

Original Article

Surgical Treatment of Colorectal Cancer Hepatic Metastases. Experience of A.C. Camargo Cancer Hospital - São Paulo

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Abstract

Introduction: Colorectal cancer is the fourth leading cause of malignancy in Brazil, as well as in the US. Hepatic metastasis, occur in up to 50% of patients during the course of the disease. To date, surgical resection is the standard treatment, and is associated with the best survival outcome. Identifying prognostic factors is important for better patient selection. **Patients and Methods:** Data of 70 patients submitted to hepatic resection of colorectal metastasis with curative intent between January 1999 and June 2005 were reviewed. Clinical data and surgical pathology features of all patients were analyzed. **Results:** 76 procedures were performed in 70 patients, Global estimated survival was 51 % in 5 years. Prognostic significantly variables were number of metastasis, bilaterality and preoperative CEA. Postoperative death occurred only in one patient, due to infection and sepsis. **Conclusion:** Surgical resection is the best treatment for colorectal hepatic metastasis, though prognostic factors imply worst outcome, survival is better than non surgical treatment. In this series we identified objective prognostic factors which might help the physician to select the best moment of resection and add systemic treatments.

Key words: Colorectal Neoplasms. Metastasis. Hepatic metastasis. Surgery.

Introduction

The colorectal cancer occupies in the developed countries and in Brazil the fourth position in the statistics of incidence of malignant illnesses behind only lung, breast and prostate cancer.^{1,2} Annually in the United States more than 120.000 new cases, and more than 50.000 deaths related to the illness are diagnosed.

The most common site of metastases of colorectal carcinoma is the liver. At the moment of diagnosing colorectal neoplasia, 15 to 25% of the patients have synchronous hepatic metastases detected either by pre- or intraoperative evaluation.³ Moreover, after primary tumor resection with curative intent, 15 to 40% of patients present metachronic hepatic metastases during evolution.⁴ Thus, about half of patients of colorectal cancer has or will have hepatic metastasis/es.

When evaluating the natural history of patients with hepatic metastases potentially resectable but had opposed to surgical treatment, we find an average survival of 14 to 24 months, and no 5-year survival.⁴ The more conservative treatment of the illness with systemic

chemotherapy reduces tumoral volume in 10% to 20% of the cases, but improvement in patients' survival was not demonstrated. One also knows that hepatic intra-arterial chemotherapy used as the exclusive treatment is followed by a significant tumoral necrosis but does not modify survival rates. On the other hand, several specialized centers show that 25% to 48% of the patients present 5-year survival after hepatic resection of hepatic metastases.⁵⁻¹⁶ This shows that that certainly surgical treatment is at the moment the only able to cure patients with colorectal cancer hepatic metastasis.

This work aims to describe our experience in the surgical treatment of hepatic metastases of colorectal cancer, evaluating short- and long-term results and

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prognostic factors of patients submitted to resection with curative intent.

Patients and Methods

A retrospective study of 70 patients with hepatic metastasis/es of colorectal cancer submitted to resection with curative intent between January 1999 and June 2005. From this group, 37 (52.9%) were women and 33 (47.1%) men, with an average age of 58.9 years (36 to 76 years) and median of 59 years.

Patients with extra-hepatic diseases, except for pulmonary metastases considered respectable were excluded.

The pre-operation staging included thorax x-ray, CT scan or magnetic resonance of abdomen and pelvis, colonoscopy and, more recently, PET SCAN. The immediate and late results were evaluated through clinical, laboratorial and the primary illness parameters. The evaluated clinical factors were age, sex, localization and staging of the primary tumor, and disease-free time after the appearance of metastasis. We consider hepatic metastasis as synchronous when the interval between the primary tumor and the detection of metastasis was less than 12 months and metachronic when the interval was more than 12 months. Variable related to metastases were the number and size of lesions and their site (uni or bilaterality).

Statistical analysis used the program Stata 7.0 (descriptive statistics) and Fisher descriptive test. The calculation of significance was done by "log rank" and estimates of survival by Kaplan Meier method. Values inferior to 0.05 were considered significant.

The operated patients were followed up in the ambulatory every three months in the first 2 years and every six months afterwards. In these evaluations laboratory examinations of hepatic function, tumoral markers and image (computerized tomography and/or ultrasonography). The period of follow-up varied from 12 to 68.3 months, with an average of 28 months. All patients were submitted, in the postoperative, to adjuvant systemic chemotherapy.

Results

76 hepatic resections were carried through in 70 patients, that is, some patients were submitted to repeat resections during the period of follow-up: two patients were submitted to two hepatectomies and two to three. The primary tumor was located in the rectum in 32

(45.7%) patient and in the colon in 38 (54.3%). Regarding the number of resected metastases, the average was 2 lesions, with a variation from 1 to 6 nodules. The size of tumors varied from 1.5cm to 12cm, with an average of 4.1cm and a median of 3.5cm. Moreover, 52 patients (74%) presented a disease limited to one only a hepatic lobe and 18 (26%) had a bilobar disease. Thirty one patients (44,2%) presented synchronous metastases and 39 (55,8%) metachronic ones. The evaluation of compromised lymph nodes in the primary tumor was not possible because only 21 patients had this data in their histories. Most resected patients had the primary tumor resected in other institution, and that made it difficult to access these data. This prevented us to carry through a statistical analysis of this variable.

The level of carcinoembryogenic antigen (CEA) measured in the preoperative was above normal limits in 37 patients (52.8%) and varied from 1 to 1100 units, with an average of 77.68 and a median of 14.9. Only one death happened in the postoperative (1.3%), in a patient who presented acute obstructive abdomen, having evolved with peritonitis, septicemia, multiple organ failure and death.

Surgery distribution was: 11 segmentectomies; 17 bi-segmentectomies; 27 right hepatectomies; 15 left hepatectomies; 4 right extended hepatectomies; 1 left extended hepatectomy and 1 mesohepatectomy (Table 1). In 3 patients resection was associated to nodules ablation by radio frequency. There was no intraoperative mortality.

The period of hospital internment varied from 3 to 60 days, with an average of 6 days. Post-operative complications were: intracavitary collections in 7 (9.21%) patients, biliary fistulas in 5 (6.57%), cardio- in 4 (5.26%) and dialytic renal insufficiency in 2 (2.63%) patients. Patients that presented collection needed surgical draining in 3 cases due to a suspicion of bleeding, other 3 patients needed percutaneous draining guided by CT scan, and only 1 received an exclusively clinical treatment with antibiotics, with good evolution. All patients with biliary fistula evolved positively with expectant clinical treatment.

Global survival was 80.7% in 2 years and 51% in 5 years (Graph 1). Among the studied variables, the number of metastases, the bilaterality of metastases and the level of preoperative CEA represented prognostic factors that in an independent way affected prognostic significantly. 2- and 5-year survival in patients with up to 2 lesions was 81% and 72% respectively (Graph 2), whereas for those with more than two metastases was 26% and 13% ($p = 0.0001$). In relation to the presence of disease in

one or both lobes, 2- and 5-year survival was 70% and 61% (Graph 3) when only a lobe was affected and 42% and 30 in cases of bilobar disease ($p=0.0226$) respectively. Preoperative CEA levels (Graph 4) when higher than 75 units presented a worse survival: 54% and 18% in 2 and 5 years, respectively, whereas in patients with levels up to 75, survival rates were 66% in 2 and 5 years ($p=0.0346$). Sex, age, tumor size, location of primary tumor, and interval between the primary and the appearance of metastasis did not present statistically significant influence in survival rates of these patients.

Table 1 – Types of surgeries performed

Type of surgery	Number
Segmentectomy	11
Bisegmentectomy	17
Right Hepatectomy	27
Left Hepatectomy	15
Extended Right Hepatectomy	4
Extended Left Hepatectomy	1
Mesohepatectomy	1
Total	76

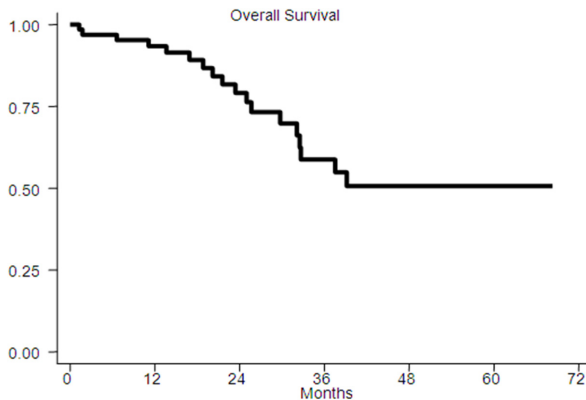


Figure 1 – Overall Survival

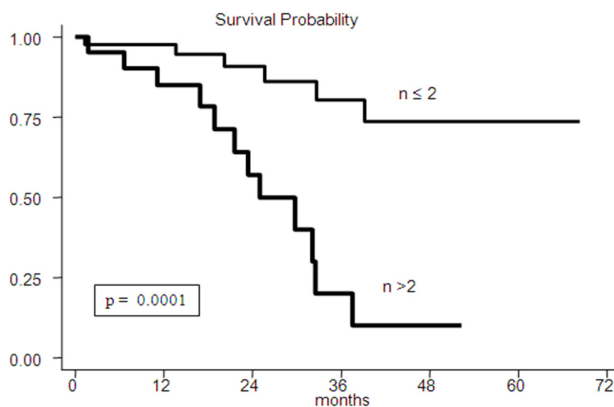


Figure 2 – Survival probability related to number of lesions

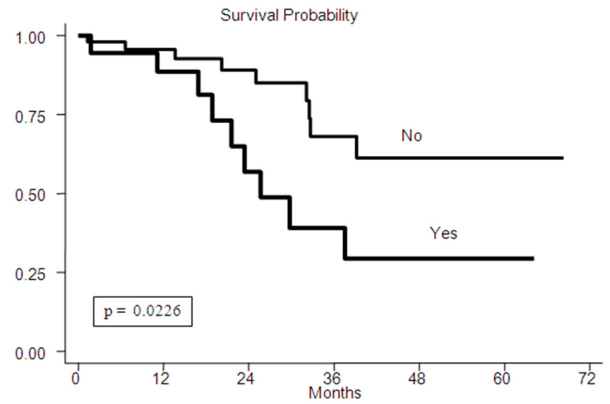


Figure 3 – Survival probability related to bilateral metastasis

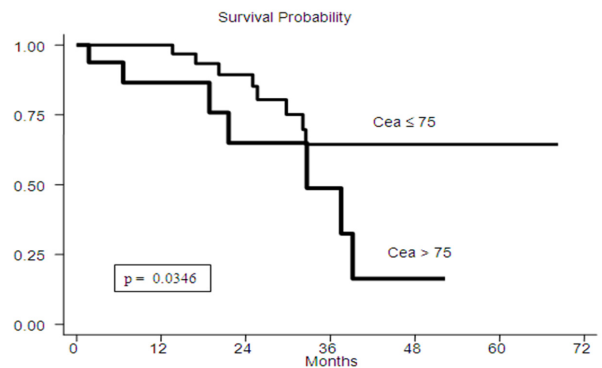


Figure 4 – Survival probability related to CEA levels

Discussion

Hepatic metastasis diagnosis can be established in preoperative stadiation, during surgery or by routine exams in the postoperative follow-up of patients submitted to colorectal cancer resection. Laboratory examinations such as hepatic canalicular gamma-glutamyl transpeptidase, alkaline phosphatase, besides carcinoembryogenic antigen (CEA) are high especially in the presence of great metastases but in cases of small nodules one generally does not observe significant rises in these examinations. In our casuistry 37 (52.8%) patients presented an increased CEA value as expected in patients with metastatic disease. CEA value higher than 75 is a negative prognostic factor.

The diagnosis of metastases is almost always established through image examinations as ultrasonography, CT scan and magnetic resonance. More recently we have used as routine in stadiation radioisotopic mapping of the whole body with dyed fluorodeoxyglucose (PET-SCAN) because recent studies had demonstrated that this method is superior to CAT scan and magnetic resonance.¹⁸

Diagnosis must always be complemented with intraoperative minute palpation of the liver and intraoperative ultrasonography. Intraoperative ultrasonography may by itself modify the surgical procedure in 10 to 25% of the cases by identifying small lesions not diagnosed by other image methods or palpation.¹⁹ In our Service IOUS is a routine procedure and a recent study proved it to be able to identify 22.8% of metastases not diagnosed by other diagnostic methods.²⁰

The universally accepted indication for hepatic resection of colorectal metastases is the presence of a total resectable hepatic lesion without evidence of extra-hepatic tumor. Contraindications are: the impossibility of radical resection; the presence of extra-hepatic tumor (except for resectable pulmonary nodules).

Following these criteria, resectability of synchronous hepatic metastatic lesions is 10% and for metachronic lesions from 20% to 25%.⁴ It is important to emphasize that many times patient are considered inoperable by surgeons without experience in hepatic surgery due to the location of the lesions or a suspicion of residual parenchyma inferior to 30% of the hepatic volume. However, nowadays there are resources for making these patients resectable. In our casuistry a patient that presented some lesions in the right lobe and segment 4 was resected after 2 years receiving palliative chemotherapy after being considered unresectable by a non specialized surgeon. After hepatometry detected that residual liver was inferior to 30% of the hepatic volume, we did portal preoperative chemoembolization in the right lobe so that an increase of left liver volume could occur. After 4 weeks the patient was submitted to a successful Right Trisegmentectomy, and the patient continues disease-free. Hepatic resection must always be done in a specialized center because of the high complexity of the procedure and, moreover, because it often presents high rates of morbimortality. A center is considered specialized when besides doing a great number of hepatic resections, it presents mortality rates for this procedure inferior to 3%.^{19,22,30} The good results currently presented by hepatic resection are due mainly to the improvement of image methods, to technical improvement of surgical and anesthetic teams, to the evolution of intensive care and to the individualization of the treatment to each patient. These results have much influenced the indications for hepatic resection in the last years.

Up to the decade of 1990, an accepted notion was that only patients with 3 hepatic nodules, either unilateral or bilateral, were resectable, considering patients with more than 3 nodules as non-treatable due to a worse prognosis.¹⁵ In the last years, because of a significant decrease

in mortality after hepatic resection, the indications have been more liberal. Scheele et al. demonstrated a 5-year survival rate of 37% for patients with up to 3 metastases and 25% for those with 4 metastases and found no significant statistical difference between the two groups.¹³ Fong et al.¹⁴ reported 5 years survival after hepatic resection of 44% for patients with 1 hepatic nodule, 25% for those with up to 3 nodules and 18% for those with more than 4, indicating a worse prognostic for these patients; however, the indication of surgery persists because no other treatment allows a late survival of 18% as is the case of resection. Makuuchi et al.³¹ also observed survival in 5 years in 255 of patients with more than 10 metastases and submitted to hepatic resection. Currently, no limitations in number or location of nodules exist and even two-phase hepatectomies were described. In the present casuistry survival was significantly worse in patients with more than 2 nodules.

An important point to insist on is the moment when hepatic resection must be done when metastases are synchronous. In the past it was almost consensual the idea that in patients with synchronous metastases up to 2 hepatic segments could be resected simultaneously to colorectal surgery but more extended surgeries should be done at a later time. More recently, two important casuistries of a Western and an Eastern center showed that one-phase surgery can result in low indices of morbidity.^{34,35} Up to now, there are no evidences that neo-adjuvant chemotherapy after hepatic resection increases survival. What is known is that some prognostic factors such as angiolymphatic invasion and more than 4 compromised lymph nodes in the primary tumor present a worse prognostic and a biological selection with chemotherapy, that is, an evaluation of the behavior of metastases would be indicated for preventing in many cases unnecessary resections.³⁴ Other authors avoid long intervals, which could increase chances of tumor dissemination and wait only 4 or 6 weeks after primary tumor surgery for doing a hepatic resection.¹² In our Service, patients with synchronous metastases have their clinical condition and metastasis pattern evaluated, aiming at a good choice for synchronous surgery. When the patients do not present bad prognostic factors such as clinically compromised lymph nodes in the primary tumor and do not need very extensive resections of the liver, simultaneous surgeries can be done; however when locally advanced primary tumor or extensive hepatic disease is detected, resection of primary tumor is followed by systemic chemotherapy, and after 8-12 weeks a new stadiation is done and they submitted the hepatic resection.

As we said, hepatic resection is a complex proce-

ture that may present a high rate (15–50%) of postoperative complications, even in experienced hands. The more frequently complications after hepatectomy are hemorrhage, pleural effusion, subphrenic ascites, collections, biliary fistulas and even hepatic insufficiency if more than 70% of the parenchyma is resected. In our experience subphrenic collections were the more common postoperative complication (10%), followed by biliary fistula (7.1%). Subphrenic collections normally occur when more extended hepatic resections leave great bleeding areas. Three of our patients needed a repeat operation because of bleeding signals, whereas stable patients are preferentially approached by the percutaneous procedure made available in our hospital in the image department. We successfully did a draining using CT scan in 3 cases. Biliary fistulas can occur when some biliary duct is injured (usually a secondary or tertiary one), but in most cases they are low debit and disappear spontaneously when well drained. Morbidity rates after hepatectomy was 25%. Trans- and postoperative mortality in specialized centers varies from 1 to 3% and in our casuistry was 1.3%.

Several works have shown that hepatic resection is the only therapeutic modality able to allow a long-term significant survival possibility. In the great series published, 5-year survival varies from 25 to 48% and about 70% of these patients are disease free after 5 years.^{5–16} Scheele et al.¹² and Fong et al.¹³ report 10-year late survival rates of 21 and 22% respectively.

After hepatic resection, relapses can occur in several sites but in 20 to 50% of cases, they are only hepatic. In these circumstances, if a new stadiation shows the injury to be restricted to the liver, a new hepatic resection must be indicated. Hepatic repeat resection is possible in 20% of the cases and its long-term results are similar to the ones of the first resection.^{12,20,21} Adam et al.³⁶ published a recent work showing that a third hepatectomy, when possible, led to a 32% 5-year survival of 60 studied patients. In our casuistry, resectable hepatic relapse was not associated with prognostic worsening. Two patients had 2 hepatectomies and others 3 resections, and all the patients are alive with an average survival rate of 40.2 months.

The presence of pulmonary lesion is not a contraindication to resection in this series: six patients presented in the evolution pulmonary relapses that were operated. Although this not statistically significant, the patients who had pulmonary resection presented a decreased average survival rate of 16.2 months and only 1 patient survived 24 months.

Several prognostic factors were studied during follow-up of patients submitted to metastases resection. Some factors as stadiation of the primary tumor,

the number of hepatic nodules, metastasis(es) size, time interval between resection of primary tumor and the appearance of metastasis (>or than< 1 year) are a consensus among authors. Factors such as sex, CEA serum level, blood transfusion or arterial hypotension during hepatectomy are not consensual despite some evidences in the literature. In our casuistry increased CEA levels, the presence of two metastases and bilobar disease had a negative impact on survival. Variable as bleeding and trans-operative hypotension seem subjective and very criticized, for this occurs due to some factors as hepatic lesions size, the experience of the team and the condition of the patient, and should not be associated to survival, but to the morbidity of procedures.

Although prognostic factors in the treatment of cancer in general have been comprehensively studied in the last years, their consideration in clinical practice has been limited. The knowledge of factors that may lead to worse results should in our opinion be used as a guide for protocols of study where patients are individualized according to prognostic and then submitted to different treatments. For example, patients whose prognostic factors are all favorable maybe should not receive adjuvant therapies; on the other hand, those with unfavorable factors must be included in protocols of study of adjuvant therapies. The presence of factors that worsen prognostic in the long run is not impeditive for resection but they can divide the patients in groups for a possible complementary adjuvant treatment.¹³

The development of new chemotherapy drugs such as Oxaliplatin and Irinotecan²³ and more recently monoclonal antibodies in association with chemotherapy drugs,²⁴ allow for good results and certainly they are one of the factors for the best results. In specialized centers, adjuvant systemic chemotherapy after hepatic resection is a routine. In relation to chemotherapy, both systemic and intra-arterial, that are no treatment plan able to compete with resection but a recent work demonstrated clear benefits of the association of systemic and intra-arterial chemotherapy used after hepatic resection, significantly improving survival in 2 years.²¹

Despite the higher aggressiveness in the treatment, in specialized centers results regarding mortality and survival are ever more positive. These data show that resection must be encouraged whenever possible.

Long-term good results after hepatic resection justify the surgery whenever possible, and it is essential that resectability be always evaluated by a surgeon experienced in hepatic surgery.

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