Objective: To report the early postoperative results and long-term survival on ten patients undergoing hepatectomy for treatment of non-colorectal and non-neuroendocrine hepatic metastases. The study was carried out by the General Surgery Service of the Department of Digestive Tract Surgery of the Teaching Hospital of the Faculdade de Medicina do ABC, Santo André, São Paulo, Brazil.

Methods: Complete follow-up data were available on 28 patients with hepatic metastases who were operated on between January 2002 and January 2007. Ten patients presented non-colorectal and non-neuroendocrine primary neoplasms, and comprised the sample of this study. There were five males and five females, mean age of 53 years (28 to 68 years). The right lobe was involved in five patients and the left lobe in five individuals. The number of metastases ranged from one to four. All metastases were unilateral. All primary tumors were identified. The histological types were adenocarcinoma (n = 7), germinative tumor (n = 1), melanoma (n = 1) and sarcoma (n = 1). The primary sites were: gastric (n = 1), kidney (n = 1), adrenal (n = 1), breast (n = 2), testicle (n = 1), ovary (n = 2), acral melanoma (n = 1) and retroperitoneal sarcoma (n = 1). All patients presented metachronous metastases. The median interval between primary tumor treatment and diagnosis of metastases was 20 months (12 to 33 months). Six patients received chemotherapy and four patients underwent exclusively surgical treatment. Results: There were seven major hepatic resections (three or more Couinaud segments) and three minor hepatic resections. The operative time varied from 180 to 425 minutes with a median duration of 240 minutes. Five patients received transfusions; blood loss ranged from 200 to 3,000 ml. There were two postoperative complications and both patients were re-operated (biliary fistula = 1; intra-abdominal abscess = 1). There were no postoperative deaths. All resections were R0. The three-year overall survival rate was 50%. Five patients developed tumor recurrence (50%). Conclusions: Hepatic resection for liver metastases other than of colorectal or neuroendocrine origin presents acceptable morbidity and no mortality. This approach may result in long-term survival in this group of patients.

Keywords: Hepatectomy; Neoplasm metastasis; Evaluation of results of therapeutic interventions; Survival rate
This recent approach has had a positive impact on long-term survival, especially in CR and NE metastases. There has been greater enthusiasm in extending the surgical indication to other metastatic tumors of the liver, given the favorable results in such patients, which are not reproducible in other types of treatment. Consequently, many articles presented series of resections of non-colorectal and non-endocrine (NCRNE) metastases as well as of other digestive and genitourinary tract tumors, sarcomas and breast malignancies, with satisfactory long-term results (9-23).

OBJECTIVE

To assess early and late outcomes of the surgical treatment of liver NCRNE metastases at the General Surgery Service, Teaching Hospital of the Faculdade de Medicina do ABC (FMABC), Santo André, São Paulo, Brazil.

METHODS

Thirty-seven patients were diagnosed with liver metastases between January 2002 and January 2007 at the Teaching Hospital of the FMABC. Six were initially excluded from this initial series and referred to other therapy. The causes of exclusion were: absence of medical conditions for resection (n = 3), extensive bilateral liver disease (n = 2) and unresectable extrahepatic disease (n = 1). Thirty-one patients were selected for surgery. Exploratory laparotomy revealed carcinomatosis in three patients, which were also excluded from this study. Finally, 28 patients underwent hepatic resection with curative intention.

Of these, there were ten patients with NCRNE metastases who underwent hepatic resection. Five were male and five were female. Age ranged from 28 to 68 years (median age of 53 years). The racial distribution was white (n = 6), black (n = 3), and yellow (n = 1). Three patients had other associated diseases, namely arterial hypertension (n = 2) and diabetes mellitus (n = 1).

All patients were asymptomatic. The right lobe was involved in five patients and the left lobe was involved in the other five patients. All metastases were unilateral. The number of metastases varied from one to four. Seven patients presented single metastases and three patients had two or more metastases. The histological diagnoses were adenocarcinoma (n = 7), germinative tumor (n = 1), melanoma (n = 1) and sarcoma (n = 1).

All metastases were metachronous. The disease-free interval between treatment of the primary tumor and the appearance of metastases varied from 12 to 30 months (median of 20 months) for NCRNE metastases. Primary sites were gastric (n = 1), kidney (n = 1), adrenal (n = 1), breast (n = 2), testicles (n = 1), ovary (n = 2), acral melanoma (n = 1) and retroperitoneal sarcoma (n = 1). Epidemiological features are shown on Table 1.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>63</td>
<td>37</td>
<td>51</td>
<td>28</td>
<td>53</td>
<td>68</td>
<td>65</td>
<td>56</td>
<td>53</td>
<td>29</td>
</tr>
<tr>
<td><strong>Disease-free survival (months)</strong></td>
<td>Ovary</td>
<td>Breast</td>
<td>Breast</td>
<td>Ovary</td>
<td>Sarcoma</td>
<td>Gastric</td>
<td>Adrenal</td>
<td>Renal</td>
<td>Acral melanoma</td>
<td>Testis</td>
</tr>
<tr>
<td><strong>Radiological findings (CT)</strong></td>
<td>4 solid-cystadenocarcinoma</td>
<td>2 solid, heterogenous, poorly-enhanced lesion w/ calcification</td>
<td>Solid, heterogenous, poorly-enhanced lesion w/ calcification</td>
<td>3 solid highly-enhanced lesions w/ calcification</td>
<td>Heterogeneous, highly-enhanced lesion</td>
<td>Heterogeneous, highly-enhanced lesion</td>
<td>Solid, heterogenous, highly-enhanced lesion</td>
<td>Solid, heterogenous, highly-enhanced lesion</td>
<td>Solid, heterogenous, highly-enhanced lesion</td>
<td>Solid, heterogenous, highly-enhanced lesion</td>
</tr>
<tr>
<td><strong>Maximum diameter (cm)</strong></td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Segments II-III</td>
<td>Segments VI-V-VII</td>
<td>Segments V-VIII</td>
<td>Segments II-III-V</td>
<td>Segments V-VII</td>
<td>Segments II-III</td>
<td>Segments III-IV</td>
<td>Segments VII-VIII</td>
<td>Segment V</td>
<td>Segment IV</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>LLS</td>
<td>RH</td>
<td>RH</td>
<td>LH</td>
<td>RH</td>
<td>LLS</td>
<td>HE</td>
<td>RH</td>
<td>S-V</td>
<td>LH</td>
</tr>
<tr>
<td><strong>Duration of surgery (minutes)</strong></td>
<td>220</td>
<td>280</td>
<td>240</td>
<td>260</td>
<td>425</td>
<td>200</td>
<td>230</td>
<td>300</td>
<td>180</td>
<td>240</td>
</tr>
<tr>
<td><strong>Postoperative complications</strong></td>
<td>-</td>
<td>-</td>
<td>Biliary fistula</td>
<td>-</td>
<td>-</td>
<td>Biliary fistula</td>
<td>-</td>
<td>Subphrenic abscess</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Blood transfusion (ml)</strong></td>
<td>-</td>
<td>900</td>
<td>1,800</td>
<td>-</td>
<td>900</td>
<td>-</td>
<td>900</td>
<td>1,200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hospital stay (days)</strong></td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>35</td>
<td>10</td>
<td>7</td>
<td>32</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td><strong>Survival time (months)</strong></td>
<td>24 (died – disease)</td>
<td>48 (alive – without disease)</td>
<td>40 (alive – without disease)</td>
<td>37 (alive – with disease)</td>
<td>13 (died with disease)</td>
<td>15 (died with disease)</td>
<td>43 (alive – without disease)</td>
<td>17 (alive – with disease)</td>
<td>20 (alive – without disease)</td>
<td>50 (alive – without disease)</td>
</tr>
</tbody>
</table>

CT = computed tomography; ml = milliliter; LH = left hepatectomy; RH = right hepatectomy; LLS = left lateral sectorectomy; S-V = Segmentectomy V; F = Female; M = Male
All patients were staged by abdominal, pelvic and thoracic computed tomography. Preoperative magnetic resonance imaging was also performed in the last nine patients and intraoperative ultrasound was done in seven patients. Serum levels of CEA, CA 19-9, CA 125, CA 15-3 and alpha-fetoprotein were studied in all cases.

Following surgery, the General Surgery and Clinical Oncology Services monitored all patients; a standard form was used, and data were collected prospectively. Follow-up was done according to the following routine: at three-month intervals (until two years after surgery), at six-month intervals (from two to five years) and at 12-month intervals (five years postop onwards). Each visit included a complete physical examination, dosage of tumor markers according to the primary tumor, abdominal ultrasound, abdominal and pelvic computed tomography, and a chest radiograph. Recurrence of tumors was defined only if there was unequivocal radiological documentation and, if possible, histological confirmation.

**RESULTS**

Seven major hepatic resections (right hepatectomy = 4 and left hepatectomy = 3) and three minor hepatic resections (left lateral sectorectomy = 2 and segmentectomy V = 1) were done. The duration of surgery varied from 180 to 425 minutes (median of 240 minutes). Transfusion was given to five patients; intraoperative bleeding varied from 200 to 3,000 ml (median of 800 ml). Hospital stay varied from seven to 35 days (median of ten days). There were two complications in two patients, representing a 20% morbidity rate. One female patient that had undergone left hepatectomy for a single metastasis (ovarian endometrioid carcinoma) developed a high-output biliary fistula that exteriorized through an abdominal drain. The fistula was blocked and resolution by endoscopic papillotomy was unsuccessful. The patient was reoperated, during which a V-segment biliary canaliculus was ligated; there were no further intercurrences. Another female patient who had a single metastasis originating from an adrenal carcinoma and underwent right hepatectomy, developed a large subphrenic abscess, which was drained by a laparotomy. There were no mortalities in this series; all resections had microscopically free margins (R0). Early surgical results are shown on Table 1.

Follow-up varied from 13 to 50 months. Five patients relapsed; four patients developed multiple recurrences (two or more organs); one patient had an exclusively hepatic recurrence. The interval between hepatic surgery and recurrences varied from 12 to 24 months. No recurrence was treated surgically. Data on the features of recurrences (primary tumor, time elapsed between hepatectomy and recurrences, site, diagnostic method, survival after diagnosis, and patient status) are shown on Chart 1. By the end of the study, seven patients were alive, four of them with no disease recurrence in an over 36-month follow-up period. Overall three-year survival was 50% and three-year disease-free survival was 40%.

**DISCUSSION**

Although the liver is a frequent site for systemic disease, the mechanisms to develop hepatic metastasis differ according to the primary tumor site. The most frequent dissemination routes for metastases in patients with gastrointestinal tract tumors (CR adenocarcinoma and neuroendocrine tumors of the digestive tract) are venous drainage towards the portal vein and retrograde lymphatic vessels. The rationale behind resecting metastases in such cases is that, theoretically, the disease is confined to the abdominal cavity. Thus, appropriate treatment of the primary tumor and metastases offers curative chances. This was confirmed mostly in CR-originated metastases, in which almost 40% of patients survive five years and nearly 25% survive over ten years(19).

In contrast, most of the remaining hepatic metastases originate outside of the abdominal cavity. These lesions usually reach the liver by systemic circulation, implying theoretically in other (extrahepatic) sites being equally affected. Thus, the resection of NCRNE liver metastases has been considered with skepticism(19).

The first studies that assessed the results of hepatic resection in patients with non-colorectal (NCR) liver metastases also included neuroendocrine (NE) tumor metastases(11,24-29). Nevertheless, the analysis of results in these series revealed that the NE groups of patients had

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (m)</td>
<td>12</td>
<td>18</td>
<td>14</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Primary</td>
<td>Ovary</td>
<td>Ovary</td>
<td>Sarcoma</td>
<td>Gastric</td>
<td>Kidney</td>
</tr>
<tr>
<td>Site</td>
<td>Peritoneum + liver</td>
<td>Peritoneum + retroperitoneal lymph nodes</td>
<td>Liver</td>
<td>Liver + lungs</td>
<td>Bones + lungs</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Laparotomy</td>
<td>Laparotomy</td>
<td>CT</td>
<td>CT</td>
<td>CT</td>
</tr>
<tr>
<td>Survival after recurrence (m)</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Status</td>
<td>Died with disease</td>
<td>Alive with disease</td>
<td>Died with disease</td>
<td>Died with disease</td>
<td>Alive with disease</td>
</tr>
</tbody>
</table>
the best long-term progression. New subsequent studies were proposed excluding metastases of NE origin from their series and designed to verify the effect of hepatic resection on long-term survival rates of patients in the group now named NCRNE(10,12-13,15). As a result of this approach, some of these studies demonstrated that hepatic resection for the treatment of NCRNE metastases was satisfactory and nearly as effective as the surgical treatment of metastases of CR origin; and five-year survival rates reached 30 to 40%(10,13,30).

Simultaneously, the treatment of liver metastases underwent significant changes in the past decade. Developments in anesthesia, surgery and imaging techniques, together with appropriate selection of patients, decreased bleeding and duration of surgery as well as lower morbidity and mortality rates have contributed significantly towards improved results of surgery, which has increased the scope of surgical indications. These results, originally and frequently aimed to treat CR and NE metastases, led to a marked increase in the use of this approach to treat NCRNE metastases. More recently, larger series of hepatectomies for treatment of NCRNE metastases have been increasingly published in the literature, furthering knowledge about survival rates in this group of patients(19-22).

The selection criteria for the resection of NCRNE metastases have been those classically used in the past for the removal of CR metastases. NCRNE metastasis resection is best defined for special conditions, such as primary tumor control, long disease-free interval (treatment of primary tumor versus onset of metastasis), exclusively hepatic disease and good clinical status of patients(18-23). When these criteria are strictly adopted, long-term survival rates are similar to those found in series containing only CR or NE metastases(19-22).

Adam et al.(19) published a major multicenter study conducted in France, involving 1,452 patients with NCRNE metastases distributed as follows: 460 breast cancer (32%), 230 gastrointestinal cancer (16%), 206 urological cancer (14%) and 148 melanoma (10%). Most patients had known primary tumors (81%); the most common histological types were adenocarcinoma (60%), sarcoma or other stromal tumors (14%), and melanoma (13%). The postoperative mortality in this series was 2.3%, the morbidity rate was 15%, and the median hospital stay was 14 days. Most metastases were metachronous (76%) and the median time between primary tumor treatment (90% treated surgically) and appearance of metastases was 38 months. Most patients underwent chemotherapy. Over half had a single metastasis (56%), and 83% of patients had less than four metastases. The overall five-year survival rate in this series was 36% (median survival of 35 months).

Following resection, hepatic recurrence occurred in 49% of patients; in 25% of patients, recurrence was exclusively hepatic; and in 25% recurrence was multiple. Of 331 patients with exclusively hepatic recurrences, 105 (32%) underwent a second hepatectomy. Subsequently, 14 patients underwent a third hepatectomy, two underwent a fourth hepatectomy and two more were submitted to a fifth procedure. When the study was written, five years after the first hepatectomy, 209 patients (14%) were still alive, with no recurrences. A multivariate analysis of prognostic factors revealed the following negative survival criteria: age above 60 years, non-breast origin, melanoma or epidermoid histology, disease-free interval below 12 months, extrahepatic metastases, R2 resection and major hepatectomy (p < 0.02). The authors created a risk prognostic model based on these factors and stratified patients as low-risk (0-3 points, five-year survival = 46%), moderate risk (4-6 points, five-year survival = 33%), and high risk (> 6 points, five-year survival < 10%).

These authors proposed that, while surgery should be the first treatment for CR metastases, with chemotherapy as adjuvant therapy, the opposite would occur in NCRNE metastases, in which chemotherapy would be the first treatment and surgery would be adjuvant therapy. Surgery, then, would be part of a multidisciplinary therapy, and would be indicated in controlled liver disease or when adequate control had been attained with chemotherapy. According to the author, hepatectomy for NCRNE metastases effectively provides satisfactory results and the prognosis depends mostly on the primary site and histology of the tumor.

Earle et al.(21) recently published a study of 95 patients with NCRNE metastases from a single institution and found similar results. Postoperative mortality was 2.1% and the morbidity rate was 15.8%. Most patients also presented single (58%) and metachronous (78.6%) metastases. The median survival rate following hepatectomy was 36 months, and five-year survival was 34.9%. Patients were divided into two groups for statistical analysis: gastrointestinal (GI) primary tumors (16.8% of patients) and extra-gastrointestinal primary tumors (EGI), which included 83.2% of patients. Overall survival in the GI group was twice as long as that found in the EGI group (49 months versus 20 months, p < 0.001). Multivariate analysis revealed a worse scenario: patients with synchronous metastases (p < 0.003), multiple metastases (p < 0.001) and extra-intestinal primary (p < 0.016). The authors concluded that increased survival was to be expected in selected patients with any types of metastatic tumor in the liver, especially in patients with single metastases originated from extra-intestinal primaries, in which the tumor was fully resectable (R0).
Yedibela et al.\textsuperscript{(22)} published a series of 162 patients who underwent resection of NCRNE metastases; these patients were analyzed separately in two different time-periods (1978-1989 and 1990-2001). They found a decrease in mortality (from 8 to 1%), in intraoperative bleeding and in the number of transfusions. There was, however, no reduction in mortality, which remained high (around 29%), although the number of re-operations dropped from 25 to 5%. The overall two- and five-year survival rates were 49 and 26%, respectively (median survival of 23 months). The authors found better results in patients that had sarcoma, breast and renal carcinoma metastases. On the other hand, a decreased life expectancy was seen in patients with gastrointestinal-originated metastases. They concluded that resection of NCRNE metastases in selected patients should be undertaken; the indication was more reserved in patients with gastrointestinal metastases, given their poor prognosis. Moreover, authors stated the presence of extrahepatic disease would be a relative contraindication for hepatectomy.

More recently, Reddy et al.\textsuperscript{(20)} compared 360 consecutive patients divided into three groups, as follows: NCRNE (n = 82), CR (n = 245) and NE (n = 33). The NCRNE group included: primary breast tumors (n = 20), primary genitourinary tumors (n = 18), sarcomas (n = 19), melanomas (n = 11) and other tumors (n = 14). They found similar postoperative mortality rates (4, 4 and 9%) and morbidity rates (30, 42 and 42%) among groups. The median survival rate in the NE group was statistically superior to the CR and NCRNE groups (p < 0.05); disease-free survival was statistically lower (p < 0.05) in the NCRNE group, compared to the CR group (13 versus 16 months). A median follow-up of 59 months in the NCRNE group revealed that the estimated overall survival rate (five years) was 37%, while disease-free survival (five years) was 16%; 15 patients in this sample survived over five years. These data were similar for those patients that had CR metastases in the same sample. The authors concluded that resection of NCRNE metastases in selected cases may be done satisfactorily, and patients reach survival rates similar to those that have CR metastases.

Although our series in the present study was small, generally speaking early postoperative results of surgery show a mortality rate (0%) and a morbidity rate (20%) similar to recently published results\textsuperscript{(19-22)}. The rate of R0 resection was greater (100%) compared to the literature, probably due to a proportionally higher number of major resections (70%), the number of single metastases (70%) and unilaterality (100%). Notwithstanding the heterogeneity of our sample, the overall three-year survival rate was 50%, and the three-year disease-free survival rate was 40%, both in agreement with the literature. The number of recurrences was also similar to that found in other published papers. We did, however, find more multiple recurrences, although most involved the liver, denoting the systemic character of these cases. In parallel, these cases received exclusive chemotherapy. The only case that presented an exclusively hepatic recurrence (case 5) had multiple and bilateral lesions; in this case, there was no possibility of doing salvage surgery as described by Adam et al.\textsuperscript{(19)}.

**CONCLUSIONS**

Hepatic resection of NCRNE metastases has acceptable morbidity and mortality rates in our context. Although the series was small and heterogeneous, this approach may yield some long-term survivors (five patients surviving over three years). It also does not exclude patients from receiving systemic adjuvant therapy. Additional, possibly multicenter and randomized studies should be done to provide final answers, given the particular rarity of this medical condition and the low survival rates of these patients when treated only systemically.

**REFERENCES**


