Coll. Antropol. **24** (2000) 2: 381–390
UDC 616.351-006.6:616-089.87
Original scientific paper

Safety of Simultaneous Resections of Colorectal Cancer and Liver Metastases

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A B S T R A C T

Liver resection is the only potentially curative method for patients with colorectal cancer metastases and 5-year survival rates are 20% – 40%. Simultaneous resection of colorectal cancer and synchronous liver metastases has been recommended if minor hepatectomy is indicated. The purpose of this paper is to analyze the treatment of hepatic colorectal secondaries and to assess the safety of simultaneous and delayed liver resections and relations of morbidity to the extensiveness of hepatectomy and perioperative factors. Analyzed were 21 patients with liver metastases from colorectal cancer operated between 1997 and 1999 in the Clinical Hospital »Sestre milosrdnice«. Operating time for simultaneous colorectal and liver resections was not significantly longer compared to liver resections alone. No significant difference in complication rate was found after simultaneous procedures and liver resection alone (38% vs. 31%). Complication rate after major liver resections was not significantly greater than after minor resections (38% vs. 31%). No statistically significant differences were found in operation time and blood replacement between patients who developed postoperative complications and those who did not. In conclusion, simultaneous resections of primary colorectal cancer and liver metastases may be considered safe. Morbidity rates are not significantly different from those after liver resections alone, nor depend significantly upon the extensiveness of liver resection, providing that the operation time and blood loss are within the range observed in this study.

Received for publication April 3, 2000.

Introduction

Colorectal cancer is the second most common cancer in the countries of the western world[1]. Liver is the most common site of spread for colorectal malignancies. In about 20% of patients liver metastases are diagnosed at the time of the primary tumor resection. In another 25% they are diagnosed some time after the operation of primary tumor, mostly within 2 years[2,3]. If left untreated, patients with liver metastases from colorectal cancer have a very poor survival[4]. However, with surgical resection of the operable metastatic lesions, their chances of five-year survival increase to about 20% – 40%[5]. Liver resection for metastases of colorectal malignancies is thereby established as the only treatment modality that can offer a chance for cure[5].

Previous standards in treating colorectal liver metastases included a period of 3-4 months between the resection of colorectal malignancy and metastases to the liver. Such an approach allowed a better selection of patients and evaluation for local, regional or extrahepatic metastases before a decision was made to perform liver resection[6].

Simultaneous resection of primary colorectal neoplasm and synchronous liver metastases has been increasingly accepted, but only for selected patients in good general condition in which liver metastases can be removed by the means of minor hepatectomy[7] when such approach is considered safe[5–9]. Such a combined surgical approach is theoretically wise and supported by the results of metastatic growth showing that two-stage approach in the treatment of synchronous liver metastases has no oncological justification[10]. The stress caused by surgery may accelerate the growth of liver metastases and waiting several months between primary surgery and liver resection provides only 5%–10% chance of revealing additional metastases[10]. However, there are authors who believe that simultaneous resections of primary colorectal cancer and liver metastasis may be responsible for high operative mortality[11] and morbidity[12,13] rate and do not recommend it[14]. Morbidity after liver resection still represents a significant problem[15], with reported morbidity between 8%–57%[12] so that the safety of simultaneous colorectal and liver resections is still controversial [7,13].

Since indications for liver resection have been extended to older patients and those with multiple, large and bilobar liver metastases, with more aggressive surgical approach that includes anatomic resections rather than wedge resections[14,16], the safety of simultaneous colorectal and liver resections needs to be reassessed.

The purpose of this research is to analyze the treatment of colorectal malignancies with liver metastases and to re assess the safety of simultaneous resections of primary colorectal neoplasm and liver metastasis by comparing patients with simultaneous and delayed liver resections in regard to the extensiveness of hepatectomy, perioperative factors, and liver function tests as well as their impact on postoperative complications.

Patients and Methods

Retrospective analysis of the available records of 21 patients with liver resections for metastases from colorectal malignancy operated between 1997 and 1999 in the Clinical Hospital »Sestre milosrdnice« was performed. Of these patients 9 had synchronous metastases and 8 were subjected to simultaneous resection of primary colorectal neoplasm and liver metastasis, whereas in one patient with too small estimated postoperative liver volume, liver resection was postponed for one month to allow liver hypertrophy after selective portal ligation.

Thirteen patients had delayed resection of liver metastases some time after the resection of primary colorectal cancer (median 24 months, range 1–48 months) and liver resection alone was performed in these patients. The median age of our patients was 61 years (range 30 – 76 years). All patients spent variable time after surgery in the intensive care unit (ICU) before they were admitted to wards.

Data regarding liver resection were collected from admission records, surgeon's and anesthesiologist's reports, ICU patient's status sheets, blood tests performed during the first 24 hours of their stay in the ICU and patohystologycal ex-

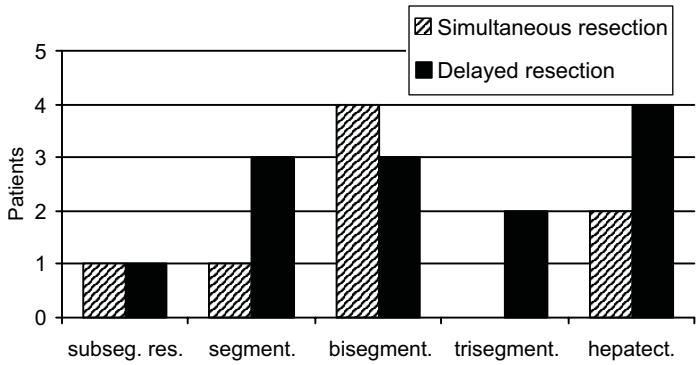

Fig. 1. The frequencies of types of liver resection in simultaneously resected patients and those undergoing delayed liver resection. Subseg. res. = small, non-anatomycal subsegmental resections; segment. = segmentectomies; bisegment. = bisegmentectomies; trisegment. = trisegmentectomies; hepatect. = hemihepatectomies.

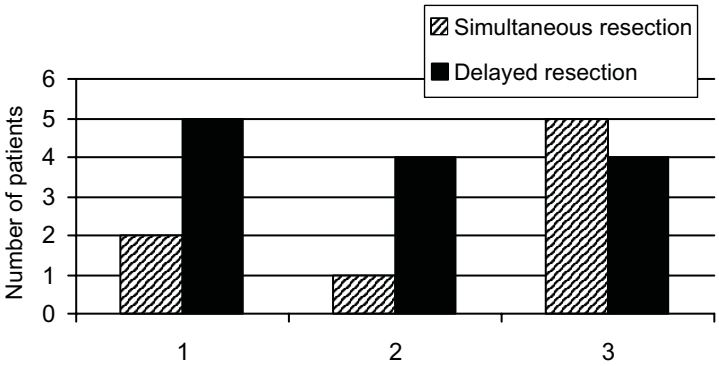

Fig. 2. The staging of liver metastases according to Gennari's classification in groups of patients who underwent simultaneous or delayed resection. Values on horizontal axis represent stages of liver metastases according to Gennari: 1 – single metastases, involving less that 25% of liver parenchyma, 2 – multiple metastases involving less that 25% of liver parenchyma or single metastases involving between 25% – 50% of liver parenchyma, 3 – multiple metastases involving between 25% – 50% of liver parenchyma or if more than 50% of liver parenchyma is involved irrespective of the number of metastases.

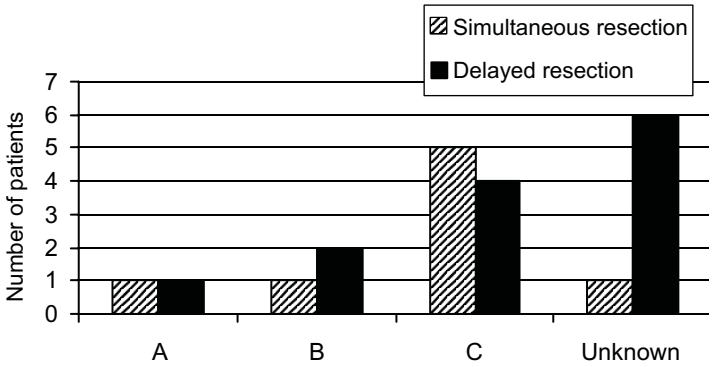

Fig. 3. The staging of primary colorectal neoplasm according to Dukes' classification in patients undergoing simultaneous resections and delayed liver resection.

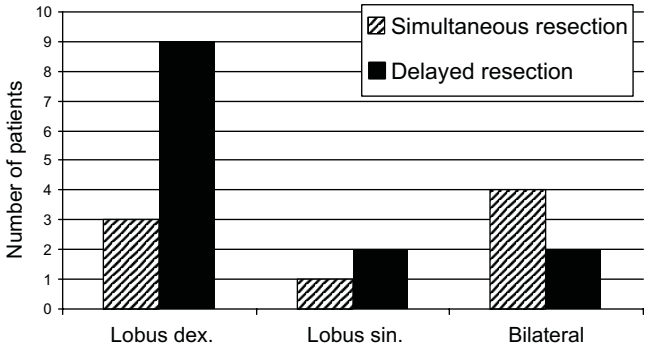

Fig. 4. The distribution of metastases in patients undergoing simultaneous colorectal and liver resections and delayed liver resections.

amination of the removed specimens (resected liver).

Age, sex, staging of liver metastases, duration of surgical procedure, blood replacement during surgery, time of liver ischemia (intermittent portal triad clamping, 15 minutes occlusion, 5 minutes perfusion) and the length of postoperative stay in the ICU were recorded. Liver resections of three or more liver segments according to Couinaud's classification were considered major resections, whereas subsegmentectomies (small wedge resections), segmentectomies and bisegmentectomies were considered minor liver resections. There were 13 minor and 8 major liver resections (figure 1). Staging of liver metastases was performed according to Gennari's classification[17] (figure 2). The staging of primary colorectal neoplasm according to Dukes' classification is presented in figure 3. Twelve patients had liver metastases in the right liver lobe, three in the left lobe and in six patients liver metastases were bilateral (figure 4). 75% of simultaneous resections and 54% of liver resections alone were minor. Types of resections of primary colorectal neoplasm were right hemicolectomy in 49%, left hemicolectomy in 38%

and anterior resection sec. Dixon in 13% of patients. Postoperative serum concentrations of bilirubin, activities of aspartat transaminase (AST), and alanin transaminase (ALT) and prothrombin time, as indicators of liver function, were measured within 24 hours after surgery. Postoperative complications diagnosed during postoperative hospital stay were noted.

Statistical analysis was performed using Mann-Whitney U test (MWU). Differences in the percentages of complications were analyzed using Fisher's exact probability test (FEP). Values of $p<0.05$ were chosen to identify statistical significance. Data were presented as median (range).

Results

Simultaneously resected patients had a median age of 56.5 years (range 30–76 years), whereas patients undergoing delayed resection had a median age of 64 years (range 54–73 years). There was no statistically significant difference in age between these two groups (MWU, p=0.096).

The difference in the duration of simultaneous surgery was not statistically significant from the one of liver resection alone (MWU, p=0.311). No significant difference in the time of liver ischemia was observed between patients who underwent simultaneous surgery and delayed liver resection (MWU, p=0.773). Simultaneously resected patients required significantly more intraoperatively transfused full blood and packed red cells compared to patients with delayed resections (MWU, p=0.036).

The postoperative stay in the ICU did not differ significantly between simultaneously resected patients and those who underwent liver resection alone (MWU, p=0.885). Difference in the duration of postoperative hospital stay between patients who underwent simultaneous or

TABLE 1
CHARACTERISTICS OF PATIENTS WITH SIMULTANEOUS COLON AND LIVER RESECTIONS AND LIVER RESECTION ALONE.

	Group A (n=8)		Group B (n=13)	
Duration of surgery (min)	320	(200–550)	240	(190–350)
Full blood and packed red cells (ml) *	1050	(0–5000)	610	(0–1460)
Postoperative hospital stay (days)	12	(9–26)	11	(6–22)
Postoperative stay in the ICU (hours)	68	(24–139)	72	(24–128)
AST (units/liter)	132.5	(57–680)	341	(139–820)
ALT (units/liter)	101	(58–520)	216	(58–717)
Prothrombin time (% of normal value)	74.5	(50–89)	75	(56–109)
Bilirubin (mol/l)	31.15	(11.5–54.3)	24.8	(9.1–66.0)

Group A = patients undergoing simultaneous resection. Group B = patients undergoing delayed resection. Full blood and packed red cells represent intraoperatively administered amounts. Bilirubin, AST, ALT and prothrombin time are presented as measured within 24 hours after surgery. Values are given as median (range)
* = statistically significant difference
ICU = intensive care unit; AST = aspartat transaminase; ALT alanin transaminase.

delayed resection was not statistically significant (MWU, p=0.192).

Postoperative activities of AST and ALT were not significantly higher in patients who underwent delayed resections (MWU, p=0.051 for AST and p=0.065 for ALT). No significant difference was found in prothrombin time between simultaneously resected patients and those with delayed resections (MWU, p=0.491). Postoperative serum bilirubin concentrations were not significantly higher in patients with simultaneous resections compared to patients with delayed resections (MWU, p=0.311)

Postoperative morbidity rate was 33% and mortality 4.8%. Seven patients developed complications in the postoperative course (two wound infections, one pleural effusion, one pneumonia, one minimal billiary secretion, one transient encephalopathy and one liver insufficiency). One patient who developed complication subsequently died from postoperative liver insufficiency due to too small remnant liver volume after extended right hepatectomy.

No statistically significant difference was found in the frequency of overall complications between simultaneously resected patients and those who underwent liver resection alone (FEP, 38% vs. 31%, p=0.557). No difference in the rate of complications was found between patients with bilobar distribution of metastatic tumors and those with unilobar metastases (FEP, 33% vs. 33%, p=0.686). Patients with trisegmentectomies and hepatectomies (major liver resections) did not differ significantly in the number of complications from patients with wedge resections, segmentectomies and bisegmentectomies (FEP, 38% vs. 31%, p=0.557).

Although patients who developed postoperative complications were somewhat older than patients with uneventful post-

TABLE 2
CHARACTERISTICS OF PATIENTS WITH UNEVENFUL POSTOPERATIVE COURSE AND THOSE WHO DEVELOPED POSTOPERATIVE COMPLICATIONS.

	Uncomp (n=14)		Comp (n=7)	
Age (years)	59.5	(30–69)	64	(54–76)
Duration of surgery (min)	235	(190–460)	300	(200–550)
Full blood and packed red cells (ml)	790	(0–1710)	1080	(260–5000)
Postoperative hospital stay (days) *	10.5	(8–13)	14	(6–26)
Postoperative stay in the ICU (hours)	67	(24–120)	96	(24–139)
AST (units/liter)	278.5	(57–700)	268	(121–820)
ALT (units/liter)	195.5	(58–717)	185	(58–680)
Prothrombin time (% of normal value)	77.5	(50–109)	68	(57–93)
Bilirubin (mol/l)	25.1	(9.1–66.0)	26.1	(9.7–54.3)

Uncomp = patients with ucomplicated postoperative course. Comp = patients who developed postoperative complications. Full blood and packed red cells represent intraoperatively administered amounts. Bilirubin, AST, ALT and prothrombin time are presented as measured within 24 hours after surgery. Values are given as median (range)
*= statisticaly significant difference
ICU = intensive care unit, AST = aspartat transaminase, ALT = alanin transaminase.

operative course, this difference in age was not statistically significant (MWU, p=0.233). Postoperative hospital stay was significantly longer in the group of patients who developed postoperative complications (MWU, p=0.017), but the difference in the stay in the ICU between patients with and those without postoperative complications was insignificant (MWU, p=0.101). No significant difference was found in the duration of surgery for patients with and without postoperative complications (MWU, p=0.682). The average amount of full blood and packed red cells was more than two times greater in patients with postoperative complications than in those without, but the difference was not statistically significant (MWU, p=0.233). The time of liver ischemia did not differ significantly between patients who developed postoperative complications and those who did not (MWU, p=0.739). However, it differed significantly between patients who underwent major and those who underwent minor liver resections (MWU, p=0.025). Patients who developed complications had higher postoperative activities of AST and ALT but not significantly (MWU, p=0.551 for AST and p=0.970 for ALT). Postoperative prothrombin time was insignificantly lower in patients who developed complications (MWU, p=0.192). No significant difference in postoperative concentrations of bilirubin was found between patients with and without complications (MWU, p>0.999)

Discussion

The association of age and postoperative complications after major liver resection was investigated, and age over 55 was found to be significantly related to morbidity[13]. Patients who developed postoperative complications in this study were generally older that those with uneventful postoperative course, but not significantly. Our results are in accordance with findings of Brunken et al. who found that patients over 70 years of age operated for liver metastases of colorectal malignancies do not differ either in the type or extend of treatment nor in the stage of disease, with survival, mortality and morbidity similar to those of younger patients[18].

Blood loss during hepatic resection and subsequent blood replacement are brought into connection with increased morbidity after hepatectomy[19], along with several other undesirable effects, mainly the transmission of viral infections and increased risk of the recurrence of malignant disease[15]. Although in this research the difference in the amount of transfused blood between patients with complications and those without them was not significant, still patients who developed postoperative complications required more blood and plasma restitution. This clearly demonstrates the significance of meticulous surgical technique with exact hemostasis that can be achieved by avoiding non-anatomical resections that result in greater blood loss[15].

Some authors have brought operating time into connection with developing postoperative complications after liver resection[20]. Hardy et al. reported that the significance of the impact of the length of operation on postoperative complications was even greater than for blood loss[21]. In our research simultaneous colorectal and liver resection naturally consumed more operating time than liver resection alone, but not significantly. Also, operation time in patients with postoperative complications was insignificantly longer than in uncomplicated patients. Authors therefore recommend that major liver resections combined with colorectal resections are performed in specialized centers and by surgeons and anesthesiologists well

equipped and trained for such procedures.

Significant positive correlation was found between the level of ALT on postoperative day 1 and the duration of vascular hepatic inflow occlusion, indicating the severity of ischemic damage[15]. Our results showed that the levels of serum transaminases activities are substantially elevated during first 24 hours after surgery, and that patients who developed postoperative complications had insignificantly lower activities of both AST and ALT. The time of liver ischemia was reported to condition postoperative clinical safety[22,23]. However, in our research the total time of liver ischemia was a function of the extensiveness of liver resection, with no significant impact on postoperative complications.

Postoperative prothrombin time is considered to be a sensitive indicator of liver function because of its inverse correlated to the weight of resected liver[15]. In our study prothrombin time was shorter in patients with simultaneous resections and in those who developed postoperative complications, although these differences were not statistically significant.

Although bilirubin serum concentrations were higher in patients with simultaneous resections, patients developing postoperative complications had bilirubin concentrations similar to those of patients without complications. Concentration of bilirubin after hepatectomy is also reported to be a sensitive indicator of liver function. It correlates significantly to the amount of resected liver, but is influenced by transfusions, underlying liver disease and billiary complications[15]. In this study serum concentrations of bilirubin measured within 24 hours after surgery were not found to be significantly related to postoperative complications.

Our data confirmed that simultaneous approach is not associated with significantly more complications compared to delayed liver resections. This is in accordance with findings of other authors[7–9]. However, in the study of acute-phase protein synthesis performed on 19 patients Kimura et al. reported a 57% complication rate after simultaneous resection compared to 8% after liver resection alone[12]. In our study no significantly increased rate of complications was found for patients undergoing major hepatectomies as compared to those undergoing minor hepatic resections. This is of particular importance also from the economic aspect, since patients who develop postoperative complications had significantly longer postoperative hospital stay. The duration of postoperative stay in the ICU was similar in simultaneously resected patients and those who underwent liver resection alone. Surgery related factors presented in this research were not significantly associated with the incidence of postoperative complications. Postoperative concentration of bilirubin and prothrombin time as sensitive indicators of liver function showed no significant difference according to the type of surgical approach (simultaneous or delayed) and higher postoperative activities of transaminases (AST and ALT) in the group of patients who underwent liver resection alone may be explained by the greater proportion of major liver resections in this group of patients.

The major weakness of this study is a rather small number of operated patients and a short postoperative follow-up that could not provide adequate assessment of survival. Therefore conclusions based solely on the statistical significance of the data presented in this study must be critically reviewed. Studies involving larger number of patients and a longer follow up are required before definite judgement of the benefit of simultaneous liver resections for colorectal metastases is made.

Based on this report authors believe that simultaneous resection of primary colorectal malignancy and liver metastases is safe and oncologycally justified approach that is not compromised by the increased rate of complications compared to liver resections alone. Patients should be carefully selected and the surgical approach should be directed on the basis of patient's status and technical considerations. Meticulous work with minimal blood loss is essential. Providing that perioperative factors are kept within the range observed in this study, their influence on postoperative complications is not significant. This can be achieved with the use of intraoperative ultrasound and the control of hepatic blood flow. Experienced staff is another requirement necessary to avoid complications and the grouping of these patients into major clinical centers may be useful.

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SIGURNOST SIMULTANE RESEKCIJE KOLOREKTALNOG KARCINOMA I JETRENE METASTAZE

S A Ž E T A K

Resekcija jetre je jedina potencijalno kurativna metoda liječenja pacijenata sa metastazama kolorektalnog karcinoma, a 5-godišnje preživljenje je 20%–40%. Resekcija kolorektalnog raka i sinkronih jetrenih metastaza u jednom aktu preporuča se ako je indicirana manja resekcija jetre. Cilj rada je analizirati liječenje kolorektalnih metastaza u jetri i procijeniti sigurnost resekcija jetre u jednom aktu i odloženih resekcija te povezanost morbiditeta sa opsežnosti resekcije jetre i perioperacijskim čimbenicima. Analiziran je dvadeset i jedan pacijent s jetrenim metastazama kolorektalnog karcinoma operiran između 1997 i 1999 u Kliničkoj bolnici »Sestre milosrdnice«. Prosječno trajanje zahvata resekcije kolorektalnog raka i metastaza u jetri u jednom aktu nije značajno dulje od trajanja izolirane resekcije jetre. Nije nađena značajna razlika u učestalosti komplikacija nakon udruženih operacija i samostalnih reskecija jetre (38% : 31%). Učestalost komplikacija nakon velikih resekcija jetre nije bila značajno veća od komplikacija kod nakon manjih resekcija jetre (38% : 31%). Može se zaključiti da nije nađena statistički značajna razlika u trajanju operacije i količini nadoknađene krvi kod pacijenata sa i onih bez postoperacijskih komplikacija. Resekcije primarnog kolorektalnog karcinoma i jetrenih metastaza u jednom aktu mogu se smatrati sigurnim. Učestalost postoperacijskih komplikacija se ne razlikuje značajno od izoliranih resekcija jetre, niti ovisi značajno o opsežnosti resekcije jetre, uz uvjet da su trajanje zahvata i potrošnja krvi unutar raspona prikazanog u ovoj studiji.