REVIEW ARTICLE

Current diagnostic and therapeutic approaches for colorectal cancer liver metastasis

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Abstract

Colorectal cancer is the second leading cause of cancer death in the developed world, due to formation of distant metastases. The liver is a primary target organ of metastatic lesions, which substantially influence the morbidity of the disease. Prompt diagnosis of colorectal liver metastases leads to early treatment, which favours a better prognosis. Consequently, the diagnostic process has shifted from traditional clinical and biochemical procedures to technologically advanced imaging modalities, such as CT, MRI, FDG-PET and PET-CT.

However, the only current curative therapeutic approach is the surgical resection of metastases, using the new methods of tissue excision and haemostasis. New therapeutic modalities like cryo- or radiofrequency ablation and portal vein embolisation as well as pharmaceutical innovations such as hepatic arterial infusion chemotherapy, isolated hepatic perfusion and contemporary chemotherapeutic regimens have emerged. While still under evaluation, they present promise for the future treatment of unresectable liver metastases. Hippokratia 2008; 12 (3): 132-138

Key words: colorectal cancer, liver metastasis, liver metastasectomy, ablation, chemotherapy

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Colorectal cancer is the 3rd most common malignancy worldwide[1], with over 1 million new cases reported each year[2,3]. It is the second cause of cancer death in North America and Western Europe[4]. In Europe during the year 2004, 203700 deaths were reported. In the UK, approximately 34500 new cases and 16200 deaths from colorectal cancer were registered in 2001[5]. The disease affects people of advanced age; 93% of all cases are diagnosed in people over 50 years and half of them are older than 70[6] .

Colorectal cancer metastasises to various organs, with the lymph nodes being the most frequent, followed by the liver and lungs[1]. By the time of diagnosis, about 25% of patients have liver metastases (synchronous metastases); another 25%-30% will present hepatic lesions in the following 2-3 years (metachronous metastases). The overall life expectancy is mainly determined by the progression of liver secondary disease and not by the primary carcinoma, even in patients with an isolated hepatic tumour. Without treatment, life expectancy is less than 1 year[4] (Figure 1).

Diagnosis of colorectal liver metastasis

The diagnostic process starts with a detailed medical history and a thorough physical examination. However, metastatic liver disease is usually diagnosed presymptomatically, through imaging. At the onset, virtually no evident symptoms or signs are present[7]; high temperature of unknown origin or unexplained episodes of thromboembolism may occur, but they are attributed to metastases only much later, when the disease has evolved. Large liver tumours may induce right upper quadrant or generalised abdominal pain. Additionally, weight loss and/or metabolic disturbances may develop. As the disease progresses, ascites, jaundice, portal hypertension, encephalopathy augur a bad prognosis[7].

Laboratory tests like carcino-embryonic antigen (CEA) and biochemical markers for liver function evaluation are routinely used and support the diagnosis, though without great accuracy (Table 1).

Only contemporary imaging modalities may establish an early reliable diagnosis[10,11]. Spiral computerised tomography (CT) or magnetic resonance imaging (MRI) show high accuracy in the detection and characterisa-

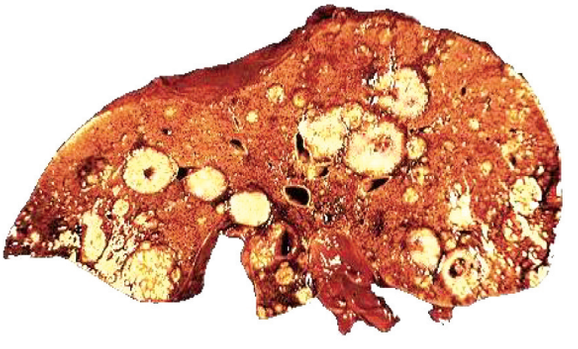

Figure 1: Liver with metastatic colorectal adenocarcinoma.

Table 1: Sensitivity of liver markers for the detection of colorectal liver metastases

Study	Liver markers	Sensitivity
Ottmar et al[8]	ALP, SGOT, SGPT	64%, 44%, 41%
Mielczarek et al[9]	Arginase	85%
	SGOT,SGPT	30%
	CEA	63%
	CA 19-9	42%

ALP: Alkaline Phosphatase

tion of liver lesions. They are the considered methods of choice in deciding surgical resectability or the determination of an adjuvant therapy[11]. Imaging is improved by contrast agents, such as iodine for CT and gadolinium or superparamagnetic iron oxide for MRI[12]. CT or MRI may be chosen according to the local infrastructure of each centre (costs, availability and expertise) and the special characteristics of each examination. CT is a radioactive procedure and the use of iodine may provoke renal insufficiency or allergy; also, it is only 45% to 53% accurate in the detection of metachronous tumours, due to distorted liver anatomy after a surgical resection[11-14]. MRI on the other hand demands higher functional cost, longer time and prolonged breath holding by the patient[11,12,15,16]. Ultrasonography is not recommended in the primary diagnosis, due to its low accuracy[11,16]. However, it is often used in the detection of metachronous tumours as an initial imaging modality, because it is non invasive, inexpensive and widely available[12].

FDG-PET is probably the most important imaging innovation, in the diagnosis of liver tumours. FDG (^{18}F-flourodeoxyglucose) is a glucose analogue, which cannot undergo glycolysis and as colorectal metastases usually contain glucose in high concentration, this compound is used to localize them through positron emission tomography (PET)[10,12]. FDG-PET can detect primary or recurrent, malignant or benign lesions, throughout the body, with high contrast resolution. Unfortunately, this method is unable to locate the tumours precisely[10,13].

More accurate tumour detection is achieved, when PET is combined with CT[10,14]. PET/CT aims to improve PET's poor anatomical reference, with CT's high spatial resolution. It uses 2 scans located side by side, in order to compare the provided images. Integration of these images with expensive, specialised software makes the procedure even more effective. Though, certain preconditions need to be fulfilled: identical patient positioning during PET and CT, difficult to follow breathing instructions, limited time gap between the two combined methods, great experience, and deep knowledge of a complicated software[14]. Hybrid hardware PET/CT fuses PET with CT in order to facilitate clinical practice, but the results are still premature. In the future, other new imaging modalities will appear, such as PET/MRI, which is expected to be clinically available by the end of the decade[14]. As clinical experience increases and all these high technological advances are tested in everyday practice, diagnosis of colorectal liver metastases will become more rapid, accurate and less time and money consuming.

Laparoscopy has no role in the diagnostic process due to its invasiveness and the small prevalence of extrahepatic disease. Similarly, biopsies should not be performed, because of the high risk of developing needle tract metastases[12]. Studies, which evaluated fine needle aspiration (FNA) for detection of various liver lesions, recorded 0.4% to 5.1% incidence of needle tract metastases[17].

Treatment of colorectal liver metastases

Surgery

Surgery is the treatment of choice and the only modality which may be considered as curative. However, only 10-25% of patients with hepatic metastases are eligible for curative surgical resection. Postoperative mortality is lower than 5%, especially in medical centres with high expertise, due to better knowledge of liver anatomy, efficient bleeding control during the operation and wide use of intra operative ultrasonography. Five year survival ranges from 25-39%[6,15].

The following criteria define a potential curative operation[12]: a) Ro resection (no microscopic residual tumour after the surgical procedure) with surgical margins ≥ 1cm, b) residual liver volume ≥30% of total liver parenchyma c) No presence of extrahepatic disease, d) Patients with adequate cardiopulmonary function.

A clinical risk scoring system, presented in 1999, evaluated the surgical eligibility or the necessity of postoperative chemotherapy using 5 criteria[18]: a) Node positive primary tumour, b) Disease free interval between colon resection and appearance of metastases < 12 months, c) Tumour > 5 cm, d) >1 tumours, e) CEA > 4200 ng/ml

This has become very popular and seems to be valuable for preoperative patient evaluation[10,15]. Nevertheless, this optimistic expectation is not widely shared. A study from Mayo clinic USA[19], evaluated all major scoring systems referring to patients with colorectal liver metastases and concluded that the available systems could not in any case be used in patient selection for hepatic metastases resection (Table 2). This American study revised 662 medical records from 1960 to 1995 and showed an overall survival of 37%; the probability of recurrence at any site was 65% within 5 years. Additionally, it was revealed that only blood transfusion and positive hepatoduodenal lymph nodes could be used postoperatively, as predictive means for survival or recurrence of the disease.

In clinical practice, there are several poorly defined aspects in patient selection and surgical feasibility.

Ambiguous issues in surgery:

Dependent on the anatomic location of a colorectal cancer liver metastasis, surgical margins <1cm are acceptable, as long as radical resection can be achieved[16].

Table 2: Major clinical risk scoring systems for colorectal liver metastases, evaluated by the Mayo study 2007

Clinical risk scoring system	Patients studied
Nordlinger et al, 1996[20]	1512

When metastases are present in the lymph nodes of the liver hilum, a curative resection can still be attempted, if an extended lymphadenectomy is performed[12]. However, various studies have recorded disappointing results after hepatic lymphadenectomy. Nordlinger et al studying a sample of 1256 patients with colorectal liver metastases, performed radical lymph node extraction in 100, who had infiltrations in the hepatic pedicle and presented 12% 3 year survival[22]. Furthermore, Jaeck et al studying 160 patients with liver metastases and 17 with coexistent positive lymph nodes, recorded 19% 3 year survival after lymphadenectomy[23,24]. These dismal observations lead to severe doubts for the necessity of radical lymphadenectomy, as the palliative chemotherapy can achieve the same outcome[22,24].

Limited lung metastases without mediastinal lymph node involvement, is not considered a contraindication for resection, if resection of a limited number of lung metastases follows radical hepatic surgery[12,16]. Colorectal pulmonary metastasectomy was first performed by the American surgeon Alfred Blalock in 1944[22]. Mc Cormack et al, in 1992, studied 144 patients with colorectal lung metastases, who underwent complete metastasectomy. Fifty seven presented a single lesion. The overall 5 year survival was 40%[25]. The International Registry of Lung metastases studying 5206 patients with pulmonary metastases of various primary sites, announced the following 3 prognostic factors: Ro resection, time free of disease > 36 months, single metastasis[22,26].

Assessing extrahepatic lesions in multiple sites in 84 patients with colorectal liver metastases, Elias et al presented an overall 5-year survival rate of 32%. They concluded that the total number of metastases (hepatic or extrahepatic) had the primary prognostic value and not the site; if they can be resected, one liver and one extrahepatic metastasis have similar prognosis to two isolated liver metastases[27].

Hepatectomy in older patients may be performed, when good cardiopulmonary function is present. Postoperative median survival for patients older than 70 years is up to 33 months and 22% live for 5 years[12].

Simultaneous resection of primary colorectal carcinoma and hepatic metastases should be avoided due to higher complication rate. Hepatic resection could follow primary resection after 2-3 months[15]. However, 3 studies from Memorial Sloan- Kettering Cancer Centre[28], Mayo Clinic[29] and Glasgow[30] concluded that synchronous colon and liver resection does not induce further postoperative complications, achieves shorter hospital stay and permits prompt adjuvant therapy[30].

More than 4 lesions in a hepatic lobe or bilobar metastases reject resectability and should be treated with chemotherapy or ablation[22]. Nevertheless, Minagawa et al[31] recorded 29% 10 year postoperative survival in patients with more than 4 hepatic lesions. In a series of 1001 patients, Fong et al[18] recorded no statistically significant difference in survival or tumour-free interval for unilobar or bilobar lesions. Similarly, Ercolani et al[32] reported that total tumour volume is more important than the location or the number of hepatic lesions. They concluded that multiple or bilobar tumours have better prognosis, if the total volume is smaller than 125 cm^3, in comparison with solitary metastases larger than 380 cm^3 [32].

If surgical margins are at least 1 cm, the amount of resected liver has no prognostic value. Also, palliative resection has no place in the treatment of colorectal cancer hepatic metastases, since overall survival is comparable to unresected patients[33]. However, French hepatobiliary medical centres have announced results of two stage hepatectomy in carefully selected patients, in order to treat multiple and bilobar lesions; some of the metastases were resected first in a non curative operation and the rest were excised after liver regeneration had occurred[34,35]. The result of a third hepatectomy has also been reported[36]. These aggressive surgical treatments are only performed in strict protocols and attempt to offer life prolongation to patients with an unfavourable prognosis[37].

While many clinical issues are not well defined, there are some contraindications for the resection of hepatic metastases, which are generally accepted (Table 3).

Unfortunately, the disease recurs within 30 months in up to 80% of patients who have undergone hepatic resection; 30% of the recurrences are confined to the liver and are resectable in 23-33%[15,38]. A follow up every 3 months for the first 2 years and thereafter every six months until 5 years is suggested to detect early recurrences (metachronous metastases) and select candidates for repeat resection. Postoperative follow up should include clinical examination, CEA measurement and chest and abdomen CT[12,38]. Repeated hepatectomy is associated with a 5-year survival similar to the first hepatectomy[12].

Nowadays, surgery is assisted by various new therapeutic modalities, which treat unresectable disease. The following methods are promising therapeutic choices, though most of them still under evaluation. They require meticulous patient selection and frequently provide successful results only in the hands of experts, in advanced medical centres.

Table 3: Absolute contraindications for the resection of hepatic metastases[6,15]

Parameter	Characteristics which contraindicate a resection
Lesions	Extrahepatic
Liver tumours	> 10 cm
Liver segments involved	> 6
Cardiopulmonary status	Bad
Necessary liver resection	> 70%
Ro resection	Not feasible

Ablation

Liver metastatic carcinoma may be destroyed either by heat application (radiofrequency ablation "RFA", laser therapy), cold (cryotherapy) or by chemical injection (ethanol). Cryo-therapy and RFA are the most widely accepted and most studied ablative methods[12,37].

In cryotherapy, a liquid nitrogen filled cryoprobe is inserted into the tumour and cycles of freezing and thawing are induced. At the end, cellular water is turned into an ice ball and the tumour is destroyed. The cryoprobe is too big for percutaneous use, so cryotherapy can only accompany either an open or a laparoscopic surgical approach[6,15,37].

RFA is a surgical procedure, whose principles were initially described by the French biophysicist Jacques-Arsène d'Arsonval in 1891[39]. It uses an RF electrode, which enters the centre of a hepatic lesion percutaneously, under US or CT guidance, laparoscopically or during open surgery. The electrode generates extreme heat in the tumour, due to tissue friction and leads to coagulative necrosis[15]. RFA can substitute for surgical resection, when adequate margins are not possible to achieve, postoperative liver reserve is considered inadequate or when coexistent morbidity favours the method[39]. Unlike cryotherapy, where major blood vessels act as heat sinks and inhibit tissue freezing close to them, RFA can be used near major vascular structures, coagulating surrounding tissue but leaving intact the vascular endothelium[39]. However, various complications may threaten the patient; symptomatic pleural effusions, fever, pain, liver hematomas, biliary tree- hepatic artery or diaphragmatic injuries, coagulopathy and hepatic abscesses are some of the most serious[15]. The procedure was evaluated recently with respect to complications and death rate in a large multicenter study; 3554 lesions were examined, 693 being liver metastases, and mortality and morbidity rates were estimated around 0.3% and 7.2% respectively[40]. Generally, ablation is considered a promising technique and RFA is its most successful form[12].

Portal vein embolisation (PVE)

This involves a percutaneous radiologic approach and deprives portal blood flow to the liver segments that are planned for resection. In 3-4 weeks, atrophy is induced in the embolised parts, accompanied by hypertrophy of the contralateral remnant[10]. PVE is used in hepatobiliary centres of great expertise for patients who cannot undergo hepatic resection so far, due to insufficient postoperative liver remnant. Only retrospective or short prospective studies have assessed the outcome. An early series of 10 patients presented a 3% complication rate and no evidence of contralateral tumour growth stimulation[41]. On the contrary, in another study including 48 patients who underwent PVE, growth of the hepatic parenchyma and metastases was measured in 5 cases. An intense growth of metastases was recorded in the regenerating liver lobe. Compared to the regenerating normal parenchyma, metastases showed 1.0 to 15.6 times higher growth rate in these 5 patients[42]. However, this last study did not evaluate the growth rate of the metastases before the operation, so it is not possible to conclude if the increased growth rate could be attributed to PVE. These contradictory results necessitate further evaluation of PVE.

Hepatic arterial infusion chemotherapy (HAI)

The initial description of this procedure dates back to 1960, but considering the technical difficulties and the serious complications, it remained unpopular among radiologists and oncologists. Its principle is based on the fact that the hepatic artery mostly supplies liver tumours, whereas the portal vein supplies blood to the hepatic parenchyma[43]. The procedure involves the surgical or subcutaneous placement of a catheter in the hepatic artery and the infusion of one or more chemotherapeutic agents at a fixed rate, with the aid of a subcutaneous pump[44,45]. Suitable patients are those who present with liver confined disease, no portal thrombosis or impairment of hepatic function and have undergone a hepatic angiography for vascular anatomy determination.

Various drugs are used with HAI: 5-fluorouracil (5-FU), mitomycin, cisplatin, doxorubicin and 5-fluoro-2'-deoxyrubicin (FUDR), which is the most common[44,45]. Unfortunately, serious complications may occur: either treatment related, like chemical hepatitis, biliary sclerosis, peptic ulceration or pump related, like hepatic artery thrombosis, catheter displacement, hematomas and infections.

Several studies have assessed the efficacy of HAI, though, with contradictory results (Table 4). While only the study of Kemmeny et al showed statistically significant difference between HAI and intravenous chemotherapy, all the studies in Table 4 concluded in favour of HAI[44-46].

Table 4: Studies evaluating HAI

Study	Patients	Compared chemotherapeutic regimens	Results
Meta Analysis Group in Cancer, 1996[47]	600	• HAI: FUDR • FUDR i.v. • 5-FU i.v.	No statistical difference
Harmantas et al, 1996 [48]	meta-analysis of 6 articles	• HAI: FUDR • HAI: 5-FU • Systemic chemotherapy	No statistical difference
Kemmeny et al, 2003 [44,45]	135	• HAI: FUDR+LV+Dexamethasone • 5-FU+LV i.v.	2.9 month benefit for HAI (22.7 vs 19.8)

HAI: Hepatic Arterial Infusion
FUDR: Floxuridin
5-FU: 5-Fluorouracil
LV: Leucovorin (folinic acid)

In general, hepatic artery infusion chemotherapy is technically highly demanding and presents the most favourable results in experienced medical centres. Moreover, patients must be very carefully selected, as complications may be numerous and serious.

The development of the systemic chemotherapy will probably reduce even more the role of HAI in the future or else it will find a new place in colorectal liver metastases therapy.

Isolated hepatic perfusion (IHP)

This technically complex method demands complete vascular liver isolation, with the aid of catheters and a heart-lung machine, before high concentrations of chemotherapeutic antitumour agents are infused. Consequently, it is used only in large specialised medical centres, usually transplantation centres, when hepatic lesions cannot be resected or ablated. With no systemic toxicity, various compounds have been utilised like mitomycin C, 5-FU and melphalan with or without TNFa in high doses, combined with mild hyperthermia (40°C)[3]. Melphalan, an alkylating agent, is the most employed drug in recent studies and the response rate is up to 75% and medial survival 27 months[3,49].

Neoadjuvant chemotherapy

Presurgical chemotherapy may be considered for unresectable lesions, aiming at surgical resectability. Multiple studies assessed the method and the succeeded resectability ranged from 6 to 33% (Table 5).

Table 5: Neoadjuvant chemotherapy for unresectable colorectal liver metastases

Study	Patients	Drugs	Resection achieved
Bismuth et al, 1996[50]	330	FOLFOX	16%
Wein et al, 2001[51]	53	Oxaliplatin+ 5-FU+LV	11%
Alberts et al, 2005[52]	42	FOLFOX	33%
Falcone et al, 2006[53]	122	FOLFIRI	6%

FOLFOX: Folinic acid (leucovorin)+5-Fluorouracil+Oxaliplatin

FOLFIRI: Folinic acid (leucovorin)+5-Fluorouracil+Irinotecan

5-FU: 5-Fluorouracil

LV: Leucovorin (folinic acid)

The drug combinations in Table 5, with the addition of cetuximab (chimeric monoclonal antibody directed against EGRF in patients EGRF+) or bevacizumab (monoclonal antibody against VEGF) have been studied in resectable hepatic malignancies, as well. The aim was to decrease the metastatic bulk, treat micrometastases and assess chemotherapeutic efficacy[53]. While, successful results occurred in carefully selected cases, severe complications may put the patient in danger. Steatosis, steatohepatitis, hemorrhagic central nodular necrosis, splenomegaly, progression of new metastases and survival of resistant clones are daunting risks for patients eligible for a potential curative operation[50].

Chemotherapy

In case of extensive and unresectable metastases, systemic chemotherapy is the standard treatment. 5-FU was the first antitumour agent to be used in the early 1990s in combination with folinic acid, against metastatic colorectal cancer. It is a fluoropyrimidine, which inhibits thymidylate synthase (a key enzyme in pyrimidine synthesis) and reduces pyrimidine availability for DNA replication[54]. Nowadays, the combination of 5-FU and leucovorin (LV) achieves a 20-30% 5 year overall survival[55]. However, newer chemo- therapeutic agents have also been added and the triple regimen, (which involves 5-FU, LV and irinotecan or oxaliplatin) is the preferred standard treatment today.

Irinotecan is a camptothecin derivative and acts as a topoisomerase I inhibitor. Topoisomerases are enzymes located in the cell nucleus which unwind DNA before replication. Inhibition of their action causes DNA strand breaks and failure of replication. Eventually, the cell dies. As topoisomerase I is overexpressed in colorectal cancer, irinotecan seems a potentially effective drug[54]. Oxaliplatin on the other hand is a platinum compound, which inhibits DNA replication by forming intra- and interstrand platinum-DNA crosslinks [54]. A randomized study published in 2000[56], compared 5-FU+LV with irinotecan+5-FU+LV. The response rate and median survival 31% and 14 months were against 49% and 17 months, respectively. Another study[57], comparing the same regimens also concluded in favour of the triple treatment. The response rate and median survival were 21% and 12.6 months against 39% and 14.8 months. An American study published in 2002, compared oxaliplatin+5-FU+LV with irinotecan+5-FU+LV and indicated a response rate of 38% and survival of 18.6 months against 29% and 14.1 months, respectively[55].

Newer drugs, like cetuximab or bevacizumab are also used in combination with first line therapy with good results. Bevacizumab in combination with FOLFIRI or 5-FU+LV is licensed in the UK as a first line treatment of colorectal cancer metastases[54].

Radiation

Irradiation of the whole liver has been almost abandoned, because the organ cannot tolerate great doses. It is well known from 1960, that if the entire liver receives doses greater than 30-35 Gy, then radiation provoked liver disease (RPLD) occurs[55]. The signs are anicteric ascites and painful hepatomegaly, accompanied by transaminases and bilirubin elevation. Some patients also develop liver failure and succumb to the disease[55].

Today there are many techniques, which irradiate only parts of the liver with high doses. Yttrium-90 microspheres showed promising results in selected patients, despite considerable technical difficulties and dosimetry inaccuracy[58]. Interstitial brachytherapy using I^{125} seed implants is another option, but presupposes open surgery. Finally, stereotactic radiation and 3-D conformal external beam radiation are also quite new methods, which will be better evaluated in the near future[59,60].

Conclusions

Diagnosis and treatment of patients suffering from hepatic metastases of colorectal cancer are rapidly changing fields. New diagnostic and therapeutic approaches emerge in high frequency and significant knowledge has been accumulated. Unfortunately, evaluation of all these new techniques and chemotherapeutic drugs is still limited, uncertain and often difficult. Randomised controlled studies are few to include every one of these new discoveries and consequently, scientific knowledge remains vague and ambiguous. Moreover, as surgery always presents the best outcomes, when resectability is feasible, no clinical trial could randomise patients eligible for surgery, in order to study another therapeutic approach. Consequently, clinical experience and expert opinions, as well as each medical centre's expertise still determine the infusion of a new antitumour agent, the use of a specific imaging technique or the practice of an ablative method, as there are no firm rules for the clinicians to follow.

New trials are currently underway and they will answer some of the existing queries. However, more well organised and unbiased studies are needed. Collaboration among different specialities (surgeons, pharmacologists, oncologists, radiologists, pathologists) appears compulsory. The aim is to guarantee a more effective and evidence based treatment for colorectal cancer liver metastasis.

References

1. Kumar V, Abbas AK, Fausto N. Robbins and Cotran pathological basis of disease, 7th ed, Philadelphia: Elsevier Saunders; 2005; p. 269-343
2. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005; 16: 481-488
3. Rothbarth J, van de Velde CJ. Treatment of liver metastases of colorectal cancer. Ann Oncol 2005; 16 (Suppl 2): ii144-ii149
4. McMillan DC, McArdle CS. Epidemiology of colorectal liver metastases. Surg Oncol 2007; 16: 3-5
5. Cancerstats. Cancer Research UK 2005
6. Al-Asfoor A, Fedorowicz Z. Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. Cochrane database of Syst Rev (Online) 2007; 4: CD006039
7. Debois JM. TxNxM1: the anatomy and clinics of metastatic cancer: Boston Kluwer Academic Publishers; 2002; p. 62-63
8. Ottmar MD, Gonda RL Jr, Leithauser KJ, Gutierrez OH. Liver function tests in patients with computed tomography demonstrated hepatic metastases. Gastrointest Radiol 1989; 14: 55-58
9. Mielczarek M, Chrzanowska A, Scibior D, et al. Arginase as a useful factor for the diagnosis of colorectal cancer liver metastases. Int J Biol Markers 2006; 21: 40-44
10. Morris KT, Song TJ, Fong Y. Recent advancements in diagnosis and treatment of metastatic colorectal cancer to the liver. Surg Oncol 2006; 15: 129-134
11. Schima W, Kulinna C, Langenberger H, Ba-Ssalamah A. Liver metastases of colorectal cancer: US, CT or MR? Cancer Imaging 2005; 5 Spec No A: S149-S156
12. Bipat S, van Leeuwen MS, Ijzermans JN, et al. Evidence-base guideline on management of colorectal liver metastases in the Netherlands. Neth J M 2007; 65: 5-14
13. Sarikaya I, Bloomston M, Povoski SP, et al. FDG-PET scan in patients with clinically and/or radiologically suspicious colorectal cancer recurrence but normal CEA. World J Surg Oncol 2007; 5: 64
14. Vogel WV, Wiering B, Corstens FH, Ruers TJ, Oyen WJ. Colorectal cancer: the role of PET/CT in recurrence. Cancer Imaging 2005; 5 Spec No A: S143-S149
15. McLoughlin JM, Jensen EH, Malafa M. Resection of colorectal liver metastases: current perspectives. Cancer Control 2006; 13: 32-41
16. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. Gut 2006; 55 (Suppl 3): iii1-iii8
17. Metcalfe MS, Bridgewater FH, Mullin EJ, Maddern GJ. Useless and dangerous-fine needle aspiration of hepatic colorectal metastases. BMJ 2004; 328(7438): 507-508
18. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999; 230: 309-318
19. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? Ann Surg 2007; 246: 183-191
20. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 1996; 77: 1254-1262
21. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 1999; 189: 291-299
22. Khatri VP, Chee KG, Petrelli NJ. Modern multimodality approach to hepatic colorectal metastases: solutions and controversies. Surg Oncol 2007; 16: 71-83
23. Jaeck D, Nakano H, Bachellier P, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. Ann Surg Oncol 2002; 9: 430-438
24. 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: 1007-1011
25. McCormack PM, Burt ME, Bains MS, Martini N, Rusch VW, Ginsberg RJ. Lung resection for colorectal metastases. 10-year results. Arch Surg 1992; 127: 1403-1406
26. Friedel G, Pastorino U, Buyse M, et al. Resection of lung metastases: long-term results and prognostic analysis based on 5206 cases--the International Registry of Lung Metastases. Zentralbl Chir 1999; 124: 96-103
27. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 2005; 12: 900-909
28. Martin R, Paty P, Fong Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 2003; 197: 233-241
29. Chua HK, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Col Rectum 2004; 47: 1310-1316
30. Moug SJ, Horgan PG. The role of synchronous procedures in the treatment of colorectal liver metastases. Surg Oncol 2007; 16: 53-58
31. Minagawa M, Makuuchi M, Torzilli G, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000; 231: 487-499
32. Ercolani G, Grazi GL, Ravaioli M, et al. Liver resection for multiple colorectal metastases: influence of parenchymal involvement and total tumor volume vs number or location, on long-term survival. Arch Surg 2002; 137: 1187-1192
33. Adam R. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. Ann Oncol 2003; 14 (Suppl 2): ii13-ii16

34. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000; 232: 777-785
35. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004; 240: 1037-1049
36. Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg 2003; 238: 871-883
37. Fusai G, Davidson BR. Strategies to increase the resectability of liver metastases from colorectal cancer. Dig Surg 2003; 20: 481-496
38. Metcalfe MS, Mullin EJ, Maddern GJ. Choice of surveillance after hepatectomy for colorectal metastases. Arch Surg 2004; 139: 749-754
39. Leen E, Horgan PG. Radiofrequency ablation of colorectal liver metastases. Surg Oncol 2007; 16: 47-51
40. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003; 226: 441-451
41. Azoulay D, Castaing D, Krissat J, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg 2000; 232: 665-672
42. Elias D, De Baere T, Roche A, Mducreux, Leclere J, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 1999; 86: 784-788
43. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. Surgery 1974; 75: 589-596
44. Cohen AD, Kemeny NE. An update on hepatic arterial infusion chemotherapy for colorectal cancer. Oncologist 2003; 8: 553-566
45. Homsi J, Garrett CR. Hepatic arterial infusion of chemotherapy for hepatic metastases from colorectal cancer. Cancer Control 2006; 13: 42-47
46. Kemeny NE ND, Hollis DR, et al. Final analysis of hepatic arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer: a CALGB randomized trial of efficacy, quality of life (QOL), cost effectiveness, and molecular markers. American Society of Clinical Oncology Gastrointestinal Cancers Symposium Hollywood, 2005
47. Meta Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Nat Cancer Instit 1996; 88: 252-258
48. 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: 1639-1645
49. Bartlett DL, Libutti SK, Figg WD, Fraker DL, Alexander HR. Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. Surgery 2001; 129: 176-187
50. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996; 224: 509-520
51. Wein A, Riedel C, Bruckl W, et al. Neoadjuvant treatment with weekly high-dose 5-Fluorouracil as 24-hour infusion, folinic acid and oxaliplatin in patients with primary resectable liver metastases of colorectal cancer. Oncology 2003; 64: 131-138
52. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol 2005; 23: 9243-9249
53. Kemeny N. Presurgical chemotherapy in patients being considered for liver resection. Oncologist 2007; 12: 825-839
54. Kelly C, Cassidy J. Chemotherapy in metastatic colorectal cancer. Surg Oncol 2007; 16: 65-70
55. Abeloff M AJ, Niederhuber J, Kastan M, Mc Kenna M. Clinical Oncology. Liver metastasis. 3rd ed: Elsevier Churchill Livingstone 2004; 1141-1171
56. 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: 1041-1047
57. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000; 343: 905-914
58. Gates VL, Atassi B, Lewandowski RJ, et al. Radioembolization with Yttrium-90 microspheres: review of an emerging treatment for liver tumors. Future Oncol 2007; 3: 73-81
59. Yin FF, Das S, Kirkpatrick J, Oldham M, Wang Z, Zhou SM. Physics and imaging for targeting of oligometastases. Semin Radiat Oncol 2006; 16: 85-101
60. Timmerman R, Papiez L, Suntharalingam M. Extracranial stereotactic radiation delivery: expansion of technology beyond the brain. Technol Cancer Res Treat 2003; 2: 153-160