Articole originale

Chirurgia (2012) 107: 298-307
Nr. 3, Mai - Iunie
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Simultaneous resection of the primary colorectal tumor and liver metastases – a safe and effective operation

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Rezumat

Rezecția simultană a tumorii colorectale și a metastazelor hepatice sincrone - o operație sigură și eficientă

Introducere: Scopul acestui studiu retrospectiv este de a compara rezultatele rezecției simultane (SR) și respectiv amânate (DR) a metastazelor hepatice colorectale sincrone.
Material și Metodă: În Centrul de Chirurgie Generală și Transplant Hepatic "Dan Setlacec" al Institutului Clinic Fundeni, între 1995 și 2010, la 117 pacienți s-a practicat SR, iar la 25 de pacienți DR. Au fost comparate rezultatele obținute la aceste două grupuri de pacienți și totodată s-a urmărit identificarea unor subgrupuri de pacienți la care rezultatele rezecției amânate sunt superioare celor ale rezecției simultane.
Rezultate: Localizarea tumorii primare, numărul și diametrul metastazelor hepatice, precum și proporția hepatectomiilor majore au fost similare în cele două grupuri (p value > 0.05). Ratele morbidității, mortalității, supraviețuirii globale și fără recidivă neoplazică nu au diferit semnificativ statistic în cele două grupuri (p value > 0.05). În subgrupurile de pacienți cu tumori rectale, cu metastaze hepatice multiple, precum și la pacienții cu hepatectomii majore, ratele morbidității, mortalității și ale supraviețuirii obținute prin rezecția simultană au fost similare celor înregistrate după rezecția amânată.
Concluzii: Rezecția simultană a metastazelor hepatice colorectale sincrone este la fel de sigură și eficientă ca și rezecția amânată, inclusiv la pacienții cu tumori rectale, cu metastaze hepatice multiple sau cu hepatectomii majore.

Cuvinte cheie: metastaze hepatice colorectale sincrone, rezecție simultană, rezecție amânată, hepatectomie majoră, tehnici reconstructive microchirurgicale

Abstract

Background: The aim of this retrospective study was to compare the results achieved by simultaneous resection (SR) vs. delayed resection (DR) in patients with synchronous colorectal liver metastases (SCRLM).
Methods: In "Dan Setlacec" Center of General Surgery and Liver Transplantation from Fundeni Clinical Institute, between 1995 and 2010, 117 patients underwent SR and 25 patients underwent DR. It was compared the outcome of the patients in the two groups. It was also assessed if certain subgroups of patients present a better outcome after DR than after SR.
Results: The location of the primary tumor, the number and diameter of liver metastases, and the proportion of major hepatectomies were similar in the two groups (p value > 0.05). For all patients, the morbidity, mortality, disease-free and

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overall surrvival rates were not statistically significant different between the two groups (p value > 0.05). In subgroups of patients with rectal tumors, with multiple liver metastases, and undergoing major hepatectomies, the morbidity, mortality and survival rates achieved by SR were similar to those achieved by DR.

Conclusion: Simultaneous resection of SCRLM is similarly safe and efficient as the delayed resection, even in patients with rectal tumors, with multiple liver metastases, or undergoing major hepatectomies.

Key words: synchronous colorectal liver metastases, simultaneous resection, delayed resection, major hepatectomy, reconstructive microsurgical technique

Introduction

Two thirds of patients with colorectal cancer will develop liver metastases (LM). Between 16 and 25% of these patients present with liver metastases at the time of diagnosis of their primary tumor (synchronous colorectal liver metastases – SCRLM) (1,2). Almost one quarter of patients present initially resectable SCRLM (3). The curative treatment of these patients is multimodal and involves radical resection of the colorectal tumor and complete resection of liver metastases, chemotherapy, targeted therapies and sometimes radiotherapy. The 5-year overall survival rates achieved by this treatment range from 20 to more than 50% (4-8). However, in patients with initially resectable SCRLM, the optimal timing of liver resection is still a subject of debate, some authors recommending simultaneous resection (SR) (2,9-11), while others advocate delayed resection (DR) of liver metastases (12,13).

The traditional approach to SCRLM consists in initial resection of the primary tumor, followed by chemotherapy and subsequent resection of liver metastases (offered mainly to the patients whose metastases did not progress under chemotherapy) (14). The advantages hypothesized by the promoters of this approach (called "delayed resection") are the safety of patients (who avoid a complex operation, theoretically associated with higher morbidity and mortality rates) and the possibility to assess the biological behavior and chemosensitivity of liver metastases during the interval between the two operations (12,15). Due to the better understanding of liver anatomy, the progresses in anesthesiology and intensive care, the use of more effective resection strategies and the advent of new devices for parenchymal transsection, the morbidity and mortality rates of liver resection have improved over the last two decades (16,17). This improved safety profile of liver resections challenged the DR approach, and some centers started to perform simultaneous resection of the primary tumor and liver metastases, reporting a similar surgical outcome as in delayed resection (9,10,18,19). The main advantages of this approach (over the DR) are the comfort of the patient (who avoids two operations under general anesthesia), the shorter hospital stay and the avoidance of metastases progression to unresectability (which is possible during the "observation interval" in the DR approach) (20). As the benefits of prehepatectomy chemotherapy in improving survival were not truly proven (by randomized controlled trials) and the postoperative risks associated with hepatotoxicity induced by chemotherapy may overweight its benefits (21), the SR gained acceptance in more centers in the last years (11,22-24).

However, the results reported till now were recorded by retrospective studies, incorporating in the SR group more frequent patients whose primary tumors were located to the colon, with smaller and fewer metastases requiring minor liver resections, than in the DR group (11,19,24-29). Thus, the most appropriate approach in patients with rectal tumors and/or multiple liver metastases requiring a major hepatectomy was not fully clarified, representing a matter of debate between the partisans of simultaneous approach and delayed approach, respectively.

In this study it was conducted a retrospective analysis of patients undergoing simultaneous resection vs. delayed resection. There were compared the morbidity, mortality and survival rates achieved by simultaneous and delayed resection, in order to assess the safety and efficacy of each of these approaches. It was also evaluated whether some subgroups of patients are suitable for delayed liver resection.

Methods

Between 1995 and 2010, there were performed 332 liver resections for colorectal liver metastases in 293 patients (39 re-resections) at the "Dan Setlacec" Center of General Surgery and Liver Transplantation Fundeni, Bucharest. In this period, 142 patients with initially resectable SCRLM were subjected to liver resection.

Colorectal liver metastases (CRLM) were considered synchronous when they were diagnosed at the same time with the primary tumor (during the work-up for the colorectal cancer or at the time of the operation for primary tumor). The diagnosis was established preoperatively – by abdominal ultrasound and computed tomography (CT) or magnetic resonance imaging (MRI), or intraoperatively – by visual and palpatory examination of the liver, or by intraoperative ultrasonography.

SCRLM were considered resectable when the liver metastases could be entirely removed (R0), the volume of the remnant liver was adequate and, in patients with extrahepatic metastases, when a complete resection of extrahepatic disease could be accomplished. Regarding the adequate volume of the remnant liver, the situation changed over the time. Until 2003 it was performed liver resection for CRLM when at least two segments of the liver could be preserved. Since 2004, (CT-based) volumetric assessment of the remnant liver was performed preoperatively whenever concerns regarding an insufficient volume of the remnant liver have been raised. Thus, in patients without chronic liver disease, who did not receive preoperative chemotherapy or receiving less than 6 cycles of chemotherapy, the volume of the remnant liver was considered adequate when it exceeded 30% of total liver volume. In patients with chronic liver disease or receiving

more than 6 cycles of preoperative chemotherapy, the volume of the remnant liver should represent more than 40% of total liver volume.

Liver resection was performed simultaneous with the resection of the primary tumor in 117 patients, while in 25 patients it was performed a delayed resection (colorectal resection first, followed by chemotherapy and hepatectomy in a second stage).

All the simultaneous resections were performed in our center, while 19 of the patients with delayed resection were operated for the primary tumor in other units, being referred to us for hepatectomy. The 6 patients with delayed liver resection operated in our center were subjected to a staged surgical approach due to a complication of the primary tumor (5 patients) and because one patient would require a right hemihepatectomy (associated with vascular resection and reconstructive microsurgical technique) after a difficult rectal resection.

In SR group, 9 out 117 (7.69%) patients presented synchronous extrahepatic metastases (peritoneal metastases – 4 patients, lung metastasis – 2 patients, hepatic pedicle lymph nodes metastases – 2 patients, right adrenal metastasis – 1 patient).

In DR group, 7 out of 25 (28%) patients presented extrahepatic disease (peritoneal metastases – 2 patients, lung metastasis – 1 patient, hepatic pedicle lymph nodes metastases – 1 patient, spleen metastasis – 1 patient and local reccurence after the primary tumor resection – 2 patients).

In the SR group 12 out of 117 (10.25%) patients underwent preoperative chemotherapy. Three patients with synchronous extrahepatic metastases, diagnosed during preoperative work-up, underwent chemotherapy before surgery, in order to assess the biological behavior and chemoresponsiveness of the metastases. Thus, two patients with synchronous lung metastases underwent 6 cycles of FOLFIRI before operation and one patient with synchronous adrenal metastasis underwent 6 cycles of FOLFOX4 preoperatively. The other nine patients receiving preoperative radio-chemotherapy presented locally advanced rectal tumors (T3 or T4) and synchronous liver metastases. These nine patients received preoperatively 3 cycles of Capecitabine (5 patients) or 5-FU continuous infusion (4 patients). As liver metastases did not progress under chemotherapy (partial response – 2 patients and stable disease – 10 patients), simultaneous resection was performed.

All the patients with delayed resection received chemotherapy before hepatectomy. The therapeutic regimens consisted in Mayo regimen (8 patients), FOLFOX4 (10 patients) and FOLFIRI (7 patients). The mean number of cycles was 5.2 cycles/patient (ranging between 3 and 8). The response to the chemotherapy was stable disease in 17 patients, partial response in 6 patients, and 2 patients, whose primary tumor resection was not curative, developed loco-regional recurrence after 6 cycles of Mayo, but the liver metastases did not progress.

In the SR group, the resection was curative (R0) in 113 patients (96.58%), R1 in 2 patients and R2 in 2 patients.

In the DR group, the resection was R0 in 22 patients (88%), R1 in 2 patients and R2 in one patient.

Major hepatectomy was defined as the resection of three or more adjacent segments.

Postoperative morbidity included complications graded between grade II and V in the Dindo-Clavien classification (30), occurred during postoperative hospitalization or within 30 days after surgery. Hepatic complications included liver failure, hemorrhage at the transsection surface, bile leak and perihepatic or subphrenic fluid collections. Colorectal complications included anastomotic leak and intraabdominal abscess.

Postoperative mortality was defined as death of the patient during postoperative hospitalization or within 30 days after surgery.

Results

Clinicopathologic characteristics of the patients and types of liver resection

The age, gender, location of the primary tumor, number and maximum size of liver metastases, preoperative chemotherapy, type and extension of liver resection, presence of extrahepatic metastases and curative resection were compared between the two groups of patients and the results are presented in *Table 1*.

In the present series, the two groups are homogenous regarding the age and gender of patients.

Anatomical resections were performed in a statistically significant higher number of patients in the DR group (60%) than in the SR group (23.6%, p value = 0.001, Fisher's exact test).

The proportion of patients with extrahepatic metastases was statistical significantly higher in the DR group (28%) vs. SR group (7.7%; p value = 0.01, Fisher's exact test), but the proportion of globally curative resections was similar in the two groups (88% in the DR group vs. 96.5% in the SR group; p value = 0.104, Fisher's exact test). (*Table 1*).

Statistical significantly more patients received preoperative chemotherapy in the DR group (25 patients) than in the SR group (12 patients) (p value = 0.0001, Fisher's exact test).

Regarding those parameters which are a matter of debate between the partisans of simultaneous approach and delayed approach (primary tumor location, number of liver metastases and extent of hepatectomy), the present goups are homogenous.

Thus, the proportion of major hepatectomies was not statistically significant different in the two groups (17.9% in the SR group vs. 36% in the DR group, p value = 0.058, Fisher's exact test). Likewise, the proportions of patients with rectal tumors or with multiple metastases were similar in the two groups (p value > 0.05) (*Table 1*).

Postoperative outcome

The morbidity rate of all the patients with simultaneous resection was 34.7% (41/117), while in patients with delayed resection the morbidity rate was 28% (7/25). The difference was not statistically significant (p value = 0.516, Fisher's

Table 1. *The clinicopathological characteristics of the patients with SCRLM treated by simultaneous or delayed approach*

		Timing of liver resection		
Caracteristics	**Parameters**	**Simultaneous n =117**	**Delayed n=25**	***p* value**
Gender	Female	54.7% (64)	64% (16)	0.506
	Male	45.3% (53)	36% (9)	
Age		59.02±10.76	56.72±11.58	0.274
Location of the primary	Colon	72.6% (85)	72% (18)	1
	Rectum	27.4 (32)	28% (7)	
LM maximum diameter	< 5 cm.	71.7% (84)	68% (17)	0.808
	> 5 cm.	28.3% (33)	32% (8)	
Number of LM	Single	53.8% (63)	36% (9)	0.125
	Multiple	46.2% (54)	64% (16)	
Preoperative chemotherapy	Yes	10.2% (12)	100% (25)	0.0001
	No	89.8% (105)	0% (0)	
Resection type	Anatomical	25.6% (30)	60% (15)	0.001
	Non-anatomical	74.4% (87)	40% (10)	
Extension of hepatectomy	Minor	82% (96)	64% (16)	0.058
	Major	18% (21)	36% (9)	
Extrahepatic metastases	No	92% (108)	72% (18)	0.010
	Yes	8% (9)	28% (7)	
Curative resection	R0	96.5% (113)	88% (22)	0.104
	R1/R2	3.5% (4)	12% (3)	

exact test). The types of complications are sumarized in *Table 2*.

The mortality rate of all the patients with simultaneous resection was 5.9% (7/117), while in patients with delayed resection the mortality rate was 12% (3/25). The difference was not statistically significant (p value = 0.279, Fisher's exact test). The causes of mortality are presented in *Table 2*.

The mortality rates dicreased over the time. Thus, between 2004 and 2010, the mortality rate after SR was 2.81% (2/71 patients), these two patients undergoing minor liver resections. The causes of death were acute miocardial infarction and pulmonary embolism. In the DR group, the mortality rate between 2004 and 2010 was zero (0/16 patients). The mortality rates in this period (2004 – 2010) were also similar in the two groups (p value = 1, Fischer's exact test).

Of note, between 2004 and 2010, no one patient undergoing major hepatectomy deceased (either in the SR group or DR group).

The 1, 3 and 5-year overall survival rates of all the patients with simultaneous resection were 78.3%, 52.2% and 21.9%, respectivelly (*Fig. 1*) and the median survival of these patients was 39.6 months.

The 1, 3 and 5-year overall survival rates of all the patients with delayed resection were 77%, 42.4% and 14.1%, respectivelly (*Fig. 1*) and the median survival of these patients was 26.6 months.

The overall survival rates were not statistically significant different between the two groups of patients (p value = 0.443, log rank test).

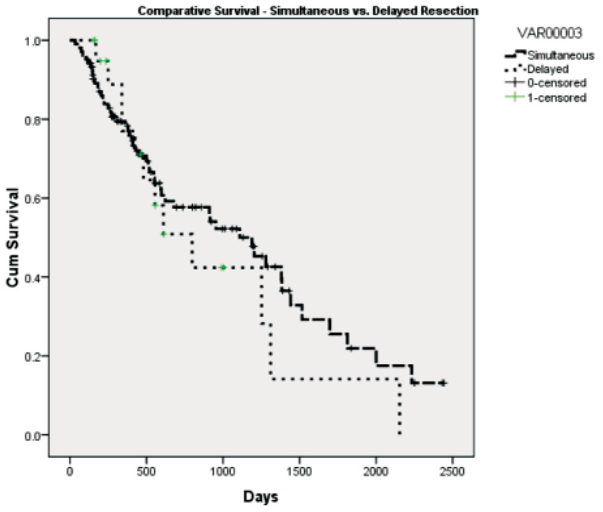
For the patients undergoing curative (R0) resections, in the SR group, the 1, 3 and 5-year overall survival rates were 78.9%, 52.6% and 25.8%, respectively.

In patients undergoing R0 resection in the DR group, the 1, 3 and 5-year overall survival rates were 86.7%, 47.7% and 15.9%, respectively.

The survival rates were not statistically significant different

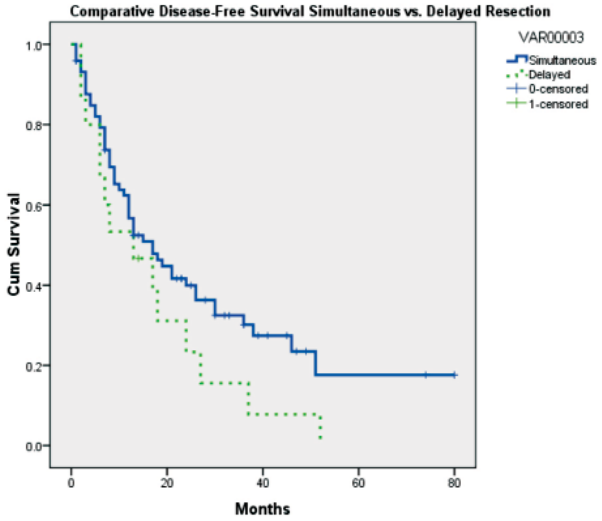
Table 2. *Causes of morbidity and mortality*

	Simultaneous resection		Delayed resection	
	Nr. complications	**Nr. deceases**	**Nr. complications**	**Nr. deceases**
Perihepatic abcess	13 (31.7%)		2 (28.5%)	
Biliary leak	5 (12.1%)		1 (14.3%)	
Anastomotic leak	13 (31.7%)	2 (28.5%)	1 (14.3%)	
Liver failure	4 (9.8%)	2 (28.5%)	2 (28.5%)	2 (66.6%)
Pulmonary embolism	2 (4.9%)	1 (14.5%)		
Acute miocardial infarction	2 (4.9%)	2 (28.5%)		
Haemoperitoneum	1 (2.4%)			
Duodenal leak	1 (2.4%)			
Pneumonia			1 (14.3%)	1 (33.4%)
Total	41	7	7	3



	1-yr	3-yr
Simultaneous resection	*65*	*25*
Delayed resection	*13*	*4*

Figure 1. *The overall survival curves of all patients with simultaneous resection (full line) and delayed resection (dotted line)*



	1-yr	3-yr
Simultaneous resection	*40*	*13*
Delayed resection	*8*	*2*

Figure 2. *The disease-free survival curves of the patients with simultaneous resection (full line) and delayed resection (dotted line)*

between the two groups of patients undergoing R0 resections (p value = 0.751, log rank test).

In patients without extrahepatic metastases, the overall survival rates were also similar in the SR group and DR group, respectivelly (p value = 0.188, log rank test) (*Table 3*).

Reliable data regarding the recurrence of the disease were not available in 36 patients in the SR group, and in 5 patients in the DR group. These patients failed to achieve the scheduled follow-up, most of them coming back in our center at long intervals after recurrence of disease. Thus, the data regarding the disease-free survival and the type of recurrence were calculated taking into account only 74 patients in the SR group and 17 patients in the DR group.

In the SR group, the recurrence rate was 67.5% (50/74 patients) after a median follow-up of 29 months. The site of recurrence was intrahepatic in 28 patients, extrahepatic in 12 patients and both intrahepatic and extrahepatic in 10 patients.

In the DR group, the recurrence rate was 94% (16/17 patients) after a median follow-up of 22 months. The site of recurrence was intrahepatic in 8 patients, extrahepatic in 5 patients and both intrahepatic and extrahepatic in 3 patients.

In patients with SR, the 1 and 3-year disease-free survival rates were 56.7% and 32.5%, respectively (*Fig. 2*), and median disease-free survival was 17 months.

In patients with DR, the 1 and 3-year disease-free survival rates were 53.3% and 15.6%, respectively (*Fig. 2*), and median disease-free survival was 13 months.

The disease-free survival rates were not statistically significant different between the two groups of patients (p value = 0.129, log rank test).

In order to determine if certain parameters influence the outcome of patients with SCRLM, it was conducted a comparative analysis of the results achieved following the simultaneous and delayed resection of SCRLM, according to the location of the primary tumor, to the number of CRLM, to their maximum diameter, to the type of liver resection and its extension, to the presence of the extrahepatic metastases and the completeness of tumor resection (R0 vs. R1 and R2).

In patients with primary rectal tumors, the morbidity rates were similar in the two groups: 40% (13/32) in the SR group and 42.8% (3/7) in the DR group (p value = 0.912, Fischer's exact test).

In patients with multiple metastases, the morbidity rates were similar among the two groups: 42.5% (23/54) in the SR group and 37.5% (6/16) in the DR group (p value = 0.716, Fischer's exact test).

In patients undergoing major hepatectomies, the morbidity rates were similar among the two groups: 33.3% (7/21) in the SR group and 33.3% (3/9) in the DR group (p value = 1, Fischer's exact test).

In patients with primary rectal tumors, the mortality rates were similar in the two groups: 3.1% (1/32) in the SR group and 14.2% (1/7) in the DR group (p value = 0.225, Fischer's exact test).

In patients with multiple metastases, the mortality rates were similar among the two groups: 7.4% (4/54) in the SR group and 12.5% (2/16) in the DR group (p value = 0.522, Fischer's exact test).

In patients undergoing major hepatectomies, the mortality rates were similar among the two groups: 14.2% (3/21) in the SR group and 33.3% (3/9) in the DR group (p value = 0.231, Fischer's exact test).

The survival rate was significant higher in the patients with liver metastases smaller than 5 cm who underwent simul-

Table 3. *Outcomes of all patients with initially resectable SCRLM, depending on the timing of liver resection*

Parameters	Outcomes	Simultaneous	Delayed	p value
Colon	Morbidity	32,9% (28/85)	22,2% (4/18)	0,371
	Mortality	7% (6/85)	11,1% (2/18)	0,559
	Median survival	31,7 mo	41,7 mo	0,573
Rectum	Morbidity	40% (13/32)	42,8% (3/7)	0,912
	Mortality	3,1% (1/32)	14,2% (1/7)	0,225
	Median survival	40,1 mo	11,3 mo	0,001
< 5 cm.	Morbidity	33,3% (28/84)	35,2% (6/17)	0,876
	Mortality	4,7% (4/84)	11,7% (2/17)	0,265
	Median survival	46,1 mo	26,6 mo	0,047
> 5 cm.	Morbidity	39,3% (13/33)	12,5% (1/8)	0,150
	Mortality	9% (3/33)	12,5% (1/8)	0,770
	Median survival	19,8 mo	71,8 mo	0,292
Single	Morbidity	28,5% (18/63)	11,1% (1/9)	0,266
	Mortality	1,5% (1/63)	11,1% (1/9)	0,103
	Median survival	39,6 mo	43,7 mo	0,826
Multiple	Morbidity	42,5% (23/54)	37,5% (6/16)	0,716
	Mortality	7,4% (4/54)	12,5% (2/16)	0,522
	Median survival	19,8 mo	20,3 mo	0,597
Non-anatomical	Morbidity	34,4% (30/87)	40% (4/10)	0,729
	Mortality	4,5% (4/87)	10% (1/10)	0,464
	Median survival	39,6 mo	26,6 mo	0,314
Anatomical	Morbidity	36,6% (11/30)	20% (3/15)	0,254
	Mortality	10% (3/30)	13,3% (2/15)	0,736
	Median survival	19,8 mo	20,3 mo	0,915
Minor hepatectomy	Morbidity	35,4% (34/96)	25% (4/16)	0,415
	Mortality	4,1% (4/96)	0% (0/16)	0,405
	Median survival	36,9 mo	26,6 mo	0,508
Major hepatectomy	Morbidity	33,3% (7/21)	33,3% (3/9)	1
	Mortality	14,2% (3/21)	33,3% (3/9)	0,231
	Median survival	19,9 mo	20,3 mo	0,529
Without extrahepatic metastases	Morbidity	33.3% (36/108)	27.7% (5/18)	0.788
	Mortality	5.5% (6/108)	11.1% (2/18)	0.323
	Median survival	39.6 mo	43.7 mo	0.188
Extrahepatic metastases	Morbidity	55.5% (5/9)	28.5% (2/7)	0.622
	Mortality	11.1% (1/9)	14.2%(1/7)	0.787
	Median survival	12.8 mo	14.1 mo	0.226
R0 resection	Morbidity	33.6% (38/113)	31.8% (7/22)	0.869
	Mortality	6.1% (7/113)	13.6% (3/22)	0.208
	Median survival	39.6 mo	26.6 mo	0.751

taneous resection (median survival 46.1 months), than in those who underwent delayed resection (median survival 26.6 months; p value= 0.047, log rank test).

The survival rate was significantly higher in the patients with the primary tumor located to the rectum who underwent simultaneous resection (median survival 40.1 months), than in those with rectal tumors and SCRLM who underwent delayed resection (median survival 11.3 months, p value = 0.001, log rank test).

In patients with multiple metastases, the overall survival rates were similar irrespective the timing of liver resection (p value > 0.05) (*Table 3*).

In patients undergoing major hepatectomies the survival rates were similar in the two groups (p value > 0.05) (*Table 3*).

In *Table 3* are presented the morbidity, mortality and overall survival rates achieved by simultaneous and delayed resection in different subgroups of patients.

Discussion

Safety of simultaneous resection

The simultaneous approach represents the concomitant resection of the primary tumor and liver metastases, followed by adjuvant chemotherapy, while the delayed resection is defined by initial resection of the primary tumor, followed by neoadjuvant chemotherapy, subsequent hepatectomy and adjuvant chemotherapy.

The simultaneous resection of the primary colorectal tumor and liver metastases was viewed with caution until approximately 25 years ago, since the association of the two resections was marked by high rates of morbidity and mortality (14).

In the last two decades, as liver resections became increasingly safer, with low rates of postoperative morbidity and mortality, a number of centers started to perform simul-

taneous resections for SCRLM (9,31,32).

In our series, the morbidity and mortality rates achieved by SR were similar to those achieved by DR. Since in the SR group more patients underwent non-anatomical resections and less patients present with extrahepatic metastases and received prehepatectomy chemotherapy, it could be hypothesized that these differences may induce a bias toward lower morbidity and mortality rates in this group.

In order to asses whether the type of liver resection may bias the results, there were recorded the morbidity and mortality rates of the patients receiving anatomical vs. non-anatomical liver resection in each of the two groups.

In the SR group, the morbidity rate of the patients undergoing non-anatomical resection was 34.4% (30/87), slightly lower than those achieved by patients undergoing anatomical resection 36.6% (11/30), but the difference was not statistically significant (p value = 0.827, Fisher's exact test). In the DR group, the morbidity rate of the patients undergoing non-anatomical resection was 40% (4/10), higher than those achieved by patients undergoing anatomical resection 20% (3/15), but the difference was not statistically significant (p value = 0.378, Fisher's exact test).

In the SR group, the mortality rate of the patients undergoing non-anatomical resection was 4.6% (4/87), lower than those achieved by patients undergoing anatomical resection 10% (3/30), but the difference was not statistically significant (p value = 0.370, Fisher's exact test). In the DR group, the mortality rate of the patients undergoing non-anatomical resection was 10% (1/10), lower than those achieved by patients undergoing anatomical resection 13.3% (2/15), but the difference was not statistically significant (p value = 1, Fisher's exact test).

Thus, in this series, neither the morbidity rates, nore the mortality rates were influenced by the type of liver resection.

Taking into account these facts, it seems that the difference between the two groups regarding the type of liver resection have no major impact on the outcome of the patients, and the bias resulted from this difference in the stucture of the groups is not so important to make the groups incomparable.

We consider that the statistically significant higher proportion of patients with extrahepatic disease in the DR group has little impact on the morbidity and mortality rates, as the operations directed to the extrahepatic metastases were usually minor interventions (lymphadenectomy, resection of few peritoneal deposits, adrenalectomy).

It could be hypothesized that the lower number of patients receiving prehepatectomy chemotherapy in the SR group may induce a bias toward lower morbidity and mortality rates in this group of patients. Hence, two trials revealed that limited course Oxaliplatin therapy (six or less cycles) was not associated with increased morbidity and mortality rates after liver resection (33,34). Thus, in patients undergoing DR (who receive usually short-course chemotherapy before liver resection), the risk of increased morbidity and mortality rates due to prehepatectomy chemotherapy is not so high, In our series, although the morbidity and mortality rates achieved by DR (28% and 12%, respectively) are higher than those reported in the literature, we consider that preoperative chemotherapy has limited influence on these parameters. This hypothesis is based on two facts: 1. most patients received short-course chemotherapy before liver resection, none of them presenting "blue liver" or "CASH" (chemotherapy-associated steatohepatitis); 2. despite that most patients operated since 2004 received Oxaliplatin or Irinotecan-based chemotherapy (whose hepatotoxicity is more important than those of 5-FU), the morbidity rates decreased in this period and no one patient in the DR group deceased after 2004.

The simultaneous approach has the advantages of ensuring higher comfort for the patient (who avoids two surgical operations and two general anaesthesia procedures) and not allowing metastasis progression in the period between the resection of the primary tumor and the resection of CRLM.

Initially, this approach was recommended especially for patients with primary tumors located in the right colon and with liver metastases amenable to minor hepatectomy (31). In present, simultaneous colo-rectal resection and minor hepatectomy is a safe operation, with low morbidity (less than 35%) and mortality rates (less than 3%) in most centers (10,24,35, 36).

In our center, minor hepatectomies performed simultaneously with the primary tumor resection led to morbidity and mortality rates of 35%, and 4%, respectively. Moreover, these results improved over the time, between 2004 and 2010, the mortality rate being 2.8% in the SR group. The reasons for these better results achieved in the last years were the improvements in preoperative imaging, in anesthesia and intensive care and a more adequate surgical technique (as it was presented above).

A similar situation was reported in two studies presenting more than 1000 hepatectomies each; the authors revealed that in the second period after starting their program of liver surgery, the morbidity and mortality rates have improved (16,17).

Thus, nowadays, most centers with large experience in liver surgery advocate the SR in patients with primary tumors located in the colon and with liver metastases amenable to minor hepatectomy (11,23,27,35).

Hence, in patients with primary tumors confined to the rectum, or in patients with multiple SCRLM and/or requiring major hepatectomies, the simultaneous approach is still a subject of debate. Many authors raised concerns regarding the safety of SR in such patients. Definitive conclusions could not be drawn because in most series, the patients undergoing SR had significantly fewer and smaller SCRLM than the patients treated by DR (11,26). As well, in most reports, in the SR group there were significantly less patients with rectal tumors than in the DR group (24,26,27,29).

Since in our series the proportions of patients with rectal tumors, multiple metastases and major hepatectomies were similar in the SR group and DR group, we consider that our results could represent a useful contribution in the debate regarding the safety and efficacy of SR in these subgroups of patients.

Major hepatectomies

Regarding the morbidity rates in patients undergoing major hepatectomies, in the series presented by Reddy et al., the only factor that independently predicted severe postoperative morbidity after simultaneous resection was major hepatectomy (24). In our series, the morbidity rates after major liver resections were not statistically significant different in the SR group (33.3%) and DR group (33.3%; *p* value = 1, Fischer's exact test). Similarly, Luo et al. in 2010 revealed that simultaneous liver resections of three or more segments would not increase the rate of complications compared to staged resections (56.8% and 42.4%, respectively; *p* value = 0.119) (23). Moreover, Capussotti et al. revealed that, considering both surgical procedures (colorectal resection and major liver resection), the rate of postoperative complications was significantly higher in the DR group (56.3%) vs. SR group (32.6%; *p* value = 0.0369, Fisher's exact test) (22).

Taking into account the mortality rates after major liver resections, a multi-institutional retrospective study revealed that in patients with major hepatectomies, simultaneous resection of the primary tumor increased mortality (8.3% vs. 1.4% in patients with delayed resection, *p* value < 0.05) (24). Hence, in this study, the patients in the simultaneous resection group less often underwent major hepatectomy (26.7% versus 61.3% in the DR group, *p* < 0.05) (24). In our series, the proportion of patients undergoing major hepatectomies was similar in the two groups, and the mortality rates after major hepatectomies in the SR group and DR group (14.2% and 33.3%, respectively) were not statistically significant different (*p* value = 0.231, Fischer's exact test). Although these mortality rates achieved between 1995 and 2010 are greater than those reported in the literature, since 2004, in our center, no one patient subjected to a major hepatectomy deceased. Such results have been reported in few recent papers, revealing similar mortality rates in patients undergoing major hepatectomies performed concomitant with, or delayed for the primary tumor resection (19,22,23).

Based on the data presented herein, we hypothesize that major hepatectomies can be safely performed at the same time as colorectal resection in most patients with synchronous metastases.

Multiple liver metastases

Regarding the patients with multiple SCRLM, in our series, the morbidity and mortality rates achieved by SR (42.5% and 7.4%, respectively) and by DR (37.5% and 12.5%) were not statistically significant different (*p* value > 0.05). Similar results after simultaneous and delayed resection of multiple SCRLM were reported in 2006 by Minagawa et al. (32).

Primary rectal tumors

In patients with primary tumors confined to the rectum, the morbidity rates achieved by SR (40%) and by DR (42.8%) were not statistically significant different (p value = 0.912). One patient deceased in each of these subgroups, the mortality rates being similar (3.1% in the SR group and 14.2% in the DR group; p value = 0.225, Fischer's exact test). Weber et al. reported such results since 2003, recommending simultaneous performance of the rectal tumor and liver metastases resection (19).

Taking into account these results we consider that the simultaneous resection of primary tumor and liver metastases is a safe approach, irrespective the primary tumor location, the number of liver metastases and the extent of hepatectomy.

One disadvantage mentioned for simultaneous approach was the necessity to perform delabrant incisions in some cases (tumors located to the left colon or rectum, with synchronous liver metastases located in the right hemiliver), thus increasing the risk of abdominal wall postoperative complications.

Due to the progress lately achieved in laparoscopy, this disadvantage can be avoided, either by performing both resections by laparoscopy (or robotic surgery) or by performing the colorectal resection by laparoscopic or robotic approach and the liver resection by subcostal incision (when the metastases cannot be safely approached by mini-invasive surgery). Within our group, 2 patients underwent simultaneous laparoscopic resection of the primary tumor and liver metastases and in 5 patients we performed colorectal resection by laparoscopic approach and hepatectomy by open approach (right subcostal incision). In another patient we performed a low anterior resection by robotic approach and liver resection by right subcostal incision. The morbidity rate of these patients was 37.5% (3/8) and the mortality rate was zero. These short-term outcomes are similar to those achieved by the open approach (*p* value > 0.05, Fisher's exact test).

Efficacy of simultaneous resection

For all the patients in our series, the 1, 3 and 5-year overall survival rates achieved by SR (78.3%, 52.2% and 21.9%, respectivelly) were higher than those achieved by DR (77%, 42.4% and 14.1%, respectivelly), but the difference was not statistically significant (*p* value = 0.443, log rank test).

Since statisticaly significant more patients presented extrahepatic metastases in the DR group, a bias toward lower survival rates in this group is possible. Thus, in order to present more accurate data, we recorded the overall survival rates achieved in patients undergoing curative resections (R0). In the R0 patients, the 1, 3 and 5-year overall survival rates achieved by SR (78.9%, 52.6% and 25.8%, respectively) and DR (86.7%, 47.7% and 15.9%, respectively) were not statistically significant different (*p* value = 0.751, log rank test). Although, the proportion of patients undergoing curative resection was similar in the two groups (96.5% in the SR group and 88% in the DR group; *p* value = 0.104), a bias toward lower survival rates in the DR group still persists, because in patients with extrahepatic disease, even when a complete resection is performed, the survival rates are lower than those achieved by patients without extrahepatic disease (37,38).

To exclude any bias between the two groups, we compared the overall survival rates achieved in patients without extrahepatic metastases. In this subgroup of patients, although the median survival was higher in the DR group (43.7 months) than in the SR group (39.6 months), the difference was not statistically significant (p value = 0.188, log rank test).

Thus, we believe that our data permit us to consider that, in terms of overall survival, SR enables similar results as DR in patients with SCRLM. Similar conclusions were presented by other authors (10,19,26,35,36).

In our series, the overall survival rates achieved by SR in patients with multiple SCRLM and in patients undergoing major hepatectomies were not statistically significant lower than those achieved by DR (p value > 0.5) (*Table 3*).

Hence, the main criticism addressed to the simultaneous resection (in terms of effectiveness) is the impossibility to select the patients who have a real benefit from the liver resection (as the biological behavior of their metastases could not be assessed before operation). By contrary, the DR approach allows a "test of time" (during the interval between the two operations) and gives more information about the chemosensitivity of liver metastases (13,39). If the metastases growth during the chemotherapy, the benefit of liver resection is limited, as Adam et al. and Allen et al. already revealed (40, 41). By this reason, most authors postpone liver resection in such situations, avoiding useless hepatectomies. Thus, the DR allows a better selection of patients, which may reflect in higher disease-free survival rates reported in few series (35,42).

In our series, although we performed delayed liver resection only in patients whose metastases did not grow during prehepatectomy chemotherapy, the 1 and 3-year disease-free survival (DFS) rates achieved by DR (53.3% and 15.6%, respectively) were not statistically significant different by those achieved in the SR group (56.7% and 32.5%, respectively; p value = 0.129, log rank test). Although, due to the limitations of our study (retrospective study, more patients in the DR group with extrahepatic metastases), we could not draw definitive conclusions, it seems that the beneficial role of prehepatectomy chemotherapy is overestimated in the literature. Similarly, in a recent review, Reddy et al. concluded that the traditional treatment paradigm centering on the utility of prehepatectomy chemotherapy for resectable SCRLM should be reconsidered (11).

Taking into account the DFS rates achieved by SR and DR in our series, we hypothesize that prehepatectomy chemotherapy could not be considered mandatory before liver resection in all the patients with SCRLM. It may have a favorable role in selected patients, presenting a number of pejorative prognostic factors (such as more than 4 SCRLM, more than 4 metastatic regional lymph nodes – N2, T4 primary tumor), as some authors already reported (25,43,44),

In conclusion, despite the inherent limitations of our study, our results suggest that the simultaneous resection of SCRLM provides a safety profile similar to those achieved by delayed resection, even in patients with rectal tumors or with multiple liver metastases, as well as in patients requiring a major hepatectomy.

Overall and disease-free survival rates achieved by simultaneous resection were similar to those achieved by delayed resection, thus encouraging us to recommend simultaneous resection as an effective therapeutic modality in patients with SCRLM.

Acknowledgement

This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/64153.

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