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Original Article

HEPATECTOMY: A CRITICAL ANALYSIS ON EXPANSION OF THE INDICATIONS

Hepatectomia: uma análise crítica da ampliação das indicações

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ABSTRACT - *Background*: Hepatic resection has evolved to become safer, thereby making it possible to expand the indications. ***Aim***: To assess the results from a group of patients presenting these expanded indications. ***Method*:** Were prospectively studied all the hepatectomy procedures performed for hepatic tumor resection. Patients with benign and malignant primary and secondary tumors were included. Were included variables such as age, gender, preoperative diagnosis, preoperative treatment, type of operation performed, need for transfusion, final anatomopathological examination and postoperative evolution. The patients were divided into two groups: group A, with a traditional indication for hepatectomy; and group B, with an expanded indication (tumors in both hepatic lobes, extensive resection encompassing five or more segments, cirrhotic livers and postoperative chemotherapy using hepatotoxic drugs). ***Results*:** Were operated 38 patients, and 40 hepatectomies were performed: 28 patients in group A and 10 in group B. The mean age was 57.7 years, and 25 patients were women. Three in group B were operated as two separate procedures. Groups A and B received means of 1.46 and 5.5 packed red blood cell units per operation, respectively. There were three cases with complications in group A (10.7%) and six in group B (60%). The mortality rate in group A was 3.5% (one patient) and in groups B, 40% (four patients). The imaging examinations were sensitive for the presence of tumors but not for defining the type of tumor. The blood and derivative transfusion rates, morbidity and mortality were greater in the group with expanded indications and more extensive surgery. ***Conclusion*:** The indications for liver biopsy and portal vein embolization or ligature can be expanded, with special need of cooperation of the anesthesiology department and the use of hepatic resection devices to diminish blood transfusion.

HEADINGS - Hepatectomy. Hepatic resection. Hepatic tumors. Morbidity and mortality.

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RESUMO - *Racional*: As ressecções hepáticas evoluíram, tornando-se mais seguras, permitindo ampliação das indicações. ***Objetivo***: Avaliar os resultados com ampliação da indicação. ***Método***: Estudo prospectivo de todas as hepatectomias realizadas para ressecção de tumores hepáticos. Foram incluídos pacientes com tumores primários e secundários, benignos e malignos e anotados idade, gênero, diagnóstico pré-operatório, tratamento realizado no pré-operatório, tipo de operação realizada, necessidade de transfusão, exame anatomopatológico final e evolução pós-operatória. Os pacientes foram divididos em dois grupos: grupo A, aqueles com indicação tradicional de hepatectomia e grupo B, com indicação ampliada (tumor nos dois lobos hepáticos, ressecções extensas de cinco ou mais segmentos, fígados cirróticos e pós-quimioterapia com drogas hepatotóxicas). ***Resultados*:** Foram operados 38 pacientes e realizadas 40 operações, 28 no grupo A e 10 no B. A média de idade foi 57,7 anos, sendo 25 mulheres. Três do grupo B foram operados em dois tempos. Os grupos A e B receberam em média 1,46 e 5,5 concentrados de hemácias por operação, respectivamente. Os pacientes do grupo A tiveram três complicações (10,7%) e os do B seis (60%). A mortalidade no grupo A foi de 3,5% (n=1) e no grupo B ocorreram quatro óbitos (40%). Os exames de imagem foram sensíveis para presença de tumor, mas não para definir o tipo. As transfusões, a morbidade e a mortalidade foram maiores no grupo com ampliação das indicações e operações mais extensas. ***Conclusão*:** Deve-se indicar a biópsia hepática com maior frequência no pré-operatório, assim como a embolização ou ligadura do ramo da veia porta. Para diminuir transfusão intra-operatória há necessidade de trabalho conjunto com o serviço de anestesia e usar equipamentos modernos para secção do parênquima.

DESCRITORES - Hepatectomia. Ressecções hepáticas. Tumores hepáticos. Morbidade. Mortalidade.

INTRODUCTION

Over the last few decades, several factors have transformed hepatectomy into a safer operation. A recent analysis on 2313 hepatectomies using data from several institutions showed a mortality rate of 2.5% and a morbidity rate of 19.6%[2]. The factors contributing towards this have included better knowledge of hepatic anatomy, development of imaging examinations, better preoperative assessment of patients and their hepatic function, multidisciplinary perioperative work and improvement of operative techniques[17].

Through these factors, strategies have been developed to increase resectability in patients with primary tumors and hepatic metastases[16]. Chemotherapy has become better developed, with new drugs, particularly for treating metastases, thus promoting better responses and enabling indications for surgical treatment among patients who earlier would not have been candidates for resection[4,16]. A recent study showed that in some situations the results from hepatectomy to treat colorectal and non-colorectal metastases were similar[6], thus further expanding the group of patients who are candidates for hepatectomy. Three and a half years ago, the authors began a prospective study with this objective, initially evaluating the associated morbidity and mortality.

The objective of this study was analyze the results of the expansions of the surgical indications for hepatectomy.

METHOD

This study was approved by the Ethics Committee of Santa Casa de Londrina under number CAAE 06389312.50000.0099

In January 2010, a prospective study began by gathering data on patients who underwent hepatectomy at three hospitals in Londrina (state of Paraná, Brazil): Irmandade Santa Casa de Londrina, University Hospital of the State University of Londrina and Cancer Institute of Londrina. Data for this study was collected until June 2012. Over this period, was expanded the indication for resection to patients with metastases in both hepatic lobes, patients undergoing salvage chemotherapy post-treatment, cases of tumors in cirrhotic livers and cases of marginally resectable tumors. Thus, these patients presented the expanded criteria that were the objective of this study.

Were evaluated patients with hepatic carcinomas, colorectal or non-colorectal metastases, gallbladder tumors, cholangiocarcinoma and benign tumors.

The preoperative preparation included fasting, indwelling bladder catheterization, administration of prophylactic antibiotic (cefalotin) and opening of two peripheral venous accesses. Central access and arterial puncture are not performed routinely, and were used in only two cases.

The operative techniques used for hepatectomy included both laparotomic and laparoscopic procedures. At the hepatic hilum, the following techniques were used: Pringle maneuver, half-Pringle maneuver, classical dissection of the vessels of the hilum and Glisson's approach[12,13]. Ligation of the corresponding hepatic vessel prior to hepatectomy, was done whenever possible. The liver was released from the ligaments before resection of the parenchyma in all cases. The technique used for resection of the parenchyma was the "silkclasy" method, described by Herman et al[7], in the majority of the open cases. Was used the "CUSA" technique (cavitron ultrasonic surgical aspirator, Integra Radionics, USA) in two cases. A radiofrequency device was used in one case performed by means of laparotomic access (radiofrequency interstitial tissue ablation – RITA - model 1500X), and Habib 4X needle bipolar resection device (AngioDynamics, Inc, USA). Three cases were performed by means of laparoscopy, with resection of segments 2 and 3. The ultracision scalpel was chosen, together with an electric scalpel and stapling. In one case, was also performed rectosigmoidectomy, with video-assisted resection of the rectal tumor[11]. In another case, staplers were not available and clips were used to ligate the vessels (Weck Hem-o-lok ligation system, Teleflex).

Blood volume replacement during and after the operation was done using crystalloid solutions. Use of fresh plasma was reserved of patients with liver cirrhosis.

The following data were gathered: age, gender, preoperative radiological diagnosis, preoperative chemotherapeutic treatment, procedure performed, blood product transfusions, anatomopathological examination of the surgical specimen and postoperative evolution. The long-term survival results with and without disease were not an objective of the present study, because of the short postoperative follow-up.

The patients were divided into two groups. Group A consisted of patients with a traditional indication for hepatectomy, with resection of four hepatic segments or fewer, independent of risk factors. Group B consisted of patients with expanded indications for hepatectomy, with lesions in both hepatic lobes. These were patients who underwent trisegmentectomy or resections performed in two separate procedures with at least one right lobe hepatectomy or trisegmentectomy procedure, or with five or more segments resected. This group also included patients with salvage chemotherapy, cases of tumors in cirrhotic livers with extensive resection and cases of marginally resectable tumors.

The statistical analysis was done using the SPSS software, version 17. Variables with normal distribution were compared using Student's t test, while nonparametric variables were compared using the Mann-Whitney U test. Survival and the number of days of hospital stay were analyzed using the Kaplan-Meyer survival curves and were compared using the Mantel-Cox (log-rank) test.

RESULTS

Thirty-eight patients were operated over this period, among whom three underwent two resections, totaling 40 hepatectomy procedures. One patient didn't have liver tumor on laparotomy and intraoperative ultrasonography was used to ratify. There were no cases of unresectable tumors in this sample.

The mean age was 57.7 years, with a range from 26 to 76. Among the patients with malignant tumors, the mean age was 61.5 years, and among those with benign tumors it was 53.2 years. Twenty-five patients were women.

The preoperative diagnosis was made from the history and from imaging examinations, given that the authors did not normally indicate biopsy for cases of hepatic tumor before the operation. Among 13 patients with a probable diagnosis of hepatic carcinoma before the operation, the anatomopathological examination confirmed the diagnosis in 12 cases, however the diagnosis made from the surgical specimen was adenoma in one patient.

Among six patients with metastases from tumors of the colon, five cases were confirmed in the anatomopathological examination, and one was found to be hemangioma. Out of five patients with metastases from breast tumors, four were confirmed from anatomopathological examination on the surgical specimen, while one case was found to be hemangioma. Among three patients with suspected gallbladder tumors, two were confirmed from the anatomopathological examination, while one case was found to be a benign lesion (porcelain gallbladder).

The preoperative diagnosis was confirmed in the following cases: two patients with metastases from pancreatic tumors; one with metastasis from melanoma; one with cholangiocarcinoma; and one with metastasis from adenocarcinoma of the stomach. In one patient with suspected metastasis from a kidney tumor, the anatomopathological examination showed that the case was one of focal steatosis. In another patient with radiologically suspected metastasis from gastric adenocarcinoma, the anatomopathological examination showed that this was a case of hemangioma. In relation to benign tumors, in two cases with radiological suspicion of adenomas, the diagnosis was confirmed in one case and the final diagnosis in the other patient operated was focal nodular hyperplasia. The radiological and anatomopathological diagnoses were concordant in one patient with intra-hepatic lithiasis. In eight cases among the 40 resections (20%), the preoperative diagnosis was not confirmed by the final anatomopathological examination.

Preoperative chemotherapeutic drug treatment was administered in five cases of tumors of the colon[14]. In another patient with a synchronic lesion, it was decided to use a surgical approach 30 days after performing colectomy and ligature of the right branch of the portal vein. In five cases of suspected metastases from breast tumors, there had been a history of chemotherapy. The same applied to two patients with metastases from pancreatic tumors, who had received chemotherapy after pancreatectomy, and to the patients with esophageal tumors and melanoma.

The standard treatment used for metastases from colorectal tumors was oxaliplatin with fluoropyrimidines. Irinotecan was second-line treatments. In breast cancer cases, anthracycline and taxanes were used. Gemcitabine and cisplatin were used for pancreatic tumors. In cases of esophageal tumors, cisplatin, fluoropyrimidines and taxanes were used. For melanoma, interferon and DTIC (dacarbazine) were used.

In three cases of tumors that affected both lobes of the liver, the resection was done in two separate procedures. Two patients underwent right hepatectomy in the first procedure, and a second operation was then performed to resect segment 2 and/or 3.

The third of these patients firstly underwent rectosigmoidectomy because of a tumor of the colon and resection of segments 2 and 3, by means of videolaparoscopy. The second operation had the aim of preserving segments 1, 4, 5 and 6. An intraoperative ultrasound examination was performed to verify the safety of this procedure. However, during the surgery, was observed that the tumor located in segment 8 was adhering to the middle hepatic vein and unable to be preserved, thereby leading to impairment of segments 5 and 6, such that the patient evolved with liver failure after the operation.

In one patient, ligature of the right branch of the portal vein was performed together with resection of the colon. Thirty days later, now presenting adequate hypertrophy of the left lobe, trisegmentectomy was performed and the patient presented good evolution thereafter. In one case, the right branch of the portal vein was embolized and, thirty days later, the patient underwent trisegmentectomy due to metastases from a pancreatic tumor. In this case, excellent hypertrophy of the left lobe was observed, and the patient's evolution was free from intercurrences (Table 1).

TABLE 1 - Types of hepatectomy performed in this study

Types of hepatectomy	n
Left (segments 4, 3 and 2)	4
Left + segment 1	1
Right (segments 5, 6, 7 and 8)	9
Trisegmentectomy + segment 1 (with partial preservation of segment 4A)	1
Trisegmentectomy (with partial preservation of segment 4A)	2
Trisegmentectomy (with partial preservation of segment 4B)	1
Trisegmentectomy (segments 4, 5, 6, 7 and 8)	3
Trisegmentectomy with partial resection of the proximal common bile duct	1
Segmentectomy 2 and 3	7
Segmentectomy 5 and 6	1
Segmentectomy 7 and 8	1
Segmentectomy 7 and 4B	1
Segmentectomy 5 and 7	1
Segmentectomy 6 and 7	1
Segmentectomy 3	3
Segmentectomy 2	1
Segmentectomy 4 and 5	2
TOTAL	40

The blood transfusions among the patients in group B were larger than those in group A (p=0.048). Table 2 shows the mean quantities of packed red blood cell units used, according to the procedure performed. It is worth emphasizing that the patients operated at Irmandade Santa Casa de Londrina received lower quantities of blood product transfusions, on average: among patients who underwent trisegmentectomy, a mean of 2.5 packed red blood cell units per operation; patients with right hepatectomy, 1.0 unit; and patients with left hepatectomy, 0.5 units. However, no statistical difference was observed. In the three cases in which it was possible to use "CUSA" or "RITA", the need for transfusion was further diminished: only 1.0 unit was used in this group. These devices for resection of the hepatic parenchyma were used in large-scale operations, consisting of two right hepatectomies and one trisegmentectomy.

TABLE 2 - Mean quantity of packed red blood cell units transfused in the patients who underwent hepatectomy

Type of resection		Packed red blood cell units
Grup A		1*
Grup B		4,5*
	Trisegmentectomy	5,5
	Right hepatectomy	3
	Left hepatectomy	2
	Segmentectomy 2 and 3	1
	Resection of one segment	0
	Resection of gallbladder tumors	0
	Laparotomy (without tumor)	0
	Other resections	1

* p = 0.048 for comparison of packed red blood cell units transfused between groups A and B.

Postoperative complications (within the first 30 days) occurred in nine patients (23.7%), and were more frequent in group B (p=0.02). There were no intraoperative deaths and there was no need for reoperation during the immediate postoperative period. There were five deaths (13.2%) during the postoperative period (first 30 days), of which one was in group A and four in group B (p=0.03) (Table 3).

TABLE 3 – Complications and deaths within the first 30 days after the operation among 38 patients who underwent hepatectomy

Group	Complications	n	Deaths
B (n = 10)	Cardiac arrhythmia	1	1
	Biliary fistula	1	0
	Liver failure	3	3
	Pleural empyema	1	0
	Subtotal	**6 (60%)***	**4 (40%)¥**
A (n = 28)	Subphrenic abscess	1	0
	Pneumonia	2	1
	Subtotal	**3 (10,7%)***	**1 (3,6%)¥**
	Total	**9**	**5**

* p = 0.02 for comparison of complications between groups A and B
¥ p = 0.03 for comparison of deaths between groups A and B

In two cases of trisegmentectomy, liver failure occurred after the resection. In the first of these, there was a large tumor occupying the entire right lobe and segment 4. Although the remaining segments presented hypertrophy and were theoretically sufficient to maintain hepatic function, this did not occur, perhaps because of the presence of fibrosis and cirrhosis in the parenchyma without tumor (seen in the anatomopathological examination). The second patient was operated on an emergency basis because of rupture of a large tumor, with large bleeding volume. Despite low blood pressure, the resection proceeded without intercurrences. Nevertheless, this patient also evolved with liver failure. Thus, out of eight cases of patients undergoing trisegmentectomy, two deaths occurred due to liver failure.

Was observed that there were two deaths for clinical reasons unrelated to hepatic function. One 56-year-old patient with severe hypertension and heart failure who underwent trisegmentectomy plus resection of segment 1 evolved to death on the fifth postoperative day, due to cardiac arrhythmia. Another patient aged 70 years who underwent hepatectomy of segments 5 and 6 also died on the fifth postoperative day due to a septic condition of pulmonary origin.

DISCUSSION

Management of patients with hepatobiliary tumors is complex, involving factors relating to the patient's clinical condition, the staging, the characteristics of the disease when malignant and also liver function. Some tumors develop in livers that are considered to be normal, while others affect organs that are compromised due to obstruction of the bile duct, or in livers presenting diseases such as steatosis, fibrosis or cirrhosis. All these factors influence the results from operations, and therefore careful attention needs to be paid to all these aspects, in order to achieve good results. Multidisciplinary work is fundamental and, in addition to the surgeon, there needs to be support from an anesthesiologist, a clinical oncologist, a gastroenterologist/endoscopist and a radiologist, so that such patients can be adequately cared for. It is also known that centered specializing in hepatobiliary surgery achieve better results[1].

Experiences relating to operations on the liver performed by the authors were published in previous studies[9,10], showing good results with low morbidity and no mortality relating to hepatic resections. Around three years ago, the already trained multiprofessional teams expanded the indications for hepatic resection. These were therefore grounded in the two basic requirements: previous experience and a multidisciplinary team.

The results from this study showed that the imaging examinations were precise for determining the presence of the tumor, its localization in the

liver, the relationship between the tumor and the vessels, and the possibility of resection. In all the patients who underwent surgery with curative intent, their tumors were resected. There was a single case in which no tumor resection was performed: not because the tumor was unresectable, but because it did not exist (false positive). However, there was a failure in the correlation between the radiological and anatomopathological findings in around 20% of the patients. With the exception of the cases of metastases of the gastric tumor, which consisted of two small lesions diagnosed intraoperatively that were resected without performing any prior examinations, the other patients had been under long-term follow-up and were referred to us by oncologists, presenting new lesions in the liver and with tomographic examination results suggesting metastasis. These eight cases, whose clinical and radiological diagnoses were not proven in the anatomopathological examination, made the authors to review the indications for preoperative biopsy. This procedure is now being indicated more frequently in the hospital services responsible for the present study. In the literature[18], it is stated that there is no imaging examination capable of unequivocally distinguishing between benign and malignant lesions in the liver, nor between their histological types.

Among the cases of one of them was shown to be a benign inflammatory process and hepatic resection was indicated because of the presence of the porcelain gallbladder sign. Although it is known that a porcelain gallbladder is not associated with increased risk of gallbladder cancer, it is now known that an association with cancer exists for gallbladder calculi larger than 3 cm (the chance of having cancer is ten times greater than among patients whose calculi are smaller than 1 cm)[1].

Radiological embolization of the branches of the portal vein and, if this is not possible, surgical ligation of the branch, is without doubt a very important armament and should be used more frequently[19]. It is possible that this management might have avoided two deaths due to liver failure that occurred after trisegmentectomy.

In analyzing the three cases of death due to liver failure, was recognized that one was in the group of patients undergoing long-term chemotherapy who then presented metastasis from the colon (salvage after chemotherapy), along with tumors in both hepatic lobes, and thus were doubly in the group with expanded indications. The other two cases consisted of marginally resectable tumors: one of them in a fibrotic/cirrhotic liver, while the other case was a ruptured tumor, which was therefore also doubly in the group with expanded indications. The analysis on these cases showed that in the first case, chemotherapy with oxaliplatin must have caused a sinusoidal lesion, in association with the extensive resection that was caused by impairment of the middle hepatic vein, which was impossible to predict even with intraoperative ultrasonography. Moreover, resection of segments 2 and 3 concomitantly with rectosigmoidectomy did not lead to any significant hypertrophy of the remaining parenchyma. In these cases, an operation comprising three separate procedures can be undertaken: resection of the colon, then right hepatectomy and then resection of segments 2 and 3. It would not be possible to embolize the right branch of the portal vein, because there would be the possibility of preserving segments 5 and 6.

In the case in which the liver tissue without tumor presented fibrosis and cirrhosis, embolization or ligature of the right portal vein would be the best option for leading to hypertrophy of the left lobe and hence safer surgery, despite the voluminous tumor in the right lobe and in segment 4.

In the case with the ruptures tumor, tumor embolization could have been performed with the aim of controlling the hemorrhaging before the operation. However, limitations on the use of interventionist radiology would impede this option in most hospital services in Brazil. A second case of ruptured hepatic carcinoma operated among this sample presented good evolution, given that the tumor was located in segments 2 and 3 and the hepatectomy was of smaller size.

In total, five deaths were observed during the postoperative period: three due to liver failure that could have been avoided; and two due to clinical complication. Thus, the mortality rate was approximately 11%. The three cases of death due to liver failure and one of the cases due to clinical complications formed part of the group with expanded indications, i.e. patients with resections of metastases in both hepatic lobes and cases of post-chemotherapy salvage, tumors in cirrhotic livers and marginally resectable tumors. Only one death was observed in the group that was considered to present classical or conservative indications for hepatectomy. These results are situation around the average in the literature[3,8].

Blood transfusions were frequently required among the patients in this study, especially in the cases of resection of four or more segments and in cirrhotic patients. Among the patients who underwent smaller-scale resection, there was a need for transfusion of large quantities of blood products in a patient with a ruptured tumor in segments 2 and 3, which required an average of one packed red blood cell unit and one plasma unit per operation. However, the majority of the patients in this group did not required transfusions. One possible explanation for the high number of transfusions of blood products in this study is that there was a lack of equipment for resection of the parenchyma, especially in large resections.

The patients operated at Cancer Institute of Londrina and Department of Surgery, State University of Londrina had larger numbers of transfusions per operation than the patients operated at Irmandade Santa Casa de Londrina, which reflects likely differences in perioperative care and management, especially during the anesthetic procedure. There is no doubt[14,15,20] that it is possible and is important to perform hepatic resections without or with little use of blood and blood

products, and this is one of the current priorities of the hospital services mentioned here.

Transfusions of blood products were associated with large resections, the group with expanded indications, ruptured tumors and also the location where the procedure was performed. Here, working together with anesthetists and refinement of the parenchymal resection technique may diminish this requirement, particularly if there is more access to the proper equipment indicated for parenchymal resection.

CONCLUSION

The indications for liver biopsy and portal vein embolization or ligature can be expanded, with special need of cooperation of the anesthesiology department and the use of hepatic resection devices to diminish blood transfusion.

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