Background: Approximately 25% of patients with colorectal cancer present synchronous metastases, most frequently located in the liver.

Aims: The assessment of optimal therapeutic strategies for the primary tumor in such patients.

Methods: We analyzed the outcomes of 209 patients who underwent simultaneous or delayed resection of the primary tumor and liver metastases, the survival rates of patients with initially unresectable liver metastases that were rendered resectable, and the prognostic factors related to the primary tumor.

Results: The outcomes of simultaneous resections were similar to those of delayed resection. In patients with initially unresectable liver metastases that were rendered resectable, the survival rates were similar to those of patients with initially resectable metastases. The survival rate of N2 patients was significantly lower than those of N1 and N0 patients.

Conclusions: Simultaneous resection provides a safety profile and survival rate similar to that of delayed resection. The N category allows for prognostic estimation in metastatic colorectal patients.

Key words: colorectal, metastases, simultaneous resection, resectability, prognostic

INTRODUCTION

In 2010, it was estimated that colorectal carcinoma represented the third most common cancer (in both men and women) and the third-ranked cause of cancer-related deaths in the United States.

The leading cause of death in colorectal cancer (CRC) patients is liver metastases, accounting for almost two-thirds of CRC death. Approximately 15 - 25% of patients with colorectal cancer present with liver metastases at the time of their primary tumor diagnosis.

In addition, approximately 15 - 30% of patients under-}

going a curative resection of their CRC will subsequently develop liver metastases, most of them within the first three years after primary tumor resection. Thus, in patients with CRC, the most common site of distant metastases is the liver (45-65%). Other less frequent sites of metastatic disease are the peritoneum (15%), lung (10%), bone (1.9%), brain (1.7%) and other sites (4.1%).

Until the mid-1990s, 5-Fluorouracil and Leucovorin were the sole chemotherapeutic agents used in the treatment of patients with metastatic CRC (MCRC), and surgical resection of distant metastases was performed in less than 6% of patients.

At that time, the median overall survival of patients with MCRC ranged between 8 and 14 months. More frequent liver resection and the advent of new therapeutic agents (e.g., Irinotecan, Oxaliplatin, Bevacizumab, Cetuximab and Panitumumab) have dramatically changed the outcomes for these patients in the last 15 years.

A two-institution study presented in 2009 by Kopetz et al. revealed that the median overall survival times of all patients with MCRC diagnosed from 1998 through 2006 improved significantly in comparison to those achieved in patients diagnosed between 1990 and 1997.

This change in median survival occurred in two stages: the first stage began with patients diagnosed in 1998 and was associated with the increased use of hepatic resection, while the second stage of survival gains began in 2004 and is most likely attributable to the use of new therapeutic agents.

Similar trends were reported in a population-based study presented in 2010 by Edwards et al., who revealed that both the incidence and death rates from CRC significantly declined in the most recent time period. Microsimulation modeling demonstrates that declines in CRC death rates are consistent with a relatively large contribution from...
screening and a smaller but demonstrable impact of risk factor reductions and improved treatments.

These two studies revealed unequivocally that liver resection of colorectal metastases and the use of new therapeutic agents were the most important therapeutic tools that improved the survival of patients with MCRC.

Moreover, Edward et al. projected that these declines in death rates from CRC should continue if risk factor modification, screening, and treatment continue at the current rates; however, they could be accelerated further with favorable trends in risk factor modification and increased utilization of screening and optimal treatments.

We consider that the improved management of the primary tumor plays an important role in the optimization of treatment of patients with MCRC.

The present study focuses on the management of the primary tumor in patients with synchronous colorectal liver metastases and on the prognostic factors related to the colorectal tumor that may impact the outcome of MCRC patients. Therefore, we conducted an analysis of the results achieved in our center by simultaneous and delayed approaches to the primary tumor and liver metastases in patients with synchronous colorectal metastases. We also present our therapeutic strategy with respect to the primary tumor in patients with initially unresectable synchronous colorectal metastases to determine whether certain patients could benefit from colorectal tumor resection.

Prognostic factors related to the primary tumor will also be addressed. Better prognostic ability may allow for better allocation of oncological treatments and thus increase the long-term survival of MCRC patients.

MATERIAL AND METHODS

Between 1995 and 2012, in the Dan Setlacec Center of General Surgery and Liver Transplantation of the Fundeni Clinical Institute in Bucharest, Romania, 483 liver resections in 430 patients with colorectal cancer liver metastases (CRLM) (39 patients underwent one liver re-resection and 7 patients underwent 2 liver re-resections) were performed.

The data were collected retrospectively for 203 patients who underwent liver resection for colorectal liver metastases from 1995 through 2005 and prospectively for the 227 patients operated on between 2006 and 2012.

Colorectal liver metastases were considered synchronous when they were diagnosed during the work-up for the colorectal cancer or at the time of the operation addressing the primary tumor.

Liver resection was performed for synchronous colorectal liver metastases (SCRLM) in 231 patients and for metachronous colorectal liver metastases (MCRLM) in 199 patients.

In patients with synchronous colorectal liver metastases, liver resection was performed simultaneously with primary tumor resection in 181 patients, whereas 50 patients underwent a delayed liver resection (initial primary tumor resection followed by neoadjuvant chemotherapy and subsequent liver resection).
were excluded from the analysis. Thus, the final simultaneous resection group (SR) included 168 patients, whereas the delayed resection group (DR) included 41 patients.

To determine the optimal therapeutic strategy for the primary tumor and for liver metastases management in patients with SCRLM, we compared the morbidity, mortality, and survival rates achieved by simultaneous resection vs. delayed resection.

Thirteen patients with initially unresectable SCRLM were scheduled to undergo an aggressive approach consisting of primary tumor resection and surgical treatment with curative intent of liver metastases rendered resectable through different therapeutic strategies. The therapeutic strategies used in these patients were as follows:

- simultaneous resection of the primary tumor associated with liver resection and radiofrequency ablation of liver metastases - 4 patients.
- resection of the primary tumor and a "two-stage approach" directed to the liver metastases - 6 patients (with right portal branch ligation - 2 patients and without portal vein occlusion - 4 patients). Resection of the primary tumor was associated with resection of few metastases from the future liver remnant (and right portal vein ligation) during the first operation; the second operation consisted of the resection of the metastatic burden from the liver. This approach achieved an R0 resection in 4 patients, but was unable to ensure a complete resection in 2 patients, whose disease progressed after the first operation.
- liver resection after right portal vein ligation - 2 patients. During the first operation, resection of the colorectal tumor was combined with right portal branch ligation; 4-6 weeks later, the patients underwent complete resection of liver metastases.
- liver resection after "down-sizing" neoadjuvant chemotherapy - 1 patient.

To assess the usefulness and efficacy of such an aggressive approach in patients with initially unresectable SCRLM, we calculated the survival rates of these patients (n=13) and compared those to a larger group of patients with initially resectable SCRLM (n=196).

To identify which parameters related to the primary tumor may impact the survival of patients with synchronous colorectal liver metastases, we compared the survival rates achieved by different groups of patients according to their T and N categories based on the available data regarding postoperative TNM (pTNM) staging. Regarding the T category, reliable data were available in 84% (176/209) patients, whereas for the N category, we collected reliable data in 79% (164/209) of patients.

Postoperative morbidity included complications between grades II and V in the Dindo-Clavien classification system11 that occurred during the postoperative hospitalization or within 30 days after surgery.

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

Overall survival was calculated from the date of surgery to the date of the last follow-up or to the time of death. Actuarial survival was calculated by the Kaplan-Meier method.

Statistical analyses were performed with univariate tests (chi-square, Fisher’s exact or log-rank). A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed with the SPSS software, version 17.0 (SPSS, Chicago, IL).

RESULTS

Survival rates of patients with SCRLM with or without extrahepatic metastases

Of the 231 patients who received operations for SCRLM in our center, 22 patients presented hepatic and extrahepatic metastases.
The 1-, 3- and 5-year overall survival rates achieved by patients with synchronous hepatic and extrahepatic metastases were 52.9%, 5.9%, and 0%, respectively (Figure 1). The median survival was 12.6 (+/- 1.02) months.

In the other 209 patients presenting liver-only SCRLM, the 1-, 3-, and 5-year overall survival rates achieved with liver resection were 84.9%, 51.9%, and 25%, respectively (Figure 1). The median survival was 37.6 (+/-3.45) months.

The difference between overall survival rates achieved in these two groups of patients was highly significant (p value < 0.001, log-rank test).

Because the outcome of patients presenting extrahepatic metastases is significantly poorer than that achieved in patients with liver-only metastases, we considered that analyzing all of the patients together may introduce a bias in the statistical analysis. Therefore, to more reliably identify the effect of factors related to the primary tumor on the outcomes of patients with synchronous colorectal liver metastases, we analyzed only the patients without extrahepatic metastases (n = 209).

MANAGEMENT OF THE PRIMARY TUMOR AND LIVER METASTASES IN SCRLM

Simultaneous vs. delayed resection in SCRLM

The morbidity rate of patients with liver-only synchronous colorectal metastases (SCRLM) undergoing simultaneous resection (SR) was 39.2% (66/168).

In patients undergoing delayed resection (DR), the morbidity rate was 26.8% (11/41).

The difference in morbidity between the SR and DR groups was not significantly different (p value = 0.1525, Fischer's exact test).

In the SR group, the mortality rate was 3.5% (6/168), whereas in the DR group, it was 4.8% (2/41). This difference in mortality was not significantly different (p value = 0.6566, Fischer's exact test).

The 1-, 3-, and 5-year overall survival rates achieved through SR were 83.9%, 48.8% and 24.5%, respectively (Figure 2). The median survival in the SR group was 33.9 (+/- 4.08) months.

The 1-, 3-, and 5-year overall survival rates achieved through DR were 89.1%, 48.8% and 24.5%, respectively (Figure 2). The median survival in the DR group was 41.3 (+/- 2.38) months.

The survival rates achieved through SR and DR, were not significantly different (p value= 0.459, Log-rank test).

Resection of the primary tumor and liver metastases in initially unresectable SCRLM

Thirteen patients with initially unresectable SCRLM were scheduled for a potentially curative treatment. A potentially curative resection was achieved in 84.6% (11/13) of patients.

In patients with initially unresectable SCRLM, the morbidity rate was 61.5% (8/13), whereas in patients with initially resectable SCRLM, the morbidity rate was 35.2%.

The difference in survival rates between patients with initially resectable SCRLM and those with initially unresectable SCRLM scheduled for a potentially curative treatment was not significant (p value = 0.667, Log-rank test).

PROGNOSTIC FACTORS RELATED TO THE PRIMARY TUMOR IN PATIENTS WITH SCRLM

T category

The 1-, 3-, and 5-year overall survival rates achieved by patients with SCRLM presenting T2 tumors (90.9%, 63.6%, and 21.2%, respectively) were higher than those associated with T3 tumors (83.3%, 47.3%, and 22.2%, respectively) and T4 tumors (87.5%, 50.3%, and 20.1%, respectively); however, the difference was not significant (p value = 0.938, Log-rank test) (Figure 4).
Regarding the usefulness of pre-hepatectomy chemotherapy for selecting tumors with favorable biological behavior, it was hypothesized that the delayed approach avoids futile liver resections, leading to higher survival rates than those achieved by simultaneous resection. In this study, the overall survival rates achieved by SR were similar to those achieved by DR, indicating that pre-hepatectomy chemotherapy has limited value for the selection of patients. Similar results were reported in most series published thus far [18,19,24,28,31,32], suggesting that the traditional treatment paradigm centered on the utility of pre-hepatectomy chemotherapy for resectable SCRLM should be reconsidered[17]. However, a few studies have shown that the delayed approach enables higher disease-free survival rates than simultaneous approach [24,33].

Taking into account all of the aforementioned arguments, our strategy is to perform simultaneous resection of the primary tumor and liver metastases in patients with SCRLM without complications of the primary tumor (e.g., perforation, occlusion, or bleeding). In patients who present with more than three liver metastases, a short course of chemotherapy before simultaneous resection could be useful. Delayed liver resection is performed for patients with complications of the primary tumor and whenever a N2 status is confirmed by intraoperative pathologic examination.

**MANAGEMENT OF THE PRIMARY TUMOR IN PATIENTS WITH INITIALLY UNRESECTABLE SCRLM**

Due to the recent excellent survival rates achieved by liver resection in patients with resectable CRLM, most groups have tried to render resectable more and more patients with initially unresectable liver metastases, thus increasing the chance of long-term survival and even cure to an increasing number of patients with MCRC. The most frequently used methods to mitigate the initially unresectable CRLM are portal vein occlusion and subsequent liver resection, "two-stage" liver resection (with or without portal vein ligation/embolization), resection of liver metastases after "down-sizing" chemotherapy and liver resection associated with thermal ablation of unresectable metastases [34-44].

In the present series, 11 out of 13 (84.6%) patients with initially unresectable SCRLM scheduled for such a therapeutic approach successfully underwent a curative treatment. This rate of conversion to resectability of selected patients with initially unresectable CRLM is similar to those reported in the literature (ranging from 50 to 81%), revealing that is difficult at the time of diagnosis to predict which patients could be rendered resectable. Because the survival rates of patients rendered resectable are significantly higher than those achieved by palliative treatment, we consider that initial radical resection of the primary tumor is worthwhile to avoid jeopardizing the chance of long-term survival and possible cure in patients whose liver metastases will become resectable. Because the survival rates of selected patients with initially unresectable CRLM were similar to those of patients with initially resectable metastases [38-41], we consider that the
principles of primary tumor resection in such patients should be similar to those undertaken in patients with initially resectable SCRLM.

Even in patients whose liver metastases could not be rendered resectable, an initial resection of the primary tumor avoids the development of complications related to the primary tumor (e.g., occlusion, perforation or bleeding). The importance of this issue has increased in recent years because advances in multidrug regimens such as FOLFOX and FOLFIRI have prolonged survival and subsequently raised the incidence of complications of colorectal tumors. Retrospective studies showed that the chance of complications related to the primary tumor in patients with SCRLM treated with initial chemotherapy is approximately 20%. Moreover, two randomized clinical trials and two observational cohort studies suggested that the incorporation of Bevacizumab into the first-line chemotherapy for patients with unresectable primary tumors and/or unresectable colorectal metastases increases the rates of gastrointestinal perforation and bleeding. Both BEAT and BRITE studies revealed that the presence of an intact primary tumor was an independent prognostic factor associated with primary tumor perforation and bleeding. Furthermore, in patients with unresectable SCRLM, the mortality rate achieved through emergency resection of the primary tumor appears to be significantly higher than that experienced by patients whose primary tumors were resected in elective operations. For these reasons, we consider that the initial resection of the primary tumor is a worthwhile operation to avoid the development of colorectal tumor-related complications and subsequently higher mortality rates due to emergency colorectal resection. Interestingly, although some authors have suggested that primary tumor resection in patients with unresectable metastases from colorectal cancer does not offer any survival benefit, two recent retrospective studies and a meta-analysis suggested that colorectal resection followed by an aggressive palliative chemotherapy provides overall survival rates significantly higher than those achieved by chemotherapy alone. Because the results of the randomized controlled trial (ISRCTN30964555) dealing with unresectable SCRLM, overall survival rates achieved by liver resection are similar to those of patients with unresectable SCRLM. The difference in survival rates among the three categories of patients according to the N status highlights the necessity of harvesting at least 12 lymph nodes to assess as accurately as possible the N status of the patients. A reliable assessment of the N category allows a better estimation of the patients’ prognosis.

ESMO clinical practice guidelines for advanced colorectal cancer indicate no perfect selection criteria for determining which patients are candidates for each type of initial chemotherapy. Thus, an estimated 15% of patients are still treated initially with a fluoropyrimidine alone, although the FOLFOX and FOLFIRI regimens provide better survival rates than do 5-Fluorouracil and Leucovorin. Moreover, an exposure to all three cytotoxic agents (fluoropyrimidines, oxaliplatin and irinotecan) in various sequences results in the longest survival. On the other hand, combinations of different chemotherapeutics may incur cumulative toxicity, thus increasing the risk of treatment discontinuation. Thus, the survival advantages may not be achieved due to the risks of toxicity and discontinuation, and it is most likely more reasonable to provide a particular chemotherapeutic regimen based on a thorough evaluation of risk factors in each patient. It seems advisable to deliver more aggressive chemotherapeutic regimens in patients at a higher risk of recurrence.

In contrast, the present study, the overall survival rates achieved by patients with SCRLM differed significantly by nodal status (N0 vs. N1 vs. N2 - p value < 0.05). Thus, the patients without lymph nodes metastases around the primary tumor (N0) experienced the best overall survival rate, while the worst survival rate was observed in patients with metastases in four or more loco-regional lymph nodes (N2). Although Minagawa et al. did not find a significant difference in the survival rates of N0 patients vs. N1 patients, the difference was highly significant in patients with N0 vs. N2 status and in patients with N1 vs. N2 status. Taking into account these results, biological selection by neoadjuvant chemotherapy seems to be more suitable for patients with 4 or more colorectal lymph node metastases, if the loco-regional lymph node status can be assessed intraoperatively. This therapeutic strategy is also supported by the findings of Fujita et al., who revealed that in patients with SCRLM with six or more metastatic loco-regional lymph nodes, the overall survival rates achieved by liver resection are similar to those of patients with unresectable SCRLM.

PROGNOSTIC FACTORS RELATED TO THE PRIMARY TUMOR IN PATIENTS WITH SCRLM

Our results revealed that in patients with SCRLM, the survival rates achieved through liver resection were not significantly influenced by the T categories. Similar results have been reported by Fujita et al. in 2006 and Minagawa et al. in 2006, revealing that the T category is not able to stratify patients with SCRLM in terms of survival after liver resection.

Based on finding that patients with N0 primary tumors achieve a better outcome than do N1 patients, who in turn present a more favorable prognosis than do N2 patients, it could be hypothesized that the N category may represent a useful tool for the allocation of the adjuvant chemotherapy. Thus, the N2 patients with SCRLM seem to be appropriate candidates for the most aggressive adjuvant regimens, while patients in the N0 category may receive the less aggressive treatment.

Moreover, patients with worse prognosis should receive a more intensive postoperative follow-up due to their higher risk of recurrence. Thus, an aggressive therapeutic approach for recurrence (e.g., liver re-resection and/or tar-
Metastatic colorectal cancer - what about the primary?

The most appropriate therapeutic management of the primary tumor in patients with metastatic colorectal cancer remains a subject of debate. Certain parameters related to the primary tumor may have a prognostic value in patients with colorectal liver metastases. Our results suggest that simultaneous resection of the primary tumor and liver metastases represents a safe and efficacious approach and that primary tumor resection provides a survival benefit in patients with initially resectable SCRLM. A wide surgical resection of the involved segment of bowel together with removal of its lymphatic drainage is mandatory for a better assessment for lymph nodes metastases, as long as the N category allows a better estimation of the prognosis in patients with SCRLM and a more appropriate allocation of adjuvant chemotherapy and of the follow-up regimen.

Chemotherapy should be tailored according to risk factors.

SHORT OVERVIEW

The most appropriate therapeutic management of the primary tumor in patients with metastatic colorectal cancer remains a subject of debate. Certain parameters related to the primary tumor may have a prognostic value in patients with colorectal liver metastases. Our results suggest that simultaneous resection of the primary tumor and liver metastases represents a safe and efficacious approach and that primary tumor resection provides a survival benefit in patients with initially resectable colorectal liver metastases that are rendered resectable. The number of metastasis-positive lymph nodes around the primary tumor is of higher prognostic value in patients with synchronous colorectal liver metastases and allows for more appropriate allocation of adjuvant chemotherapy and follow-up regimens.

SUMMARY

METASTATSKI KOLOREKTALNI KARCINOM - ŠTA JE SA PRIMARNIM?


REFERENCE


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Abbreviations: CRC - colorectal cancer, MCRC - metastatic colorectal cancer, CRLM - colorectal liver metastases, SCRLM - synchronous colorectal liver metastases, SR - simultaneous resection, DR - delayed resection

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