachronous liver metastases, US was used as initial modality in 14, CT in 2 hospitals, and 57 hospitals used one or the other (mainly US). As additional modality, CT was performed (71) and to a lesser extent MRI (38) or PET (22). Diagnostic laparoscopy and biopsy were performed incidentally. The choice for an imaging modality was mostly influenced by the literature, and to a lesser extent by the availability and by costs, personnel and waiting lists. Substantial variation exists in the US, CT, MRI and PET techniques. The absence of extrahepatic disease and the clinical condition were considered as the most important factors influencing resectability. Surgery was performed in 30 hospitals; hemihepatectomy in 25, segment resection in 27, multisegment resection in 23, wedge excision in 27 and combination of resection and RFA in 18 institutions. In 52 hospitals (neo)adjuvant chemotherapy was administrated to improve surgical results, partly (35%) in trials. In nine hospitals portal vein embolisation was performed, with the volume of the remnant liver as the most important factor. Local ablative techniques were considered as a treatment option in 48 hospitals and actually performed in 16 hospitals, without clearly defined indications. Experimental IHP was considered a treatment option by 45 (62%) responders, irrespective whether this treatment was available at their centre. Patients with extensive metastases received systemic chemotherapy in all 73 hospitals and regional chemotherapy in ten hospitals.

Conclusion: This survey shows substantial variation in the diagnostic and therapeutic work-up of patients with colorectal liver metastases. This variation reflects either under- or over-utilisation of diagnosis and treatment options. Evidence-based guidelines taking into account the available evidence, experience and availability can solve this variation.

KEYWORDS

Colorectal neoplasms, diagnosis, liver metastases, survey, treatment

INTRODUCTION

Colorectal carcinoma is one of the commonest solid tumours and is responsible for approximately 10% of cancer-related deaths in the Western world. Liver metastasis is a common consequence of colorectal carcinoma; 50 to 60% patients develop liver metastases. Early and accurate diagnosis of liver metastasis is crucial for clinical decision-making. Surgery is the only therapy that offers any possibility of cure with five-year survival rates after resection of all detectable disease up to 40%.[1-4] Unfortunately, only 20 to 25% of patients are deemed suitable for hepatic resection. To improve the results of surgery, a subgroup of these patients either receive neoadjuvant or adjuvant chemotherapy. Patients not suitable for surgery, due to extensive liver metastases or extrahepatic diseases, in general undergo systemic chemotherapy. Several newer therapies such as cryosurgery, radiofrequency ablation (RFA), portal vein embolisation and isolated hepatic perfusion (IHP) and regional chemotherapy are being evaluated in patients not suitable for surgery due to the number or distribution of liver metastases.[5-11]

Imaging modalities such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and laparoscopy (combined with US) represent important tools in the selection of patients for the appropriate treatment.[12-17]

Most of these diagnostic and therapeutic modalities are available in the Netherlands and there are concerns about variability in diagnosis and treatment policies. Clinical experience has highlighted several problems: variation in diagnostic strategies, factors determining the resectability (presence of extrahepatic diseases), use of neoadjuvant or adjuvant chemotherapy, extent of use of experimental treatment modalities (RFA, portal vein embolisation, IHP and regional chemotherapy) and the use of different systemic chemotherapy regimens. In addition, evidence-based guidelines concerning the diagnosis and treatment are not available in the Netherlands at the moment.

Current policies are usually based on consensus meetings, expert opinions, results from studies, and personal and/or institutional experience and preferences, resulting in variable and inconsistent choices and regimens among specialists and institutions.

By means of a written survey, we evaluated the policies on the management of patients with colorectal liver metastases in the Netherlands. The primary aim of this survey was to summarise the extent of variation in the diagnosis and treatment strategies. The second aim was to obtain relevant information for developing and implementing evidence-based guidelines.

MATERIALS AND METHODS

A written survey on the management of colorectal liver metastases was sent to all Dutch hospitals dealing with this group of patients in November 2002. A total of 107 questionnaires were sent to chairmen of the oncology committees in each hospital. All eight academic hospitals participated in this survey. The replies were returned in prepaid stamped envelopes and collected until June 2004. Due to the diversity of specialists involved in the work-up, the questionnaire was divided into three parts: 1) In the general part, questions were asked about the presence of registration systems, the number of patients diagnosed and/or treated, specialists involved in the treatment policy, availability of guidelines, existence of meetings, factors that needed to be improved and research on both diagnostic and treatment field. 2) In the diagnostic part, information on the availability of modalities and the complete diagnostic work-up of synchronous and metachronous liver metastases was requested. This included information on technical details of US, CT, MRI and PET and the factors influencing the choice between these approaches. 3) In the treatment part, questions were asked about factors influencing the choice for surgical treatment, the types of surgery performed, whether (neo)adjuvant chemotherapy was administrated, whether liver perfusion and local ablation were considered as treatment options irrespective of availability, types of local ablation performed, portal vein embolisation performance and whether systemic or regional chemotherapy was administrated. In addition, information on schedules of the chemotherapy approaches was requested.

RESULTS

Response rate

Seventy-four (69%), 73 (68%) and 73 (68%) replies were returned for the general, diagnostic and treatment parts of the questionnaire, respectively, (including from all eight academic institutions).

General

Specialists involved in the management were surgeons in 70, medical oncologists in 66, radiologists in 42, internists in 21, gastroenterologist in 17 and nuclear medicine specialists in three hospitals. In all hospitals meetings were held frequently (once every two weeks) between

specialists of one hospital (25), specialists of more hospitals (11) or between specialists and consulting specialists of the Comprehensive Cancer Centre in most centres (58).

Registration and guidelines
Registration of patients with colorectal liver metastases was only carried out in 26 hospitals. The number of patients for diagnosis ranged from 10 to 150, for surgical treatment from 1 to 40 and for palliative chemotherapy from 6 to 45 patients. Practical guidelines were available in only 16 hospitals; however these guidelines were not evidence-based. In addition, most hospitals (66) indicated they preferred national or regional evidence-based guidelines.

Factors needing improvement
The most important points of concern in the daily practice, according to the responders, were the absence of general guidelines for diagnosis and treatment of patients with colorectal liver metastases, absence of registration systems and to a lesser extent absence of guidelines for indications and performance of radiofrequency ablation (RFA).

Diagnosis
Availability of imaging modalities
US and CT were available in all 73 hospitals, MRI in 71 and PET in 11 hospitals, respectively. Diagnostic work-up of synchronous liver metastases occurred in 71 (97%) hospitals; in 69 mainly by US and in two by means of CT. Diagnostic work-up of metachronous liver metastases was performed step by step, starting with an initial screening modality followed by an additional modality for further detection and characterisation of liver metastases. As initial modality US was used in 14 hospitals, CT in two hospitals, while 57 hospitals used one or the other (mainly US). As additional modality for characterisation and determining resectability, CT was generally performed (71) and to a lesser extent MRI (38) or PET (22). In 33 hospitals a one-stop-shop imaging (for detection, characterisation and determining resectability) was performed by means of CT. Diagnostic laparoscopy and biopsy (US-guided or CT-guided) were performed incidentally in 14 and 67 hospitals, respectively.
Factors affecting the choice for a diagnostic modality were mostly influenced by the literature, to a lesser extent by availability and occasionally by costs, personnel and waiting lists.
The technical details on US, CT, MRI and PET were provided by 62, 62, 60 and 7 hospitals, respectively.

Ultrasonography (n=62)
In all hospitals a convex transducer was used for imaging; the use of an additional linear transducer for detailed visualisation of the liver surface was limited to seven hospitals. US with 'harmonic frequency' in combination with conventional US was performed in 43 hospitals. The use of contrast agents for the assessment of vascularisation of focal lesions was limited to two hospitals.

Computed tomography (n=62)
In 57 hospitals spiral CT scanners were used, including 37 multislice scanners. The number of detectors in the multislice scanners varied from 2 to 16 (modus: 4) and the slice thickness ranged from 1 tot 11 mm (modus: 5 mm). The introduction of multislice scanners made it possible to perform scanning with lower slice thickness and therefore to improve the detection of smaller lesions. In most institutions (36), four-phase scanning was performed (unenhanced, arterial, portal and late phase). In general the unenhanced and the portal phases are used for detection of liver metastases; however, arterial and late phases are helpful in distinguishing other lesions. The amount of iodine ranged from 24 to 72 g (modus 30 g). Detection of liver metastases is expected to improve by using large amount of iodine.

Magnetic emission tomography (n=60)
The magnetic strength of the MRI equipment was mainly 1.0T or 1.5T (n=47). The most frequently used contrast agent was nonspecific gadolinium (n=42); to a lesser extent (n=14) liver specific contrast agents such as Endorem® (dextran-coated ferumoxide), Resovist® (ferucarbotran), Teslascan® (mangafodipir trisodium) and Multihance® (gadobenate dimeglumine) were used to increase detection of small liver metastases, due to selective accumulation of contrast agent in liver parenchyma.

Positron emission tomography (n=7)
Six centres had a dedicated full-ring scanner. The amount of fluoro-2-deoxyglucose varied from 150 to 600 MBq and the analysis was mostly qualitatively and incidentally semi-quantitatively.

Treatment
Factors influencing resectability are summarised in *table 1*, with absence of extrahepatic disease and the clinical condition considered to be the most important factors.
Surgery was performed in 30 hospitals: hemihepatectomy in 25, segment resection in 27, multisegment resection in 23 and wedge excision in 27, and a combination of resection and RFA in 18 institutions.
In 52 (71%) hospitals either neoadjuvant or adjuvant chemotherapy was administrated to improve surgical results with a substantial variation in the treatment regimens, mostly 5-fluorouracil + leucovorin or 5-fluorouracil + leucovorin + oxalipatin, while irinotecan was administrated less often. Approximately 35% (18) of the responders explicitly mentioned that (neo)adjuvant chemotherapy was administrated in trials.

Table 1. *Factors influencing resectability of liver metastases*

Factor	Number of hospitals
Number of lesions	57 (78%)
Size of lesions	40 (55%)
Location of lesions	58 (79%)
Ro resection (clear surgical margins)	26 (36%)
Extrahepatic metastases	63 (86%)
Anatomic structure of the liver	26 (36%)
Stage and grade of the primary tumour	14 (19%)
Age of the patient	27 (37%)
Clinical condition of the patient	69 (95%)
Wish of the patient	52 (71%)
Time between primary tumour and metastases detection	24 (33%)

Response: 73 (68%) hospitals.

Portal vein embolisation was only performed in nine hospitals to achieve a hypertrophy of the remnant liver. The most important factor determining the choice for portal vein embolisation was the volume of the remnant liver.

Ablation techniques were considered treatment options in 48 hospitals (47 RFA, 19 cryoablation, 10 laser-induced interstitial thermotherapy). The actual use of these techniques was limited to 16 hospitals (RFA in 15, cryoablation in two and laser-induced interstitial thermotherapy in one hospital), however without evident indications or guidelines.

Of the responders, 62% (45) indicated that they considered experimental IHP to be a treatment option irrespective of whether this treatment was available at their centre. IHP involves complete vascular isolation of the liver to allow regional delivery of high-dose chemotherapy to the liver with little systemic toxicity. This experimental technique is being evaluated at Leiden University Medical Centre and Erasmus Medical Centre in Rotterdam.

Patients with extensive metastases are only suitable for chemotherapy, either systemic or regional. In all 73 hospitals patients received systemic chemotherapy and in ten regional chemotherapy was given. For systemic chemotherapy, several protocols were used: 5-fluorouracil and leucovorin with either oxalipatin or irinotecan and the use of capecitabine (instead of 5-fluorouracil).

DISCUSSION

In most institutions, the strategy for diagnosis was comparable: US was used as an initial screening imaging modality to detect patients with liver metastases. Easy availability and noninvasiveness are some of the reasons for the widespread use of US. As additional modalities mostly CT and to a lesser extent MRI were used; however, with a substantial variation in CT and MRI techniques, such as the use of different phases and amount of contrast for CT and different contrast agents for MRI. The variation is mostly a consequence of technical developments (e.g. introduction of multislice CT and liver specific MRI agents)[12-17] and uncertainties in the literature (different outcomes), indicating the need for evidence-based guidelines.

In general, diagnostic laparoscopy is performed in selected cases to detect extrahepatic disease, thereby preventing unnecessary laparotomies. However, in patients selected for surgery based on extensive imaging, the prevalence of extrahepatic disease will be low and therefore the additional value of diagnostic laparoscopy will be limited.[18-20]

There were concerns about surgery in patients with extrahepatic disease. However, most of the responders indicated that extrahepatic disease is a major contraindicative factor for surgery. In 52 hospitals (neo)adjuvant chemotherapy was given to improve surgical results. Due to the structure of the written survey, no data on the frequencies of neoadjuvant or adjuvant therapy are available. (Neo)adjuvant chemotherapy was also administrated in trials, explaining part of the variation. We were aware of this variation and tried to summarise the extent of use of (neo)adjuvant, without describing regimens and/or indications. In addition, the effect of (neo)adjuvant chemotherapy has not been significantly proven.[21,22]

Portal vein embolisation was performed in nine hospitals, with the volume of the remnant liver as the most important selection criterion. RFA was considered as a treatment option in most hospitals; however, this technique was performed in a limited number of hospitals, with no uniform indications or selection criteria. A paper by Mutseart *et al.* reporting on the initial experience with RFA of malignant hepatic tumours in the Netherlands showed recurrence in 52% of the patients.[23] In addition, there are no randomised trials; RFA is being evaluated in an ongoing randomised trial comparing chemotherapy plus local ablation with chemotherapy (CLOCC) alone. The advice of the British National Institute for Clinical Excellence (NICE) is as follows: Current evidence of the safety and efficacy of local tumour ablation by RFA for colorectal cancer metastases does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.[24]

Most of the responders (62%) indicated that they considered IHP a treatment option for selected patients with extensive liver metastases. IHP has good efficacy in terms of response rate and duration; however, due to the high toxicity rate, the use of this technique is appropriately limited to research protocols at dedicated centres.[25-29]

The value of regional chemotherapy in patients with nonresectable tumours is unclear. A higher response percentage is obtained compared with intravenous 5-FU; however, no improvement of survival is shown.[30] This technique is therefore performed in limited cases in the Netherlands.

An important limitation of this survey is the suboptimal response (69%), not representing the overall situation in the Netherlands. However, all the academic hospitals and institutions using the experimental treatment options were included in this survey, thus indicating that the hospitals that did not respond represent hospitals with a limited number or no patients with this disease.

Two major points of concern in the management of patients with colorectal cancer which need to be addressed are the absence of guidelines and registration systems. Registration systems are important tools in evaluating management. The collaboration between specialists and consulting specialists of the Comprehensive Cancer Centres will make it possible to establish a national registry. A national evidence-based guideline is being developed to overcome the problem concerning the absence of guidelines.

Substantial variation exists in the diagnostic and therapeutic work-up of patients with colorectal liver metastases. This can be explained by recent developments, the availability of techniques, expertise, uncertainties in the literature (e.g. diagnostic value, effect, survival) and mostly by the absence of guidelines. Research and evidence-based guidelines taking into account the available evidence, experience and availability can solve this problem.

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