Simultaneous approach of primary colorectal carcinoma and liver metastases

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Background: Optimal surgical approach to synchronous colorectal liver metastases is a subject of debate. Aims: This retrospective study compares the outcomes of patients undergoing simultaneous resection or delayed resection. Methods: All 238 patients undergoing liver resection between 1995 and 2014 for liver only resectable synchronous colorectal metastases were included in this study. Outcomes were compared between patients undergoing simultaneous resection and delayed resection. Results: The morbidity and mortality rates were similar between the two groups (p value > 0.05), even in patients with rectal tumors or undergoing major hepatectomies. The overall survival rates achieved in the SR group were not significantly lower than in DR group (p value = 0.817), either in N-positive patients, or in patients presenting multiple liver metastases. Conclusion: Simultaneous resection provides similar morbidity, mortality and survival rates as delayed resection, even in N-positive patients or those with primary rectal tumors, multiple metastases or undergoing major hepatectomies.

Key words: colorectal metastases, simultaneous approach, outcome

INTRODUCTION

Colorectal cancer is the third cause of cancer-related death among the adults, most of these patients dying due to the metastatic disease. In patients with colorectal cancer, the most common location of the metastases is the liver, almost 70% of these patients presenting liver metastases at the time of their death.

Between 16 and 25% of patients with colorectal cancer present liver metastases at the time of their primary tumor diagnosis synchronous colorectal liver metastases.

The treatment of patients with colorectal liver metastases is multimodal, involving surgery, chemotherapy, targeted therapies and, sometimes, radiotherapy. However, the highest survival rates and even cure) are achieved by patients undergoing radical resection of the primary tumor and complete resection of liver metastases. The optimal surgical approach of synchronous colorectal liver metastases (CLMs) is still a subject of debate. Few decades ago, it was recommended initial resection of the primary tumor followed by liver resection (few months later delayed resection – DR). In the last two decades, due to the surgical advances mainly in liver resection) and improvements in anesthesiology and intensive care treatment, in specialized centers was performed simultaneous resection of the primary tumor and liver metastases simultaneous resection – SR. The advantages of the latter approach are the avoidance of two operations under general anesthesia, the shorter hospital stay and a more rapid recovery, resulting in a better comfort of the patient and a more cost-effective surgical treatment. Moreover, the simultaneous approach avoids the progression to unresectability of initially resectable liver metastases, which is possible during the period between the two operations in the DR approach). However, the promoters of the delayed approach raised concerns regarding the safety and effectiveness of the SR especially in patients with rectal tumors and/or requiring major hepatectomies), hypothesizing that the morbidity and mortality rates are higher following simultaneous approach, and the “test of time” allowed by DR could offer a better selection of patients reflected in higher survival rates. In this study are compared the outcomes of these two approaches, trying to disclose if one strategy is superior to the other, even in some groups of patients featuring specific characteristics e.g. primary rectal tumor, major hepatectomies, etc.)
MATERIAL AND METHODS

Patients undergoing liver resection for synchronous CLMs were identified from a database including all the patients with CLMs undergoing liver resection in “Dan Setlacec” Center of General Surgery and Liver Transplantation from Fundeni Clinical Institute, Bucharest, Romania.

The inclusion criteria of the patients enrolled in the present study were: 1. liver metastases detected during the work-up for the colorectal cancer or at the time of the operation addressed to the primary tumor; 2. CLMs were resectable at the moment of their diagnosis; 3. absence of extrahepatic metastases metastases with other location than the liver); 4. histologically proven colorectal adenocarcinoma and liver metastases; 5. absence of prior liver directed therapy e.g. hepatectomy, ablative therapies) for CLMs.

Synchronous CLMs were detected either before operation by abdominal ultrasonography and computed tomography (CT scan) or magnetic resonance imaging (MRI), or intraoperatively by visual and palpatory examination of the liver and by intraoperative ultrasonography.

The decision to perform simultaneous resection or delayed resection was based on the surgeons’ opinion regarding the safety of the resection taking into account mainly the clinical status of patient and the presence of primary tumors’ complications.

CLMs were considered resectable when at least two adjacent liver segments could be preserved with adequate vascular inflow and outflow and biliary drainage and functional liver remnant represented more than 30% of the total liver volume in patients with underlying chronic liver disease or receiving more than 6 cycles of preoperative chemotherapy the functional liver remnant should exceed 40% of total liver volume).

A liver resection was considered as major hepatectomy whenever at least three segments were entirely resected.

Postoperative morbidity included all wound, liver resection, colorectal resection and general) complications occurring within 30 days after surgery. Hepatic complications included liver failure, hemorrhage at the transection surface requiring reoperation, bile leak and perihepatic fluid collections. Colorectal complications included anastomotic leak, intraabdominal abscess and peritonitis.

Postoperative mortality was considered the decease of a patient during postoperative hospitalization or within 30 days after operation.

Chi-square and Fisher’s exact test were used to evaluate the association of independent variables with postoperative complications and postoperative deaths. Overall survival probabilities following liver resection were estimated by Kaplan-Meyer method and compared with the Log rank test. Differences were considered statistically significant when p value < 0.05. The statistical analysis was performed with SPSS version 13.0 software SPSS, Chicago, Illinois, USA).

RESULTS

Between January 1995 and June 2014, 238 patients with liver only initially resectable synchronous colorectal metastases underwent liver resection. Simultaneous resection was performed in 193 patients (SR group), while 45 patients underwent delayed liver resection (DR group).

There was a similar distribution in the two groups regarding age, gender, transmural extension of the primary tumor T3 and T4) and number of liver metastases.

In the SR group there were statistical significantly more patients with primary tumor located within the rectum than in the DR group (Table 1). Lymph node metastases were significant more frequently identified in the DR group (86% vs. 67% in the SR group, p value = 0.0477). The patients undergoing DR underwent statistical significantly more frequent preoperative chemotherapy, as well as major hepatectomies (Table 1).

Overall, postoperative complications occurred in 97 patients taking into account the complications following both operations in patients undergoing DR). Although morbidity rate was higher in the SR group (41% vs. 37% in the DR group), the difference was not statistically significant (p value = 0.7371). In patients presenting the same location of their primary tumor either colonic or rectal), the postoperative complication rates were not significantly higher following SR than in patients undergoing DR (Table 2). In patients undergoing major hepatectomies, the morbidity rates following simultaneous resection (54%) were not statistical significantly higher than those observed in patients undergoing DR (50%, p value = 1).

The mortality rates were similar in the SR group and DR group, even in patients undergoing major hepatectomies or presenting primary tumors within the rectum (Table 3).
The overall survival rates achieved by patients under-going SR 85.7%, 50.1% and 30.4% at 1-, 3- and 5-years, respectively) were not statistical significantly different \( p \text{ value} = 0.817 \) of those achieved by DR 87.7%, 63% and 29.7% at 1-, 3- and 5-years, respectively) (Figure 1).

In patients with T3/T4 primary tumors, the overall survival rates were not statistical significantly different between SR group 85.9%, 49.4% and 28.6% at 1-, 3- and 5-years, respectively) and DR group 85.9%, 62.5% and 25.4% at 1-, 3- and 5-years, respectively) – \( p \text{ value} = 0.957 \) (Figure 2a).

For N-positive patients N1/N2) the overall survival rates achieved by SR 84.8%, 46.2% and 25.8% at 1-, 3- and 5-years, respectively) were not statistical significantly lower than those achieved by DR 91.3%, 72.1% and 25% at 1-, 3- and 5-years, respectively) – \( p \text{ value} = 0.519 \) (Figure 2b).

In patients with multiple CLMs, although the overall survival rates achieved by DR 86.5%, 62.5% and 31.6% at 1-, 3- and 5-years, respectively) were higher than those achieved by SR 78%, 38.9% and 19.8% at 1-, 3- and 5-years, respectively), the difference was not statistically significant – \( p \text{ value} = 0.221 \) (Figure 2c).

The 1-, 3- and 5-years overall survival rates of patients undergoing SR without preoperative chemotherapy 85.2%, 51.4% and 29.9%, respectively) were not statistical significantly lower than those achieved by patients undergoing DR after neoadjuvant chemotherapy 93.5%, 67.3% and 33.2% at 1-, 3- and 5-years, respectively) – \( p \text{ value} = 0.629 \) (Figure 2d).

Also, there were no statistical significantly differences between the survival rates achieved by SR and DR in patients with primary tumor located within the rectum \( p \text{ value} = 0.693 \), as well as in patients undergoing major hepatectomies \( p \text{ value} = 0.979 \).

**DISCUSSION**

Despite the inherent limitations of any retrospective study, this report revealed that SR is similar to DR in terms of morbidity, mortality and survival rates. These results are consistent with those reported in several other
retrospective studies and few recent meta-analysis.

Moreover, few retrospective studies and meta-analysis found a lower morbidity rate in patients undergoing SR than in their counter partners that received DR. The authors revealed that the most important factor contributing to this decreased morbidity rate following SR was a bias induced by the significantly lower number of metastases in patients selected for this approach. In the light of this assumption, the similar morbidity rates in the two groups of patients presented in our study may be attributable to the similar percentage of patients with multiple CLMs included in the SR and DR group of the present study.

However, in the present study, to reduce the bias generated by the inhomogeneous characteristics of the two groups of patients regarding the location of the primary tumor, the frequency of lymph node metastastases, the percentage of the patients undergoing major hepatectomies or preoperative chemotherapy, it was conducted a comparison between outcomes of SR and DR taking into account the subgroups of patients featuring similar characteristics.

Because most studies published in the last years revealed that SR generates similar morbidity and mortality rates as DR in patients with primary tumor located within the colon and requiring minor hepatectomies, a multidisciplinary international consensus conference, held in 2012, recommended simultaneous resection as the treatment of choice in such patients. However, in patients whose primary tumor is located within the rectum and/or requiring a major hepatectomy, the Consensus recommendations favored separate resections either delayed liver resection or liver-first resection), with a level C strength of recommendation, due to the potentially higher morbidity and mortality rates associated with SR. In the present study, we compared the morbidity and mortality rates following SR and DR in patients presenting either primary rectal tumors or requiring major hepatectomies. In these groups of patients, the morbidity rates following SR were not statistical significantly higher than the morbidity rates of both operations in the

### Table 1. Comparison of Demographics, Tumor Characteristics, Medical and Surgical Therapies Between Patients Undergoing SR and DR for Synchronous CLMs

<table>
<thead>
<tr>
<th>Variable</th>
<th>SR group</th>
<th>DR group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54% (105/193)</td>
<td>45% (20/45)</td>
<td>0.2491</td>
</tr>
<tr>
<td>Female</td>
<td>46% (88/193)</td>
<td>55% (25/45)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>colon</td>
<td>67% (130/193)</td>
<td>86% (39/45)</td>
<td>0.0103</td>
</tr>
<tr>
<td>rectum</td>
<td>33% (63/193)</td>
<td>14% (6/45)</td>
<td></td>
</tr>
<tr>
<td>T3/T3*</td>
<td>94% (164/173)</td>
<td>91% (31/34)</td>
<td>0.4210</td>
</tr>
<tr>
<td>N1/N2**</td>
<td>67% (110/163)</td>
<td>86% (26/30)</td>
<td>0.0477</td>
</tr>
<tr>
<td>Chemotherapy before LR</td>
<td>20% (39/193)</td>
<td>93% (42/45)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number of SLMs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>57% (110/193)</td>
<td>42% (19/45)</td>
<td>0.0961</td>
</tr>
<tr>
<td>Multiple</td>
<td>43% (83/193)</td>
<td>58% (26/45)</td>
<td></td>
</tr>
<tr>
<td>Extension of LR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor LR</td>
<td>87% (169/193)</td>
<td>73% (33/45)</td>
<td>0.0218</td>
</tr>
<tr>
<td>Major LR</td>
<td>13% (24/193)</td>
<td>27% (12/45)</td>
<td></td>
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</tbody>
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*Missing data of 31 patients, ** Missing data of 45 patients, LR—liver resection
DR group \( p \text{ value} > 0.05 \). Moreover, the mortality rates following SR and DR in patients with primary rectal tumors or requiring major hepatectomies were equal \( p \text{ value} = 1 \). Although other authors revealed statistical significantly higher morbidity and mortality rates after SR in patients with rectal tumors and/or undergoing major liver resections \cite{14,22,23}, our findings are concordant with similar reports published in the last decade \cite{16,27}.

However, our institutions’ policy is to avoid the performance of a simultaneous resection when liver metastases are noted on exploration for emergency colorectal resection perforation, obstruction or bleeding). In selected patients requiring difficult rectal resections or demanding hepatectomies, in the last year, we preferred the liver first approach, which avoids the potentially higher risks of a simultaneous resection, offering the chance of a potentially curative liver resection to more patients with synchronous CLMs than the delayed approach. In the two patients undergoing “liver-first approach” there was noted no one complication following two major hepatectomies and two colorectal resections.

Although primary tumor resection can be safely associated with liver resection in most patients with synchronous CLMs, concerns regarding the long-term outcomes of patients undergoing SR were raised by the supporters of the DR approach, based on several theoretical assumptions: 1. preoperative chemotherapy delivered during the interval between the first and the second operation could eliminate dormant tumor cells, thus reducing the recurrence rates after delayed resection; 2. during the interval between the two operations could be assessed the aggressiveness of the tumor, avoiding a useless liver resection in patients whose metastases progress under chemotherapy; 3. the observation interval allows a better selection of patients for hepatectomy, improving survival rates after delayed resection; 4. the response and/or tolerability to preoperative chemotherapy may guide postoperative chemotherapeutic regimen \cite{28-30}.

Hence, in the present study, the overall survival rates of patients undergoing SR were not statistical significantly lower than those achieved by DR \( p \text{ value} = 0.817 \). Moreover, to better evaluate the ability of preoperative

<table>
<thead>
<tr>
<th>Categories</th>
<th>SR group</th>
<th>DR group</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>41% (80/193)</td>
<td>37% (17/45)</td>
<td>0.7371</td>
</tr>
<tr>
<td>Major LR</td>
<td>54% (13/24)</td>
<td>50% (6/12)</td>
<td>1</td>
</tr>
<tr>
<td>Minor LR</td>
<td>39% (67/169)</td>
<td>33% (11/33)</td>
<td>0.5612</td>
</tr>
<tr>
<td>Rectum</td>
<td>46% (29/63)</td>
<td>50% (3/6)</td>
<td>1</td>
</tr>
<tr>
<td>Colon</td>
<td>39% (51/130)</td>
<td>35% (14/39)</td>
<td>0.8514</td>
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</table>

<table>
<thead>
<tr>
<th>Categories</th>
<th>SR group</th>
<th>DR group</th>
<th>( p \text{ value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4.1% (8/193)</td>
<td>4.4% (2/45)</td>
<td>1</td>
</tr>
<tr>
<td>Extension of LR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major LR</td>
<td>8.3% (2/24)</td>
<td>8.3% (1/12)</td>
<td>1</td>
</tr>
<tr>
<td>Minor LR</td>
<td>3.5% (6/169)</td>
<td>3% (1/33)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>1.5% (1/63)</td>
<td>0% (0/6)</td>
<td>1</td>
</tr>
<tr>
<td>Colon</td>
<td>5.3% (7/130)</td>
<td>5.1% (2/39)</td>
<td></td>
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</table>
chemotherapy to improve survival following liver resection, we compared the survival rates of patients undergoing SR without neoadjuvant chemotherapy with those achieved by patients undergoing DR after preoperative chemotherapy. Although the survival rates were higher in patients undergoing DR after chemotherapy than in simultaneous resected patients without preoperative chemotherapy, the difference was not statistically significant \(p \text{ value} = 0.629\). These results, which are concordant with those already reported by other authors dealing with this subject, could be explained by the fact that short-course chemotherapy is not able to differentiate the responders by non-responders. This fact could be expected, taking into account that in most recent studies, the patients presenting unresectable CLMs achieved a median progression-free survival after the first-line chemotherapy longer than 6 months\(^9,32,33\). Thus, a prolonged interval between the first and second resection should be necessary to better select the patients, but such an extended interval could expose the patients to two dangerous scenarios: 1. The higher number of preoperative chemotherapy cycles increases the risk of chemotherapy-induced liver injury, increasing the morbidity and eventually) mortality rates after hepatectomy\(^4,5,6\). 2. The initially resectable CLMs could progress to unresectability during this observation interval. Because both of these situations jeopardize the chance for a long-term survival of patients with initially resectable synchronous CLMs, such a prolonged observation interval is not acceptable.

However, different authors identified few factors correlated with a poor prognosis in patients with synchronous CLMs, hypothesizing that in such situations the DR could improve the survival rates due to the beneficial effects of prehepatectomy chemotherapy and better selection of patients. Among these factors were multiple CLMs, locally advanced primary tumors T3/T4), the presence of lymph nodes metastases N-positive patients)\(^13,37,38\). To evaluate whether DR represents a more efficient strategy than SR in such patients, there were compared overall survival rates achieved by these two approaches in each category of patients.

Although other reports\(^37,39,40\) suggested that in patients with multiple synchronous CLMs the overall survival rates achieved by DR are significant statistically higher than those achieved by SR, in the present study, the survival rates achieved by SR and DR were similar, both in patients presenting at least two CLMs \(p \text{ value} = 0.221\) and in patients with more than three metastases \(p \text{ value} = 0.782\). Moreover, few years ago we found that the lymph node metastases are an important predictor of poor survival in patients with synchronous CLMs, hypothesizing that delayed resection after preoperative chemotherapy may improve the long-term outcomes\(^13\). In the present study we did not found any statistical significantly difference between survival rates achieved by SR and DR, neither in N-positive patients, nor in N2 patients \(p \text{ value} > 0.05\). Similar results were reported by other retrospective studies which demonstrated that the use of prehepatectomy chemotherapy does not change the dismal outcome of patients with poor prognostic indicators of disease and therefore does not alter long-term survival\(^37,41\).

Although other authors consider that SR is preferable due to its short-term results regarding safety and comfort of the patient) but has a negative impact on long-term outcome, the present report suggest that DR does not offer any benefit over SR in terms of safety and efficacy for patients with synchronous CLMs. Moreover, the partisans of the DR do not take into account, when compare the survival rates after SR and DR, the patients scheduled for o DR) whose metastases progress during “observation interval” and did not undergo liver resection drop-off patients). Thus, an intention to treat analysis, comparing SR and DR, could no longer reveal the survival benefit of DR, but a study aiming directly this question is not available.

To overcome the drawbacks of both SR and DR approaches, in the last years, a new onco-surgical approach emerged to treat the patients with synchronous CLMs, especially those with rectal tumors or border-line resectable CLMs. This therapeutic strategy, called “liver first resection”, consists in preoperative chemotherapy, followed by hepatectomy and subsequent colorectal resection. Moreover, the patients with rectal cancer may undergo radiotherapy during the interval between the two operations. The “liver first resection” seems to be more convenient in such patients because it combines the advantages of the two previous mentioned approaches. Thus, in patients with primary rectal tumors or requiring major hepatectomies, for whom different reports raised concerns regarding the safety of a simultaneous approach, this new strategy offers a staged resection of their malignant burden, decreasing the cumulative risk of a simultaneous difficult colorectal and liver resection. By an oncologic point of view, similar to the delayed liver resection, these approach offers to the patients presenting poor prognostic factors the advantages of the prehepatectomy chemotherapy. Unlike DR approach, in which high levels of growth factors are released following the primary tumor resection stimulating CLMs growth and making possible their progression to unresectability, the “liver first” approach allows initial clearance of the metastases\(^42,43\). Because most patients with synchronous CLMs decrease due to their metastases progression, this approach avoids progression to unresectability of their initially resectable CLMs, increasing the chance of a long term survival. Moreover, in patients with initially unresectable or border-line-resectable metastases, preoperative chemotherapy associated with targeted therapies) could down-size CLMs rendering resectable. In such instances, “liver first approach” offers the chance of a potentially curative liver resection, avoiding metastases re-growth which would compromise the chance of long-term survival in such patients.

In conclusion, simultaneous resection of the primary tumor and colorectal liver metastases provides similar morbidity, mortality and survival rates as delayed resection. Even in patients with primary rectal tumors or undergo-
ing major hepatectomies, the morbidity and mortality rates after SR were not higher than those observed following DR. In patients with synchronous colorectal liver metastases presenting poor prognostic factors N-positive, multiple metastases) the survival rates were not improved by DR. “Liver first resection” is a promising onco-surgical strategy, able to overcome the disadvantages of SR and DR, particularly in patients with rectal tumors, requiring major hepatectomies, or presenting poor prognostic factors.

**SUMMARY**

**SIMULTANEOUS APPROACH OF COLONIC METASTASES**

Optimal hiirški pristup sinhronim kolorektalnim metastażama je predmet debate. Cilj: Ova retrospektivna studija poredi ishode leéenja pacijenata od kojih su neki bili podvrgnuti simultanoj, a neki odloženoj resekciji jetre. Metode: U ovu studiju smo ukluèili sve 238 pacijenata kojima je uéinjena resekcija jetre u periodu od 1995 do 2014 godine zbog resektabilnih kolorektalnih metastaža koje su se javile samo u jetri. Rezultati su poredjeni izmedju grupa sa simultanom i odloženom resekcijom jetre. Rezultati: Stopa morbiditeta i mortaliteta je slièna izmeðu ove dve grupe p<0.05, èak i kod pacijenata sa tumorom rektuma ili kod kojih je raèena opseºnja hepatoktomija. Ukupna stopa preºivljavanja u grupi sa simultanom resekcijom nije bila znaèajno niža od grupe sa odloženom p=0.817), èak i kod N-positivnih pacijenata ili kod onih sa primarnim karcinomom rektuma, multiplim metastazama ili onima podvrgnutim opseºnim resekcijama jetre.

Kljuèe reèi: metastaze kolorektalnog karcinoma, simultani pristup

**REFERENCE**


