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ORIGINAL ARTICLE

Aggressive surgery in the multimodality treatment of liver metastases from colorectal cancer

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Summary

Purpose: *The purpose of this study was to analyze the impact of aggressive surgery concerning resection of liver metastases (LMs) from colorectal cancer (CRC) on morbidity, mortality and survival rates and to establish the benefits of multimodal strategies in increasing the resectability rates of LMs.*

Patients and methods: *From January 2004 - April 2006 184 patients with CRC underwent surgical interventions at our clinic. Thirty-four (18.4%) of them had LMs at the time of initial diagnosis, and 26 patients developed LMs in a certain period of time after resection of the primary CRC. Multimodal therapeutic approach included thermoablation, neoadjuvant chemotherapy and surgery.*

Results: *44 resections were performed in 29 patients: one-stage resection of the primary CRC and the LMs in 15 (40%) cases, resection and thermoablation after adjuvant chemotherapy in 2 (4.3%), resection after neoadjuvant chemotherapy in 8 (17.2%), two-stage liver resection in 1 (2.15%), resection after recurrence or because of a newfound LM in 3 (6.45%). Five resections of metastases larger than 5 cm, and 4 resections of 4 or more liver metastases were performed. Morbidity rate was 15.9% (bile leakage in 4 patients, liver abscess in 1 and wound disruption in 2). Mortality rate was 2.2% (1 patient).*

Conclusion: *Multimodal approach in the treatment of LMs of CRC increases resectability and patient survival and has no influence on morbidity and mortality.*

Key words: colorectal cancer, liver metastases, multimodal strategies, surgery, resectability

Introduction

About 4000 new cases of CRC are been diagnosed annually in Bulgaria [1]. Approximately 60% of the patients develop metastases, half of which are located in the liver. LMs are the most common cause of death in patients with CRC. In the last two decades patients with LMs are a target of more radical therapeutic strategies [2-9]. With the development of diagnostic imaging techniques like contrast- enhanced spiral computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and intraoperative ultrasound (IUS), an early detection of LMs could increase the possibilities for radical surgical treatment [2,10]. Surgical treatment of LMs from CRC is the most effective therapy, associated with 30-50% 5-year survival. Only 10-15% of LMs are primarily resectable. Current strategies aim to turn unresectable metastases into resectable ones with the help of neoadjuvant chemotherapy, embolization of the portal vein, two-stage hepatectomy, resection with cryotherapy, thermoablation, and "*ex vivo*" resections. Using these approaches success has been reported in 15-25% of primarily unresectable LMs [3,5,9,11-14]. Despite the proper surgical resection, recurrences are observed in about 70% of the cases. In 43% of the cases recurrences are again located in the liver, while 27% of the patients develop extrahepatic metastases [15,16].

The aim of this study was to analyze the impact of aggressive surgery in treating LMs from CRC on morbidity, mortality and survival and to establish the

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benefits of multimodal strategies in increasing the resectability rates of LMs.

Patients and methods

During the period January 2004 - September 2006 184 patients with CRC have been operated at our clinic. There were 102 (55.43%) men and 82 (44.57%) women with median age 64 years (range 34-79). In 34 (18.4%) of them LMs were present at initial CRC diagnosis and in 26 (14.1%) LMs were diagnosed after resection of the primary cancer.

In 44 out of 60 cases with LMs (no regional lymph node involvement in cases with metachronous metastases) a radical resection with clear margins and without residual disease was performed: one-stage resection of the primary tumor with LMs in 15 (25%) cases, one-stage resection of the primary tumor with resection of some of the metastases and thermoablation of the rest of them in 2 (4.5%), resection and thermoablation after neoadjuvant chemotherapy with irinotecan, 5-fluorouracil and folinic acid (FOLFIRI) in 2 (4.5%), resection after neoadjuvant chemotherapy with oxaliplatin, 5-fluorouracil and folinic acid (FOLFOX) in 8 (18%), resection of metachronous LMs in 8 (18%), two-stage liver resection in 1 (2.25%), resection after recurrence or newly appeared LMs in 4 (9%), percutaneous thermoablation (at an interval) of newly appeared LMs in 2 (4.5%), and resection after ligature of the right branch of the portal vein in 2 (4.5%) (Table 1).

In the context of aggressive surgery, resections of large metastases (>5 cm) were performed in 5 patients, with tangential resection of the inferior vena cava in 1; surgical resection of more than 4 metastases in 4; hemihepatectomy with metastasectomy in 2 patients. In 8 patients we performed one-stage major liver resection with more than 3 liver segments along with resection of the primary tumor (Table 2).

Table 1. Multimodal approaches in this series

Approach	*Patients, n*
Resection of a LM after neoadjuvant chemotherapy	8
Two-stage liver resection	1
Resection after TVO	1
Resection of the primary tumor + ligature of the right branch of the portal vein	2
Liver resection of recurrent LM	3
Resection of the primary tumor + liver resection + thermoablation	4
Total	19 (43%)

LM: liver metastasis, TVO: total vascular occlusion

Results

Pathological tumor characteristics are shown in Table 3. Grades (G) 1 and 2 prevailed (24 and 20 patients, respectively). In 53 patients the tumor infil-

Table 2. Types of liver resections

Liver resection	*Total patients (n=42)*	*%*
Right hemihepatectomy with resection of v.cava inferior	1	2.25
Right hemihepatectomy with segmentectomy	1	2.25
Right hemihepatectomy	10	22.7
Left lobectomy with bisegmentectomy	2	4.5
Left lobectomy with thermoablation	2	4.5
Left lobectomy	8	18.1
Segmental resections		
IV	1	2.25
VI	2	4.5
VIII	2	4.5
V+VI	2	4.5
VI+VII	2	4.5
V+VI+VII	2	4.5
Two-stage resection	1	2.25
Resection after portal vein ligature	2	4.5
Segmental resections with thermoablation	2	4.5
Metastasectomies	2	4.5

Table 3. Pathological tumor characteristics of the operated patients

Stage	*Grade*	*Patients, n*	*%*
pT2NxM1	G2	2	3.33
pT2N0M1	G3	2	3.33
pT2N1M1	G3	3	5
pT3NxM1	G1	2	3.33
pT3N0M1	G1	3	5
pT3N1M1	G1	10	16.76
pT3N2M1	G1	6	10
pT3NxM1	G2	2	3.33
pT3N0M1	G2	2	3.33
pT3N1M1	G2	8	13.33
pT3N2M1	G2	4	6.76
pT3N0M1	G3	1	1.67
pT3N1M1	G3	6	10
pT3N2M1	G3	2	3.33
pT4N1M1	G1	1	1.67
pT4N2M1	G1	2	3.33
pT4N1M1	G2	2	3.33
pT4N2M1	G3	2	3.33

M1 denotes liver metastases only

trated the serosa (T3), in 32 it was mucous-producing and in 46 regional nodal involvement was found: N1 in 30 patients and N2 in 16. Eight of the remaining patients were N0 and 7 Nx.

The mean hospital stay was 11 days (range 6-32). The number and size of LMs did not change survival in cases with radical resections (Figure 1). The mean survival rate in the group of patients with metachronous LMs was greater than in the group of patients with metachronous LMs (p=0.015; Figure 2). Multimodal strategies in this series increased the resectability rate to 31.6% (Figure 3). Postoperative complications were observed in 7 (15.9%) patients (Table 4).

One of the patients (2.25%) died of postoperative hepatic failure (Table 4). Aggressive surgery for LMs from CRC was performed with low morbidity and mortality. At the time of analysis one-year survival of all radically operated patients was 91%.

Discussion

Better results of the surgical treatment of LMs require proper selection of patients [4]. With the development of better surgical techniques and intensive care some of the indications for surgical treatment have changed (Table 5) [3,4,6,8,9,12,17].

Before planning a liver resection it is necessary to prove the absence of local CRC recurrences and extrahepatic dissemination, find the exact localization, and measure the liver parenchyma involved. IUS is a standard diagnostic technique before liver resection. Up to 20% of the LMs can be detected by IUS if not

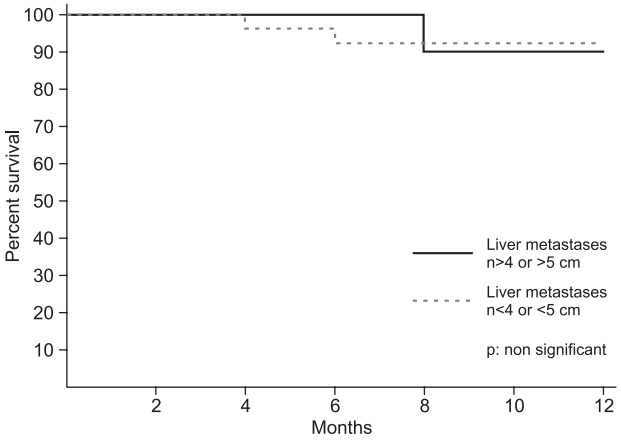

Figure 1. One-year survival after radical resections.

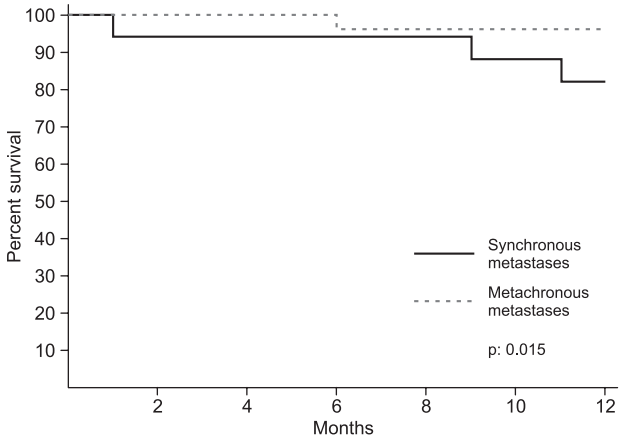

Figure 2. One-year survival after radical resections.

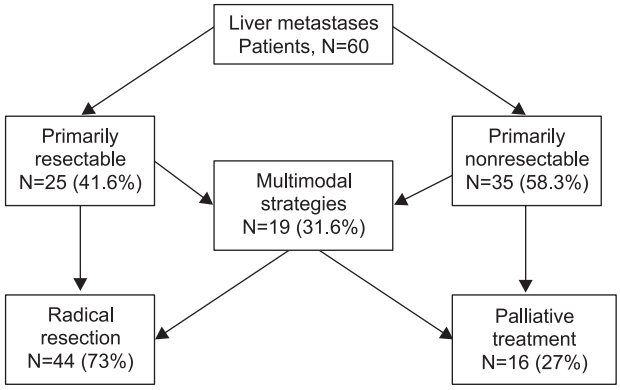

Figure 3. Increase of resectability with multimodal approach.

Table 4. Complications and mortality

Complication	*Patients, n*	*%*
Death	1	2.25
Liver abscess	1	2.25
Bile leakage	4	9.09
Wound disruption	2	4.5
Total	8	18.09

Table 5. Changed indications for surgery of CRC LMs

Conventional indications	*Contemporary aggressive approach*
< 4 unilobar LM	No limitations - multiple bilobar metastases are treated after neoadjuvant chemotherapy/resection/ablation
Size < 5 cm	No limitations
Without extrahepatic spread	1-3 lung metastases can be resected
Margin > 1 cm	Margin < 1 cm should be treated by ablation (cryotherapy, radiofrequent ablation)
Insufficient volume of the remaining liver parenchyma	Preoperative embolization/ligature of the portal vein and two-stage resection for increasing the remaining liver volume
Resection of all macroscopically detected lesions	Resection combined with ablation

CRC: colorectal cancer, LM: liver metastasis

detected by palpation or before the operation. We performed IUS in all of the cases. In practice we used the Japanese classification for grouping LMs (Table 6).

The aim of the surgical treatment of LMs is resection with a margin of at least 1cm of healthy liver parenchyma. To avoid postoperative development of liver failure, enough of the liver parenchyma should remain. Preoperative liver function is a factor that limits the liver resection and defines the risk of postoperative liver failure. Removal of more than 70-75% of healthy liver parenchyma and 60% of the parenchyma of a cirrhotic liver leads to hepatic failure. In patients with neoadjuvant chemotherapy, a larger volume of the liver should remain after the resection. For the preoperative assessment of the remaining liver volume after the operation a CT-volumetry is used [3].

The optimal time between setting the diagnosis and performing the resection is also a matter of concern. Usually the resection is performed immediately after the diagnosis no matter whether the metastases are synchronous or metachronous. Multiple smaller metastases, localized in different segments, demanding major liver resections are observed for a period of about 3 months during which they are treated with neoadjuvant chemotherapy. The absence of development of new LMs is an indication for operative treatment [2,5,9]. We consider that metastases assessed as primarily resectable should be resected immediately and the unresectable ones should be treated with multimodal strategies which can increase resectability up to 20-25%. Neoadjuvant chemotherapy may achieve downstaging and lead to surgical resection at a second stage. Even if the tumor is technically resectable, a radical surgery might be contraindicated because of the small volume of the remaining liver parenchyma. In such cases preoperative embolization/ligature of the relevant branch of the portal vein (EPV/LPV) could be performed to induce atrophy of the correspondent lobe and hypertrophy of the contralateral lobe of the liver. Adequate hypertrophy is present 4-5 weeks after the EPV. In most of the cases, despite downstaging procedures, a resection is not performed because of disease progression and/or extrahepatic involvement [2,3,9, 13,18,19]. Chemotherapy after EPV helps to reduce tumor progression without influencing liver hypertrophy [2].

Table 6. Number of patients in this series according to the Japanese classification for LM

Japanese classification		*Resections, n*
H1	Single or multiple LM in one of the liver lobes	25
H2	Multiple LMs in one of the lobes and single in the other lobe	16
H3	Multiple LMs in both liver lobes	3

LM: liver metastasis

Patients, whose tumors are primarily unresectable because of large bilobar lesions, can be treated with two-stage liver resections. The second stage is indicated only if there is an adequate healthy liver regeneration and absence of disease progression [5]. One or two months are necessary for the liver to gain 80% regeneration. Chemotherapy may be administered between the two stages of resection to reduce tumor progression in the regenerating part of the liver, as well as in other parts of the body.

LMs that involve hepatic veins or the inferior vena cava cannot be resected with the standard surgical techniques because of possible life-threatening bleeding [12]. Most of the LMs can be resected with the help of total vascular occlusion (TVO). TVO should be applied carefully in major vascular resections and reconstructions with synthetic prostheses and when the warm ischemia time is expected to be more than one hour [2]. The upper boundary of liver tolerance towards warm ischemia time is 120 min with intermittent clamping of the blood flow in 10 min intervals. In these cases a possibility for radical operation turns out to be the "*ex vivo*" technique. A hypothermic liver perfusion and venovenous bypass are used. This gives the possibility for extraordinary liver and vascular resections. After the tumor resection the liver is reimplanted. In the "*in situ*" technique the liver blood flow is clamped as in TVO, but the liver is perfused with hypothermic solution for increasing the time of tolerance to ischemia up to 4 h [2,3,5,19-21]. In H2 and H3 patients (Japanese classification), when curative surgery is impossible with the above mentioned methods, a resection and intraoperative radiofrequent ablation could be performed for obtaining local control and better survival.

The most significant complications of liver resections are bleeding during and after the operation as well as the development of hepatic failure. Operative blood loss and blood transfusion are significant prognostic factors of morbidity after liver resection. Contemporary possibilities for vascular control during resection, anesthesia supporting lower blood pressure and better surgical techniques lead to minimal blood loss and minimal need for blood transfusion. Low blood pressure, anesthesia and preconditioning significantly reduce blood loss and morbidity in comparison to patients to whom these techniques have not been used. Changes in hemostasis may lead to postoperative bleeding. Prophylaxis from such kind of bleed-

ing is obtained by administering fresh frozen plasma 10 ml/kg every 6-12 h [6]. Other complications that are observed are bile leakage, pleural effusions and wound infection.

The presence of LMs is not a sign of incurability. Adequate resection can lead to 16-22% 10-year survival [2,4,16,21].

Strategies for downstaging and aggressive surgical treatment may increase resectability in CRC LMs more than 20%, leading to improved results without influencing perioperative morbidity and mortality.

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