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Hepatic Surgery for Colorectal Cancer Metastasis — Possibilities and Prerequisites

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Abstract

Colorectal cancer is among the most frequent malignant tumours. Liver metastases develop in 70–75% of patients affected by colorectal carcinoma. Nowadays, surgical treatment can significantly improve the 5-year survival ranging 40–58% of the patients undergoing liver surgery. The operation extent ranges from nonanatomic minor resection to major hepatectomy. Recently, liver transplantation has been performed for metastatic colorectal cancer. Laparoscopic approach and robotic surgery can be used by experienced specialists. The prerequisites for successful surgical treatment include exact radiologic diagnostics to determine the number and size of metastases and their association with anatomic structures; individual anatomic peculiarities and remnant liver volume, ranging 20–40% in respect to functional liver status. Magnetic resonance imaging is the most sensitive method that has marked advantages in the diagnostics of lesions smaller than 1 cm and metastases on the background of liver steatosis. Computed tomography is an acceptable alternative that benefits from high spatial resolution and optimal reconstructions to evaluate the anatomy. Additional information can be obtained from tumour markers, including traditional, e.g., carcinoembryonic antigen (CEA) and novel, e.g., microRNAs. To ensure that each colorectal cancer patient receives the best care, the medical society should be well informed about the possibilities in the treatment of liver metastases of colorectal cancer regarding the methods, indications and limits.

Keywords: Colorectal cancer, liver metastasis, liver resection, magnetic resonance imaging

1. Introduction

Colorectal cancer (CRC) represents one of the leading malignant tumours both by incidence and death rate [1, 2]. Metastatic spread to liver occurs in 70–75% of patients, and 20–35% of CRC patients present with synchronous liver metastases [1, 3, 4]. Although the presence of metastatic disease significantly adversely affects the survival, a wide scope of treatment options exists. To ensure that each colorectal cancer patient receives the best care, the medical society should be well informed about the possibilities in the treatment of liver metastases of colorectal cancer regarding the methods, indications and limits.

Surgery is the preferred option for long term survival. The operation extent ranges from major hepatic resection (trisegmentectomy, hepatectomy, extended hepatectomy, and hemihepatectomy) to parenchyma-sparing minor resection such as segmentectomy or wedge resection [4]. Laparoscopic approach and robotic surgery can be considered, especially in advanced centres [5, 6]. In patients with questionable adequacy of the liver remnant and wide intrahepatic tumour spread, portal vein occlusion, forced liver hypertrophy and staged resection can be helpful [7, 8]. Recently, liver transplantation for metastatic colorectal cancer has been performed [9].

Surgery at present assumes significant role in treatment of metastatic liver lesions. However, it demands not only appropriate surgical technique but also correct preoperative diagnosis and reliable plan for postoperative treatment.

Adequately timed and exact imaging is necessary prior to the surgical or nonsurgical treatment to reveal the metastases and assess the feasibility of resection. Magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography (US) and 18F-2fluoro-D-glucose positron emission tomography in association with computed tomography (PET-CT) are used for imaging metastatic lesions in the liver [1]. The radiologic evaluation can be combined with traditional and novel cancer markers [10–12] and biopsy examination. Among serological markers, carcinoembryonic antigen (CEA) has been used traditionally despite the limitations [4] and lack of unified guidelines. MicroRNAs represent a rapidly advancing research field hopefully yielding diagnostic blood tests to diagnose the cancer by location and to identify the presence of residual tumour or early recurrence.

If the surgical treatment is not possible, other options must be considered, including systemic or transarterial chemotherapy; embolisation; ablation by cryotreatment, radiofrequency or microwaves; or radiotherapy and targeted external beam radio therapy [1].

Due to the wide scope of treatment options, the median survival of patients affected by metastatic colorectal cancer has increased significantly [13, 14]. The 5-year and 10-year survival reaches 58% and 36%, correspondingly [15].

In conclusion, liver metastases of colorectal cancer represent a frequent and serious condition. The remarkable medical advances request dynamic systematisation of up-to-dated evidence. The present chapter on the surgical treatment of colorectal cancer metastases is intended to summarise the present knowledge in regard to the approach to patient with liver metastases of colorectal cancer, discussing the diagnostics, treatment and evaluation of response.

2. Epidemiology of colorectal cancer

Colorectal cancer is among the leading malignant tumours both by incidence and by death rate [1]. Globally, in the year 2012, it was the 3rd most frequent cancer in men and the 2nd in women [2]. The incidence and mortality is higher in males (Table 1). The highest incidence rates are found in Australia and New Zealand, Europe and North America contrasting with low incidence in Africa and South Central Asia. As shown in Table 2, the incidence is generally higher in more developed countries [2]. The decrease in colorectal cancer incidence in USA reflects successful screening and removal of colorectal adenomas. The incidence growth, recently observed in Western Asia (Kuwait and Israel) and Eastern Europe (Czech Republic and Slovakia), reflects increased prevalence of risk factors as diet, obesity and smoking.

Gender	Incidence		Mortality	
	ASR	Proportion[1], %	ASR	Proportion[1], %
Males	20.6	10.1	10.0	8.0
Females	14.3	9.2	6.9	9.0

[1] Among all cancers.

ASR, age-standardised ratio per 100,000.

Table 1. Global incidence and mortality attributable to colorectal cancer (2012) by Globocan data [16]

Gender and welfare status	Incidence		Mortality	
	ASR	Cumulative risk, %	ASR	Cumulative risk, %
More developed areas[1]				
Males	36.3	4.3	14.7	1.6
Females	23.6	2.7	9.3	1.0
Less developed areas[2]				
Males	13.7	1.6	7.8	0.8
Females	9.8	1.1	5.6	0.6

[1]Includes Europe, North America, Australia, New Zealand and Japan.

[2]Includes Africa, Asia (except Japan), Latin America, Melanesia, Micronesia and Polynesia.

ASR, age-standardised ratio per 100,000.

Table 2. Incidence and mortality caused by colorectal cancer by regional welfare [2]

Colorectal cancer could be prevented avoiding obesity, alcohol, smoking and excessive consumption of red and processed meat, as well as maintaining physical activity. There are

also several screening methods, including guaiac-based or immunochemical test for occult blood in stools, faecal DNA test, virtual colonoscopy by computed tomography imaging, double-contrast barium enema, flexible sigmoidoscopy and colonoscopy [2]. MicroRNA stool test could appear in the nearest future. Despite the possibilities of prevention and screening, metastatic disease is common. Metastatic spread to liver occurs in 70–75% of patients, and 20–35% of CRC patients are diagnosed with synchronous liver metastases [1, 3, 4]. Although the presence of metastatic disease significantly adversely affects the survival, a wide scope of treatment options exist.

3. Radiologic imaging techniques in the diagnostics of liver metastases of colorectal cancer

The radiologic techniques of liver examination comprise computed tomography, magnetic resonance imaging, ultrasound evaluation and fluorodeoxyglucose positron emission tomography [17]. CT and MRI represent the cornerstone in the diagnostics of liver metastases of colorectal cancer [1, 18]. US has the benefits of wide accessibility and lack of irradiation. However, it is considered a historical method in developed countries as USA [18] due to lower sensitivity and specificity. These parameters can be improved by contrast-enhanced US [19]. Positron emission tomography (PET) has certain indications.

MRI is characterised by the highest specificity and sensitivity, especially regarding metastases smaller than 1 cm in diameter [1, 20]. The imaging technology is based on different physical status of water and fat protons [18]. To identify liver metastases, MRI routinely includes T1, T2 and diffusion-weighted sequences before and after administration of gadolinium-containing contrast agent. The CRC metastases are hypointense on T1 but hyperintense on T2 and diffusion-weighted imaging sequences. The contrasting reveals metastasis as a hypovascular focus with an irregular rim of enhancement [18].

In the identification of liver metastases, MRI is characterised by the highest sensitivity that reaches 76.0–85.7% if enhancement by extracellular contrast agents and dynamic acquisition is used. The sensitivity can be further improved by diffusion-weighted imaging. Diffusion-weighted imaging is based on the assessment of Brownian motion of water molecules and water diffusion within a voxel (a tridimensional pixel). As cell membranes limit the diffusion, greater cellularity results in diffusion restriction [21]. Thus, the metastasis creates an obstacle in water molecule diffusion and is revealed by diffusion-weighted imaging at higher sensitivity and specificity than routine MRI [17, 22, 23]. The hepatobiliary phase MRI represents another improvement in the diagnostics of liver metastases by contrast agents that are absorbed by hepatocytes and excreted in biliary system, e.g., gadoxetate disodium and gadobenate dimeglumine. These agents differ from the traditional MRI contrast agents by the dual elimination, including both biliary excretion (50%) and renal glomerular filtration, while the traditional agents, as gadopentetic acid, are almost completely excreted via kidneys [1, 18]. The hepatobiliary phase of MRI corresponds to the peak parenchymal enhancement due to contrast uptake in hepatocytes. It is observed 20 min after injection. Metastatic foci lack liver

cells and therefore do not absorb hepatobiliary contrast agents. In the diagnostics of colorectal cancer liver metastases, the sensitivity of hepatobiliary phase MRI reaches even 90–97% [1, 24, 25]. In comparison with diffusion-weighted imaging, hepatobiliary phase MRI enhances sensitivity for the detection of colorectal cancer metastasis, e.g., from 78.3–97.5% to 94.4–100.0%. The combination of diffusion-weighted imaging with hepatobiliary phase MRI yields better results than isolated techniques [26].

Gadolinium-containing contrast agents can induce nephrogenic systemic fibrosis in a subfraction of patients (2.9–4%) with severe renal insufficiency [1, 27, 28]. Sufficient enhancement quality can be reached by half-dose gadoxetic acid [29]. However, other research groups have not observed any case of gadoxetate-related nephrogenic systemic fibrosis in a prospective multicentre study [30]. The risk of nephrogenic systemic fibrosis also varies by different contrast agents [1].

In comparison with CT, MRI has advantage in the diagnostics of lesions measuring less than 1 cm and shows better ability to discriminate metastases on the background of spontaneous or treatment-induced (e.g., 5-fluoruracil and irinotecane) liver steatosis [1, 17, 31]. However, CT provides better resolution of anatomic details that are necessary to plan the surgery [18]. Consequently, controversies have been expressed if the liver imaging in colorectal cancer patient should be started with CT or MRI [1, 18].

MRI is contraindicated in patients having incompatible implants, e.g., pacemakers; affected by claustrophobia or impaired glomerular filtration rate, or unable to hold the breath for longer than 20 seconds. CT should be performed in these patients [1, 18].

Multidetector CT can be used for chest, abdominal and pelvic imaging to reveal the total visceral metastatic burden. Contrasting with intravenous iodinated agents is necessary to reveal liver metastases that represent hypodense hypovascular foci with variable heterogeneity, seen in portal venous phase [18]. Rim enhancement can be observed [17]. Due to low tumour vascularity, arterial phase is more important for detection of arterial anatomy than for identification of metastases. In nonenhanced CT, the metastases are hypointense but can be inconspicuous [17, 18]. The possibilities of CT are limited in detection of small lesions and in assessment of steatotic liver. MRI is helpful in these situations. The benefits of multidetector CT include high spatial and temporal resolution exceeding that of MRI. Thus, CT is useful for planning before surgery. The individual anatomic features can also be detailed by CT [18].

PET-CT reflects the metabolic activity in tumour cells by analysing glucose uptake. It has advantage in detecting extrahepatic metastatic spread [1] or local recurrence and in evaluation of indeterminate liver lesions [17]. In a prospective study of 133 consecutive patients, PET-CT had a major impact on staging of extrahepatic spread in 20% of patients. It resulted in upstaging (from surgically treatable to inoperable) in 6% of patients and downstaging (from indeterminate or suspected inoperable to operable) in another 6% of patients [32]. As extrahepatic spread is more likely in patients who already have liver metastases, PET-CT should be considered a standard evaluation prior to curative liver surgery for metastatic colorectal cancer. PET-CT reduces futile laparotomies by 38% [33]. Combination with diagnostic intravenous contrast-enhanced CT is strongly advised as opposed to noncontrast low-dose CT providing anatomic data only [1, 34]. The sensitivity of PET-CT is impaired after chemotherapy [1, 35].

In the early studies, liver US was considered effective in the follow-up after surgical treatment of colorectal cancer metastases as it disclosed all the resectable cancer metastases as it disclosed all the resectable with thoracic X-ray [36]. However, more recent data evidence that transabdominal US has limited sensitivity in the diagnostics of CRC liver metastases: 50–75% [17]. Despite the serious shortcoming, US still can be used for screening purposes by experienced specialist who is aware of these limitations and will combine US by more sensitive methods of radiologic diagnostics. Intravenous contrast-enhanced US imaging using microbubbles to contrast blood increases the sensitivity of US by 20% [17, 19] and exceeds the sensitivity of CT, especially for small lesions [17]. Contrast-enhanced US affords diagnostic benefit in 13.7% patients with liver mass lesions [19]. The increased sensitivity of contrast-enhanced US in detection of tumours is explained by the vascularisation pattern and the phagocytosis of contrasting microbubbles by Kupffer cells that are present in liver parenchyma but absent in liver tumours. Thus, CRC metastases would be an adequate object for contrast US. The tumours are hypoechoic. The sensitivity and specificity of US and contrast-enhanced US in diagnosing malignant liver tumours is around 58.8% and 50.7% for US versus 68.7–90% and 67–88% for the contrast-enhanced modality. Deep lesions, small metastases and liver steatosis are known limiting factors. Colorectal cancer metastases may occasionally be hyperechogenic and lack hypoechoic structure on contrast-enhanced US embarrassing differential diagnosis with benign lesions, e.g., haemangioma [19].

Hepatic lesions can be missed even by combined radiologic investigation, including US, CT and MRI. The proportion of such lesions can be as high as 30% [19]. Intraoperatively, US can be applied. The sensitivity of intraoperative imaging is again enhanced by contrast US [37].

4. Preoperative radiologic evaluation: the target parameters

To plan the surgical treatment, the number, the size and the location of metastases must be detected [1]. The number of affected segments, the relations between metastases and arteries, veins and bile ducts as well as the size of remnant liver must be ascertained as well [18]. The anatomical variations of bile ducts as well as arterial and portal blood vessels must be established. CT or MRI can be used for these purposes. Although similar efficacy of both methods has been shown regarding vascular anatomic evaluation, CT can yield better contrast [1].

Diagnostic problems can be associated with identification of small lesions, imaging of metastases on the background of liver fibrosis, steatosis or sinusoidal congestion due to preceding chemotherapy (or other reasons) and detailed characteristics of deep metastasis that necessitates careful planning of surgical approach and exact data on the involvement of anatomical structures. Occasionally, differential diagnosis with benign lesions can be complicated. The presence and extent of extrahepatic disease must be estimated [18].

Software-based three-dimensional CT volumetrics is used to calculate the volume of the remnant and total liver volumes excluding nonfunctional spaces as tumours, cysts and ablation cavities. The remnant liver volume is expressed as a proportion of the preoperative total liver volume. The minimal volume of remnant liver has not been established by exact experimental

studies therefore the described desirable values differ slightly. The remnant liver volume after the operation is expected to be 25–30% in young patients with normal liver parenchyma and 40% in cirrhotic patients [4, 18]. In a consensus statement, remnant liver volume is recommended to be at least 20% for patients with normal extratumoural liver tissue, 30% for patients having chemotherapy-induced liver injury and 40% in cirrhotic patients [17, 38–40]. As metastatic tumour is spreading systemically and recurs in most patients, higher preserved proportion of liver parenchyma provides more options for repeated future surgery if necessary. The risk factors for postoperative liver dysfunction due to insufficient remnant include older age, liver fibrosis, cirrhosis and preoperative chemotherapy. Except liver cirrhosis, these factors are frequent as many patients with CRC liver metastasis are elderly and have received chemotherapy [4]. To estimate the compromised liver function more exactly, functional tests are helpful. The liver function is reflected by albumin level, hemostasis, bilirubin level, lidocaine conversion test or clearance of indocyanine green [18].

5. Traditional and novel tumour markers in the diagnostics of colorectal cancer

The patients with metastatic colorectal cancer nowadays survive longer, thus they need prolonged follow-up. CT is a sensitive method but some authors have expressed fears that the patient is subjected to radiation exposure [41]. MRI benefits from high sensitivity and lack of ionising radiation, but it is expensive. Blood test for surveillance thus seems to be an attractive, patient-friendly and radiation-free option. Although the follow-up of colorectal cancer patients after resection of the primary tumour is controversial, increased blood level of the carcinoembryonic antigen (CEA) can disclose cancer recurrence and is used traditionally. In a recent study, 25% increase of CEA level in comparison with the previous value detected 23% of recurrences while 46% of recurrences were evident both by radiology and CEA and 31%—only by radiology data. The radiologic imaging in this study comprised US after surgical treatment and CT after thermal ablation as well as in difficult cases. The resectability of the recurrent cancer did not differ in patients who were identified through CEA or by imaging [41]. Thus, CEA alone is not sensitive enough to identify the recurrence but can be helpful in complex diagnostic protocol. In contrast, CEA alone did not identify any additional case of curable recurrence after liver resection for metastatic colorectal cancer in comparison with CT [42].

CEA has several benefits, including cheapness and availability. In addition, prognostic information can be obtained. High perioperative CEA levels indicate worse survival after liver resection for CRC metastases [43].

CEA has been explored in association with other biological markers both for comparison and in order to create wider diagnostic protocol. Regarding circulating tumour cells, the findings along with CEA level added prognostic information in patients with metastatic colorectal cancer undergoing chemotherapy. In a multivariate analysis, circulating tumour cells but not CEA at the baseline predicted the survival, but both parameters predicted survival at 6–12 weeks after the initiation of treatment. There was no correlation between CEA and circulating tumour cells [10]. The levels of circulating tumour cells in colorectal cancer are reported to be lower than in other cancers due to homing within the liver [44]. The complex mechanism of

metastasis involving epithelial–mesenchymal and mesenchymal–epithelial transformation as well as blood clearing in the liver and secondary spread from liver metastasis to systemic circulation hypothetically can influence the results and interpretation of circulating tumour cell tests.

Plasma levels of the tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) have also been explored in parallel with CEA in patients undergoing chemotherapy for metastatic colorectal cancer. High plasma TIMP-1 and CEA levels both before and during treatment were related to poor response. Worse survival was predicted by high TIMP-1 level before or during chemotherapy, and by high CEA values before treatment [45]. However, chemotherapy and radiation treatment itself influenced serum levels of these markers, decreasing CEA and increasing TIMP-1 [46]. The treatment-induced switches in the biomarker levels would limit their application in the surveillance.

MicroRNAs (miRNAs) are small noncoding RNAs that post-transcriptionally modulate the expression of the target genes [47, 48]. These endogenous molecules are evolutionarily highly conserved, suggesting an important functional role in cell biology [48]. MiRNAs are located either between protein-coding genes, or in the introns of protein-coding genes. Transcription of miRNAs results in primary miRNAs that undergo processing within the nucleus. The processing yields miRNA precursors that are transported to the cytoplasm and transformed into mature miRNAs. These molecules perform their regulatory function by complementary binding to mRNA [11]. miRNAs regulate such crucial steps in cancer development (Table 3) as cell proliferation, invasion, angiogenesis, epithelial-mesenchymal transformation and the reverse process [47]. The value of miRNAs is the ability to function as large genomic switches.

Target process	Result	MicroRNAs
Angiogenesis	Activation	miR-194; miR-17-92; miR-126; miR-210; miR-424
	Suppression	miR-221; miR-222; miR-497
Invasion	Activation	miR-31; miR-122; miR-200; miR-145; miR-103; miR-107; miR-29a; miR-21; miR-17; miR-19a
	Suppression	miR-122; miR-328; miR-143
Metastasis	Vascular invasion	miR-21
	Loss of cell adhesion	miR-126
	Immune regulation	miR-155; miR-17-92
	Colonisation	miR-328; miR-103; miR-107
Apoptosis	Induction	miR-26b

Table 3. MiRNAs involved in different steps of carcinogenesis

From the practical standpoint, miRNAs at present are explored as diagnostic markers and therapeutic targets [11]. In contrast to mRNA, miRNAs are stable in formalin-fixed, paraplast embedded tissues [48–50]. In the blood and plasma, MiRNA also circulate in persistent form, suitable for testing [51, 52]. The stability might be ensured by development of extracellular microvesicles [52]. The specificity and sensitivity issues still must be finalised, but promising

results have already been reported. Thus, 6 serum miRNA-based biomarker signature, including miR-21, let-7g, miR-31, miR-92a, miR-181b and miR-203, had high sensitivity (93%) and specificity (91%) in the diagnosis of colorectal cancer. The sensitivity of such traditional serum markers as CEA and CA19-9 was significantly lower: 23% and 35%, respectively. The tested panel could discriminate stage I and II colorectal cancer from healthy controls [12], thus showing appropriate sensitivity for low tumour burden. Moreover, miR-92a, miR-21 and miR-29a serum levels could discriminate healthy controls from patients affected by colorectal cancer or advanced adenomas, the well-established precursor lesion of colorectal cancer [53, 54]. The levels of miR-17-3p, miR-92 and miR-221 also differed in plasma of colorectal cancer patients and healthy controls [55, 56].

Early relapse of colorectal cancer is associated with increased plasma levels of miR-29c [48, 57]. More intense surveillance or postoperative treatment could be offered to these patients.

Patients with liver metastasis exhibit significantly higher miR-21 level in colorectal cancer tissues. MiR-29a serum level is increased in colorectal cancer patients affected by liver metastasis and is considered a promising novel marker for early detection of liver metastasis [58]. In more recent studies, increased serum levels of miR-141 and miR-21 as well as down-regulation of miR-126 were advised for early diagnosis of liver metastasis of colorectal cancer while let7a up-regulation was associated with extrahepatic metastases [59]. The applicability of this or similar biomarker signature for metastatic cancer remains to be subjected to deeper analysis as at least few controversies can be expected. It has been shown in gastric and hepatocellular carcinoma that serum and tissue levels of miRNAs can change in opposite directions [60–62], possibly because cancer cells can selectively retain certain miRNAs [63]. In colorectal cancer, liver metastasis exhibits higher levels of miR-29c, although miR-29c is significantly down-regulated in primary colorectal cancers giving rise to distant metastasis. The seeming controversy can be explained by epithelial–mesenchymal and mesenchymal–epithelial transition [64]. In addition, surgical treatment can influence the miRNA level; thus, in hepatocellular carcinoma, miR-92a levels are high in tumour tissue, low in plasma before the treatment and high in plasma after the operation [61]. In colorectal cancer with liver metastases, tissue levels of 28 miRNAs were different (Table 4) from nonmetastatic cancers [65]. The tissue miRNA profile hypothetically could also discriminate between colorectal cancer metastases in liver and lymph nodes [66].

MicroRNA	Change in the target tissue compared to the control	Target tissue or body liquid	Control tissues or body liquid
miR-21; let-7g	Increase	Plasma of cancer patients	Plasma of healthy controls
miR-31; miR-181b; miR-92a; miR-203	Decrease	Plasma of cancer patients	Plasma of healthy controls
miR-21	Increase	Colorectal cancer	Normal colonic tissue
miR-143	Decrease	Colorectal cancer	Normal colonic tissue
miR-21; miR-224; miR-96; miR-31; miR-155	Increase	Colorectal cancer	Normal colonic tissue
miR-21	Increase	Liver metastasis of colorectal cancer	Normal colonic tissue

MicroRNA	Change in the target tissue compared to the control	Target tissue or body liquid	Control tissues or body liquid
miR-143	Decrease	Liver metastasis of colorectal cancer	Normal colonic tissue
miR-21	No difference	Liver metastasis of colorectal cancer	Colorectal cancer
miR-143	Decrease	Liver metastasis of colorectal cancer	Colorectal cancer
miR-150; miR-125b-2; miR-1179; miR139-3p	Increase	Colorectal cancer with liver metastasis	Colorectal cancer without distant metastasis
miR-93; miR-548e; miR-19b; miR-96; miR-548c-5p; miR-140-5p; miR-19a; miR-17-5p:9.1; miR-101; miR-579; miR-18b; miR-18a; miR-455-5p; miR-549; miR-219-5p; miR-33b; miR-330-5p; miR-301a	Decrease	Colorectal cancer with liver metastasis	Colorectal cancer without distant metastasis
miR-196a-5p; miR-200b-3p; miR-223-3p	Decrease	Colorectal cancer with liver metastasis	Colorectal cancer without distant metastasis
miR-UL70-3p; miR-154-5p; miR-221-3p; miR-301b; miR-320b; miR-371a-5p; miR-486-5p; miR-572; miR-654-3p; miR-923	Increase	Colorectal cancer with liver metastasis	Colorectal cancer without distant metastasis
miR-29c	Decrease	Colorectal cancer with liver metastasis	Colorectal cancer without distant metastasis
miR-29c	Increase	Liver metastasis of colorectal cancer	Colorectal cancer
miR-21; miR-31; miR-93; miR-103	Increase	Colorectal cancer	Normal tissues
miR-566	Decrease	Colorectal cancer	Normal tissues
miR-21; miR-31; miR-93	Increase	Liver metastasis of colorectal cancer	Normal tissues
miR-21	Increase	Lymph node metastasis	Normal tissues
miR-181a	Increase	Colorectal cancer with liver metastasis	Colorectal cancer without liver metastasis

[1]References: [12, 64–69].

Table 4. MiRNAs in colorectal cancer[1]

Prognostic value has been reported regarding has been reported. In colorectal cancer, shorter disease-free interval was found in patients who exhibited higher miR-21 and higher miR-143

levels in tumour tissues. Notably, in this study, higher miR-21 and lower miR-143 was found in cancer and liver metastases in comparison to normal colonic and liver tissues [67]. The seeming logic discrepancy between the prognostic levels and the differences in normal and neoplastic tissues suggests multiple mechanisms of a single miRNA. These findings are warning about high complexity in the elaboration of diagnostic tests. MiRNAs have also been explored to predict the response to treatment. Thus, increased plasma concentrations of miR-106a, miR-484 and miR-130 are associated with lack of response to oxaliplatin-based treatment [48, 70]. Similar markers would be valuable to identify patients that would benefit from preoperative tumour burden reduction by chemotherapy. The predicted nonresponders could be treated by ablation techniques. As miRNAs function as large genomic switches, they are also attractive potential targets of therapy [11].

6. Biopsy in the differential diagnostics of liver lesions

Biopsy evaluation can yield reliable diagnosis of colorectal cancer. The tubular and cribrous glandular architecture in combination with high cylindrical neoplastic cells frequently is straightforward (Figure 1). Upon necessity, immunohistochemical evaluation can be applied as colorectal cancer is characterised by specific markers. Thus, the cytoplasmic expression of cytokeratin 20 (Figure 2) and nuclear presence of CDX2 protein (Figure 3) is virtually diagnostic of colorectal cancer.
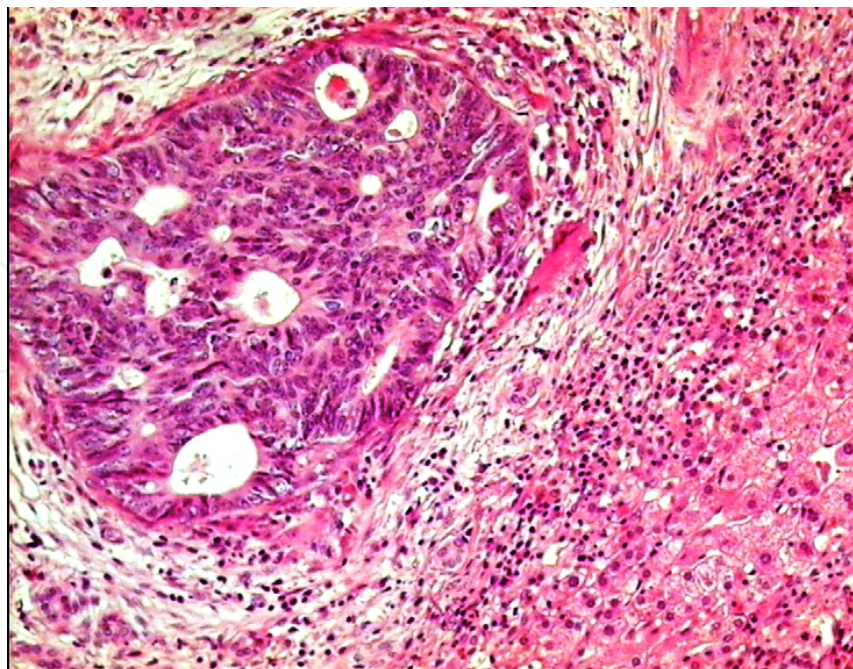

Figure 1. Metastasis of colorectal cancer in liver tissue. Haematoxylin–eosin, original magnification 50×.
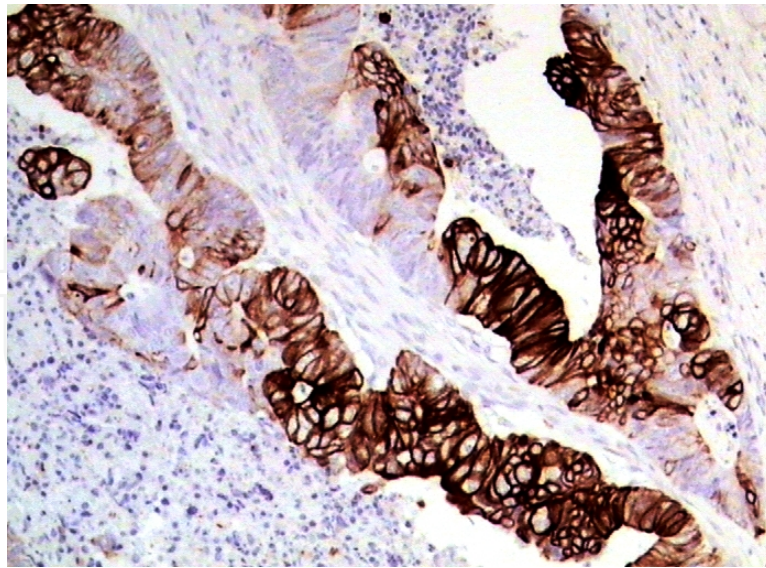
Figure 2. Intense cytoplasmic expression of cytokeratin 20 in colorectal cancer. Note the heterogeneity. Immunoperoxidase, anti-cytokeratin 20, original magnification 50×.
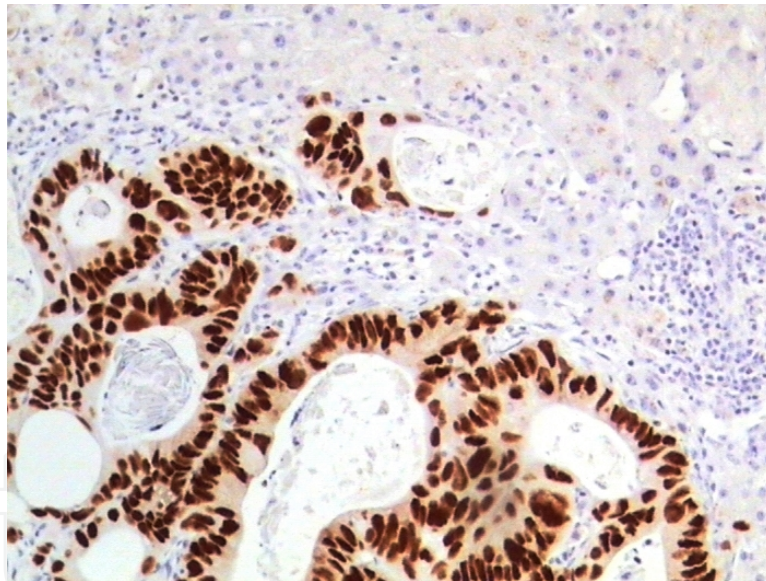

Figure 3. Diffuse intense nuclear expression of CDX2 in colorectal cancer. Immunoperoxidase, anti-CDX2, original magnification 100×.

In contrast to many other metastatic carcinomas, colorectal cancer lacks cytokeratin 7. Metastatic neuroendocrine tumours (Figures 4 and 5) can be excluded by the absence of chromogranin A, synaptophysin and CD56. The combination of several neuroendocrine markers is advisable, especially in a patient with clinically and/or endoscopically identified colorectal tumour, due to differential expression of these markers by gut origin (foregut *versus* midgut *versus* hindgut). The clinical relevance of correct differential diagnosis between metastatic colorectal adenocarcinoma and neuroendocrine tumours is high.
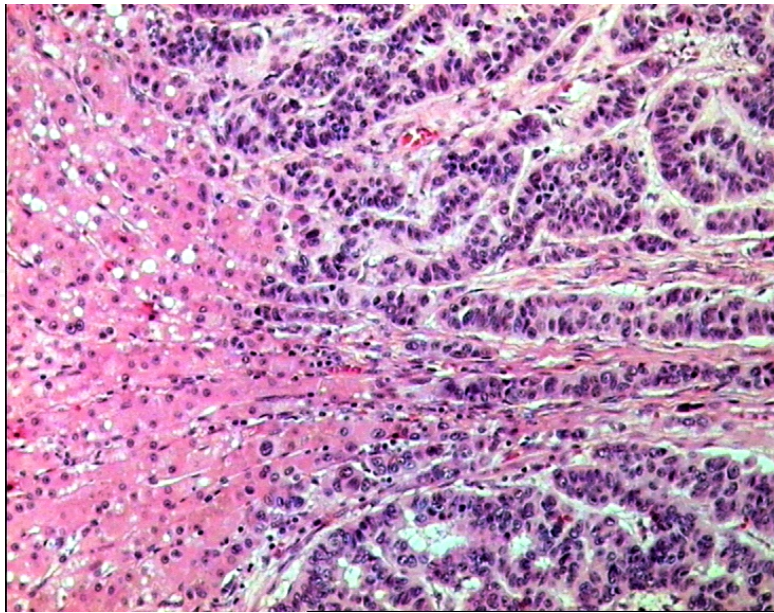
Figure 4. Metastasis of neuroendocrine carcinoma in the liver tissue. Haematoxylin–eosin, original magnification 50×.
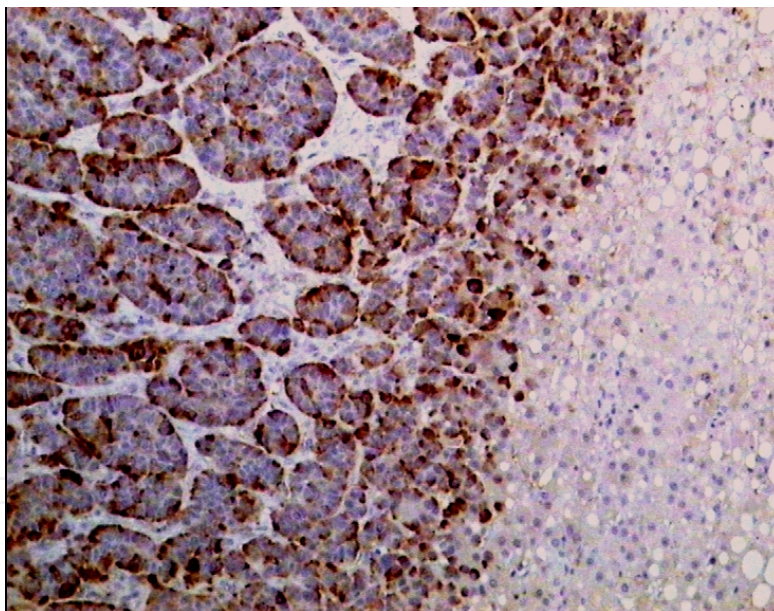

Figure 5. Metastasis of neuroendocrine carcinoma in the liver tissue. Immunoperoxidase, anti-chromogranin A, original magnification 50×.

In contrast to hepatocellular carcinoma, colorectal cancer lacks hepatocyte antigen, glypican and cytoplasmic TTF-1 expression. Alpha-fetoprotein is absent from colorectal cancer tissues, although the differential diagnostic value is lower because of relatively infrequent expression in hepatocellular carcinoma. CD10 can be misleading in the differential diagnosis of hepatocellular and metastatic colorectal cancer. Hepatocellular cancer mostly develops in the background of liver cirrhosis while metastases are rare in cirrhotic liver. However, hepatocel-

lular carcinoma, and especially fibrolamellar variant, can arise in the absence of cirrhosis. In contrast, colorectal cancer metastasis can be surrounded by liver tissue that is damaged by peritumoural or treatment-related cell damage, fibrosis and inflammation [71].

The tissue analysis of cardinal tumour features and cancer microenvironment, production of cytokinesand growth factors in the metastasis, evaluation of circulating neoplastic cells, analysis of tumour hypoxia and angiogenesis atprotein, gene and miRNA levels can also bring prognostic and predictive information [72–77]. Besides the tumour characteristics, hepatic lymphatic anatomy and its involvement by tumour can be evaluated to predict the recurrence [15].

7. Surgical treatment of the liver metastasis of colorectal cancer

The prognosis of metastatic colorectal cancer is serious. The 5-year survival of patients receiving chemotherapy is low. In contrast, hepatic metastasectomy is an accepted procedure with low perioperative mortality (2.3–2.8%) ensuring 5-year survival 28–58% and 10-year survival 22-36% [15, 18, 78, 79]. The median survival of surgically treated patients is 42.5 months [4].

The CRC metastases can be treated surgically if all metastases can be completely resected, at least 2 adjacent liver segments can be spared and sufficient liver function is expected [1].

The liver is composed of segments defined by vascular branching. As described by the International Hepato-Pancreato-Biliary Association, the liver segments are unified in four sections: left lateral and medial, right lateral and medial. Thus, segmentectomy, singular sectionectomy, hemihepatectomy involving two sections and trisectionectomy can be performed [4]. Nonanatomic liver resection shows no differences from anatomic resection regarding morbidity, mortality, recurrence rate or survival. In addition, it has the benefit of parenchymal sparing providing more opportunities for repeated resections that are usually limited by insufficient remnant liver. Nonanatomic resections can be carried out during shorter operation time and are associated with less blood loss [80].

Extrahepatic vascular anatomy must be carefully considered before the operation as only 55% of persons have typical arterial anatomy. Aberrant right hepatic arteries can arise from superior mesenteric artery and from left gastric artery. The trifurcation of portal vein can be observed. Computed tomography is the method of choice for vascular imaging [4].

Liver resection necessitates parenchymal dissection and haemostasis. The liver parenchyma can be divided by finger-fracture or crush-clamp technique, by scissors using scratch or sharp dissection technique, or by ultrasound or radiofrequency knives. Small vessels must be occluded by bipolar coagulation, titan clipping or ligation. Bipolar or ultrasound coagulation devices can be used for dissection and closure of small vessels. Larger vessels must be ligated. Liver resection with staplers involves tissue dissection and automatic vessel clamping [4].

To limit the bleeding, total inflow occlusion can be used but can result in ischemia/reperfusion injury if prolonged. Intermittent occlusion (15 min, alternating with 5 min of perfusion) better

preserves liver function. Bleeding from hepatic veins can be decreased by low central venous pressure (less than 4 mm Hg) or total vascular occlusion of the liver with or without in-situ cooling of the liver [4].

Laparoscopic approach sincreasinglyapplied for liver resections, including even hemihepatectomy [4, 81]. The best indications for laparoscopic resection are single metastases, not exceeding 5 cm in diameter, in readily accessible segments 2–6. In contrast, segments 1, 7 and 8 are considered difficult to access except for skilled professionals. Single incision laparoscopic surgery has been used for liver resection but faces technical difficulties in spatial manoeuvres with the instruments. As human ergonomics is limited, robotic surgery has been developed and applied for liver resections facilitating the manipulations with the instruments and improving the overview of operating field at the expense of remote contact with tissues and patient. The lack of tactile feedback compromises the estimation of interaction strength and pressure applied on the tissues. The conversion to open operation necessitates reorganisation of the operation team [82]. Despite these shortcomings, in a recent review, robotic liver resection was found to be a safe procedure [83]. Robotic malfunction is rare (2.4–4.5%). Major hepatectomies have been performed by robotic surgery [82]. However, the greatest advance of robotic surgery can be the possibility to remove small, but hardly accessible lesions by small sectoral, segmental or subsegmental resections instead of extensive routine liver resection [82, 84].

The surgical treatment can be precluded by involvement of portal vein, hepatic artery or common bile duct. The goal of surgery is to resect all malignant tissue. If this would lead to insufficient remnant liver, as in case of multiple bilobar metastases or deep metastases close to hilum or major vessels, the surgery also is contraindicated [18]. To increase the size of liver remnant, two-stage hepatectomy [85] or portal vein embolisation or ligation can be applied. Both procedures take advantage of the regenerative capacity of the liver [4]. Portal vein embolisation increases the resectability rate [86]. The portal vein occlusion can be performed as intraoperative ligation of portal vein branches, transileocolic embolisation or percutaneous transhepatic ipsilateral or contralateral embolisation. The spectrum of applied embolisation materials includes polyvinyl alcohol particles, coils, gelatine sponge, fibrin glue, lipoiodol or butyl cyanoacrylate. In a recent review, authors showed that preoperative portal vein embolisation has a high technical and clinical success rate. Liver cirrhosis impaired the regeneration. However, cirrhosis is rarely encountered in association with metastatic cancers. Cholestasis and preceding chemotherapy had no negative impact [87]. The resectability can also be improved by chemotherapy-induced downstaging [86, 88, 89]. By chemotherapy, resectability can be achieved in up to 40% of patients [90]. If the downstaging is successful and followed by the resection, the 5-year survival reaches 33% that is comparable with the results in patients with initially resectable metastases [86]. Preoperative chemotherapy is not indicated for resectable lesions [89] and should not be excessively extended (9 cycles or more) to avoid marked hepatotoxicity without improving the pathologic response [91]. Among the chemotherapy-related liver damage, steatosis can be induced by 5-fluorouracil, nonalcoholic steatohepatitis by irinotecan and sinusoidal obstruction syndrome by oxaliplatin [92]. For successful downstaging, the type of chemotherapy is more important than the number of

cycles. Thus, the inclusion of bevacizumab in the chemotherapy schedule in addition to FOLFOX improves the outcome in terms of achieving resectability [91].

The planning of liver surgery can be challenging in patients presenting with colorectal cancer and synchronous liver metastases. Simultaneous resection of primary tumours and liver metastases can be performed in selected patients. Liver resection can safely be performed as the first operation followed by the large bowel operation [93]. The safety of liver-first approach has been confirmed in a recent review [94].

The risk factors of cancer recurrence include the presence of lymph node or extrahepatic metastases, high CEA (above 200 ng/mL), multiple and large (above 5 cm) metastases, short disease-free survival [18], high tumour grade and positive resection lines [4]. Regarding the resection line, the minimal requirements are under discussion regarding R0 resection with distance between tumour and resection line less than 1 cm. In the recent literature, lack of 1 cm margin is not considered a contraindication for liver resection [80], and generally the requirement for tumour-free tissue border has decreased from 10 to 2 mm or even 0 mm [95–98]. The presence of hilar lymph node metastases is an adverse prognostic factor in comparison to metastases affecting only liver but can be less hazardous in prognostic terms than metastases in lymph nodes adjacent to truncus coeliacus or aorta [4].

After resection, MRI or CT should be used for surveillance. The examinations must be repeated every 3–6 months for 2 years after resection and every 6 months for 3–5 years after the surgery [1]. Perioperative chemotherapy, including adjuvant treatment, increases recurrence-free survival [99].

8. Liver transplantation for colorectal cancer metastases

Liver transplantation is indicated for end-stage chronic liver disease and acute liver failure. In addition, transplantation has certain indications regarding malignant tumours. The classic indications include hepatocellular carcinoma on the background of liver cirrhosis if the patient corresponds to the Milan criteria; fibrolamellar hepatocellular carcinoma, hepatoblastoma and epithelioid haemangioendothelioma. Transplantation is researched in patients having hepatocellular carcinoma with tumour burden exceeding the Milan criteria, hepatocellular carcinoma in noncirrhotic liver, cholangiocellular cancer and liver metastases from neuroendocrine tumours. Hepatocellular carcinoma with extrahepatic spread or portal vein invasion, hepatoblastoma with uncontrolled extrahepatic spread and other malignancies are regarded as contraindications for liver transplantation. Thus, until recently, colorectal cancer metastases to the liver also were considered a contraindication for liver transplantation [100] due to allocation justice in the background of organ shortage and due to the risk of tumour recurrence on the background of immunosuppression.

A revolutionary approach has been undertaken in Norway by Hagness et al. offering liver transplantation to patients with unresectable liver metastases of colorectal cancer. The resulting life quality was good. The 5-year survival was 60%, that exceeds the survival

obtained by chemotherapy and is comparable to the survival after liver resection in suitable cases [9].

Interestingly, the recurrence patterns after liver transplantation differ from those after liver resection. The most frequent event is single-site recurrence in the lungs, followed by recurrence in multiple sites. In the present group of patients, no single-site recurrences in liver were observed, although the liver was involved by tumour metastases in patients having recurrence in multiple sites. Regarding the outcome, the pulmonary metastases followed indolent course, but metastases to the transplanted liver were prognostically adverse. The immunosuppressive treatment did not enhance the growth of those pulmonary metastases that were present at the time of transplantation [9]. The m-TOR inhibitors used for immunosuppression can have beneficial influence as they block angiogenesis and proliferation [9, 100].

9. Nonsurgical treatment of liver metastases of colorectal cancer

Although surgical treatment ensures the best 5-year survival, only 15–25% of liver metastases are amenable to resection [98]. If surgical treatment is not possible, radiofrequency ablation, cryotherapy, microwave ablation, stereotactic body radiotherapy, radioembolisation or percutaneous alcohol injection canbe used to decrease the tumour burden [101, 102]. Generally, ablation therapies are not recommended for resectable lesions [103].

The liver metastases can be targeted by radiofrequency ablation although the benefits of it are controversial. Positive estimates have been published [104, 105]. However, later data showed that radiofrequency ablation alone or in combination with surgery resulted in inferior survival in comparison with liver resection. The outcome of radiofrequency ablation was only slightly better than the results of chemotherapy [39]. The resulting 5-year survival was around 24% [106–110]. Still later, 5-year survival of 43% has been reported [98]. After the procedure, either local recurrence or new liver metastases can develop. The risk of local recurrence is higher if the lesion is larger than 3 cm: 21.7% vs. 1.6–3.8% [111–113]. The development of new metastases predominates over local recurrence and can be promoted by liver regeneration and production of cytokines [98, 113]. To avoid complications, proximity to bile ducts but not vessels is of utmost importance as the blood vessels are moderately sensitive to heat and can be protected by vascular clamping and Pringle manoeuvre involving alternation of clamping and perfusion. In contrast, bile ducts are very sensitive to heat-induced damage [113].

Radiofrequency ablation belongs to the group of thermal ablation procedures comprising also laser-induced interstitial thermotherapy. In this method, laser light is directly transmitted to the neoplastic tissue through flexible optic fibres, and the absorption of laser photon energy causes local rise of temperature inducing coagulation necrosis. The results are highly dependent on the completeness of tumour destruction. The 5-year survival after thermal ablation is 44% if the ablation is complete and 20% if it is partial. The frequency of partial ablation ranges from 38% to 52% [114–116]. The size of neoplastic mass is the main predictive factor for the completeness of the ablation, with better results achieved in metastases smaller than 3 cm [116, 117].

Cryoablation involves tissue destruction by low temperature, i.e., intended freezing of the target in order to induce local necrosis. Although percutaneous, laparoscopic or open surgical approach generally is possible, cryotreatment of liver tumours is mostly performed via open surgical access. Occasionally, laparoscopic approach is used [118]. The temperature is decreased by liquid nitrogen or argon gas that is delivered to the target by special probe under US guidance. The freezing is rapid, so the formed ice crystals destroy the cells, including tumour cells. Ice crystals also propagate in the microvessels. The procedure includes alternating cycles of freezing and thawing. Multiple masses are treated consecutively rather than simultaneously. Necrosis develops within the next 2 days and is well-demarcated in the third to fourth day after the procedure. Large masses (>5 cm) are not amenable to complete treatment. Another limitation includes tumours close to large blood vessels [119]. Cryoablation ensures 5-year survival in 17% of patients [109, 120–122].

In microwave ablation, tissue destruction is induced by microwaves. The electrode is inserted in the tumour mass under US or CT guidance using percutaneous, laparoscopic or open surgical access. An alternating high-frequency (900–2450 Hz) electromagnetic field induces vibration of water molecules representing dipoles. The energy created by the induced movement of water molecules is released as heat that results in coagulative necrosis [3]. The method can ensure wider and quicker tissue destruction than radiofrequency ablation. It is not limited by the temperature 100°C, does not rely on the conduction of electricity and is less limited by impedance of the destroyed tissues or scars [123]. The 5-year survival after microwave ablation was 16% in the older reports [109, 124, 125]. Recently, intraoperative microwave ablation ensured 4-year survival of 35.2% [123] and 3-year survival of 36% [126].

External beam radiation treatment for liver metastases has limited effect due to high sensitivity of hepatocytes towards ionising radiation. Thus, therapeutic radiation doses would induce serious liver damage but small doses lack efficacy. The treatment of liver metastases by external beam radiation is associated with high rate of local recurrence and side effects, both contributing to low survival. Three-dimensional conformal radiotherapy is more targeted. In stereotactic body radiation treatment, a robotic arm is used to target the lesion in synchronisation with the respiratory movements. This allows delivering higher radiation dose to the lesion while retaining appropriate safety profile with only tolerable complications. After stereotactic body radiation treatment, the 1-year survival of complex, pretreated patients with the frequent presence of extrahepatic metastases was 45.5% [110]. The 2-year survival is reported to be 45% [127].

Hepatic arterial infusion can be applied due to the fact that metastases larger than 3 mm receive 95% of blood supply from the hepatic artery. This technique yields higher concentration (up to 16 times higher) of the medication within the metastasis in association with lower systemic toxicity due to concentrated supply and first-pass effect with maximum absorption in the liver. Skilled team and qualitative radiologic imaging are the prerequisites [102]. There are several technically related approaches that also involve direct supply of the therapeutic agent to the target via hepatic artery, such as placement of hepatic arterial infusion pumps, selective internal radiation therapy, drug-eluting bead embolisation and irinotecan-containing drug-eluting particles [128].

Although successful surgery can yield long term survival, recurrence develops either in liver or in other distant sites in 60–70% of patients [15]. Therefore, adjuvant systemic chemotherapy, hepatic arterial infusion chemotherapy and molecular targeted therapy represent important adjuncts to surgical treatment. Systemic chemotherapy results in significantly better survival [129, 130] but can cause systemic adverse effects along with vascular liver damage and steatosis [131]. Hepatic arterial infusion of specific chemotherapeutic agents has the benefits of directly targeting the metastasis within liver and thus causing less systemic toxicity. However, biliary tract damage can follow [132, 133]. Monoclonal antibodies against VEGF and EGFR are attractive by the targeted mechanism [101, 134]. However, bevacizumab, cetuximab and panitumumab have also caused controversies regarding liver metastases of colorectal cancer [13].

10. Radiologic evaluation before nonsurgical treatment

In general, the metastatic process must be characterised similarly as before the operation. If ablation is planned, the relation between the metastasis and the intrahepatic bile ducts and vessels must be carefully established to avoid heat-induced damage [1]. If the medical centre has the necessary skills to provide hepatic artery infusion with chemotherapeutic agents for neoadjuvant therapy to decrease lesion size and allow resection, for adjuvant for treatment after resection or treatment of unresectable liver disease, hepatic artery must be visualised by CT angiography [18].

11. Radiologic assessment of the treatment outcome

Classically, the tumour response to treatment is measured by decrease of the tumour mass diameter as defined by the Response Evaluation Criteria in Solid Tumours (RECIST). The RECIST criteria, described in 2000 and refined in 2009 [1, 135, 136], necessitate one-dimensional measurements to detect the sum of maximal diameter of five lesions. The relative difference of this parameter before and after treatment is interpreted as follows: progressive disease, increase of at least 20% and at least 5 mm in the sum, or appearance of a new lesion; stable disease, lack of dynamics or changes within the borders between progressive disease and partial response; partial response, decrease for at least 30%; and complete radiologic response, disappearance of all lesions. It must be emphasised that radiologic complete response is not always equivalent to pathologic complete response; therefore, all the responded lesions still must be removed surgically [17]. Several controversies exist regarding RECIST criteria. First, it is suggested that early response for 10% correlates with the outcome better than the border of 30% [17, 137]. Further, not only size but also the composition of the mass lesion matters as it can include not only viable tumour but also necrosis, fibrosis, granulations or haemorrhage. By ablation techniques, the surrounding liver tissue is intentionally damaged and fuses together with the metastatic mass. After intra-arterial treatment by chemotherapy, drug-eluting beads, irinotecan drug-eluting beads or radio embolisation, the response evaluation is

confounded by haemorrhage, necrosis resulting in size enlargement, peripheral thin rim of granulation tissue mimicking metastasis, fibrosis, peritumoural ischemia or hepatitis [1]. Therefore, the evaluation of treatment response includes not only the changes in the lesion size, but also its morphology and functional status [17].

Morphologic radiologic features, including changes in tumour heterogeneity and internal structure, enhancement and margins, can indicate favourable tumour response to treatment [138]. On CT, CRC metastases in the liver have heterogeneous structure and ill-defined margins. Responding lesions obtain homogeneous structure and outlined margins [17]. The morphologic response on CT correlates with pathologic response and with the survival [138].

PET-CT characterises the metabolic activity in the lesions [1], suggesting pathogenetically substantiated accurate estimate of tumour response. However, the sensitivity of PET decreases after chemotherapy [17]. Clinically importantly, PET can identify lack of chemotherapy efficacy just after 1 cycle [139].

Preceding treatment can induce not only tumour shrinkage but also liver parenchymal damage. By CT, steatosis that affects more than 30% of parenchyma can be diagnosed by the liver attenuation index characterising the difference in the attenuation between liver and spleen. By MRI, the analysis of water and fat proton signals is possible, leading to more accurate estimates of steatosis than by CT and US [1, 140]. Sinusoid obstructive syndrome can be caused by oxaliplatin-based chemotherapy. It is characterised by sinusoidal injury that may lead to fibrosis or veno-occlusive disease. The radiologic findings are nonspecific [1].

12. Complete radiologic response

Complete radiologic response can be obtained in 5–38% of patients. The frequency of complete radiologic response depends on the efficacy of preoperative treatment and on the quality and completeness of radiologic investigation. Metastasis can become difficult to observe on CT if the size decreases and/or the surrounding liver tissue develops steatosis. MRI can be used to identify the residual lesions. The MRI-documented disappearance of the metastasis is suggestive of true complete histologic response.

The correlation between radiologic and pathologic complete response ranges 20–100% in different studies. Thus, at present, all sites of disease should be resected surgically. A fraction of lesions (up to 24% of patients with complete response on CT) can be grossly identified during the operation. Full mobilisation of liver and palpation, followed by intraoperative conventional and contrast-enhanced US, are the subsequent options rising the yield to 45% of patients. Contrast-enhanced US identifies additional 10–15% of nodules, compared with palpation and conventional ultrasonography technique. The intraoperative yield is lower in patients who have had preoperative MRI, suggesting that MRI is the method of choice to identify true small residual metastases that are missed by less sensitive CT [17].

If the radiologically regressed metastases are not resected, they tend to recur. The frequency of durable clinical response, usually defined as disease-free period for 1 year, correlates with

the frequency of complete pathologic response. The recurrence mostly develops in 10–20 months. The median time to recurrence is 11 months. The recurrence occurs more frequently in patients who have unresected radiologically disappeared metastases in comparison to those who underwent the surgery, although a more effective adjuvant treatment can diminish these differences. Hepatic arterial infusion treatment lowers the incidence of intrahepatic recurrence and increases the frequency of durable response similarly as increasing the rate of complete pathologic response [17].

13. Survival

The median survival of patients affected by metastatic colorectal cancer has increased significantly, e.g., from 27.3 months in 1994 to 39.4 months in 2007 [13]. Analogous increase in the survival is reported also by other authors [14]. The 5-year and 10-year survival can reach even 58% and 36%, correspondingly [15]. Lower 5-year survival after surgical treatment has been reported earlier, e.g., 25–40% [78, 110, 141–144], contrasting with the 5-year survival of 15% in patients with unresectable metastases [33, 145, 146]. The 10-year survival of 25–26% has been described [123, 147, 148]. Better survival is observed in case of delayed metastases [14].

14. Conclusions

1. In conclusion, liver metastases of colorectal cancer must be treated surgically whenever possible as surgery ensures the best survival.

2. Contraindications for surgery include wide tumour spread within the liver or to extrahepatic organs, expected insufficient liver remnant and poor general status. Neoadjuvant treatment should be attempted to downstage the tumour.

3. If the metastatic lesions are not amenable to surgery, ablation or radiation modalities can be applied in association with chemotherapy.

4. High-quality radiologic investigation is necessary to reveal the metastases of colorectal cancer. Magnetic resonance imaging is considered the most sensitive technique that has remarkable advantages revealing subcentimeter metastases and lesions within steatotic liver. Computed tomography benefits from high discrimination and can be used to replace magnetic resonance.

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