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Original Article

SURGICAL MARGIN SIZE IN HEPATIC RESECTIONS FOR COLORECTAL METASTASIS: IMPACT ON RECURRENCE AND SURVIVAL

Dimensão da margem cirúrgica nas ressecções de metástase hepática de câncer colorretal: impacto na recidiva e sobrevida

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ABSTRACT - *Background*: Approximately 50% of the patients with a colorectal tumor develop liver metastasis, for which hepatectomy is the standard care. Several prognostic factors have been discussed, among which is the surgical margin. This is a recurring issue, since no consensus exists as to the minimum required distance between the metastatic nodule and the liver transection line. ***Aim***: To evaluate the surgical margins in liver resections for colorectal metastases and their correlation with local recurrence and survival. ***Methods***: A retrospective study based on the review of the medical records of 91 patients who underwent resection of liver metastases of colorectal cancer. A histopathological review was performed of all the cases; the smallest surgical margin was verified, and the late outcome of recurrence and survival was evaluated. ***Results***: No statistical difference was found in recurrence rates and overall survival between the patients with negative or positive margins (R0 *versus* R1); likewise, there was no statistical difference between subcentimeter margins and those greater than 1 cm. The disease-free survival of the patients with microscopically positive margins was significantly worse than that of the patients with negative margins. The uni- and multivariate analyses did not establish the surgical margin (R1, narrow or less than 1 cm) as a risk factor for recurrence. ***Conclusion***: The resections of liver metastases with negative margins, independently of the margin width, had no impact on tumor recurrence (intra- or extrahepatic) or patient survival.

HEADINGS - Colorectal cancer. Metastasis. Hepatectomy. Surgical pathology. Local recurrence of neoplasia. Recurrence. Survival analysis.

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RESUMO - *Racional*: Aproximadamente 50% dos pacientes com tumor colorretal apresentam metástase hepática sendo a hepatectomia o procedimento terapêutico de escolha. Discutem-se diversos fatores prognósticos; entre eles, a margem cirúrgica é fator sempre recorrente, pois não existe consenso da distância mínima necessária entre o nódulo metastático e a linha de secção hepática. ***Objetivos***: Avaliar as margens cirúrgicas nas ressecções de metástases hepáticas de câncer colorretal e sua correlação com recidiva local e sobrevida. ***Métodos***: Estudo retrospectivo, baseado na revisão dos prontuários de 91 pacientes submetidos à ressecção de metástases hepáticas de neoplasia colorretal. Foi realizada revisão histopatológica de todos os casos com aferição da menor margem cirúrgica e observar o resultado tardio em relação à recidiva e sobrevida. ***Resultados***: Não houve diferença estatística nas taxas de recidiva e no tempo de sobrevivência global entre os pacientes com margens livres ou acometidas (R0vsR1), assim como não houve diferença entre as margens subcentimétricas e as maiores de 1 cm. A sobrevida livre de doença dos pacientes com margens microscopicamente acometidas foi significativamente menor do que dos com margens livres. A análise uni e multivariada não identificou a margem cirúrgica (R1, exígua ou menor que 1 cm) como fator de risco para recidiva. ***Conclusões***: As ressecções de metástases hepáticas com margens livres de doença, independentemente das dimensões da margem, não influenciou na recidiva tumoral (intra ou extra-hepática) ou na sobrevida dos pacientes.

DESCRITORES - Câncer colorretal. Metástase. Hepatectomia. Patologia cirúrgica. Recidiva local de neoplasia. Recidiva. Análise de sobrevida.

INTRODUCTION

Colorectal cancer is the third most common cancer in the Western hemisphere, and the most prevalent gastrointestinal tumor. Approximately 50% of patients with colorectal tumor develop liver metastasis at some point over the course of their disease[20]. The liver is frequently the first location of metastasis, and the only site of metastasis in 30% to 40% of patients with advanced disease[17].

Resection is a procedure potentially curative even to metastatic disease. Formerly, the selection of patients who were eligible for surgical treatment was based on criteria that traditionally focused on tumor characteristics, such as nodule number and size, concurrent extrahepatic disease, and impossibility of resection of lesions with a surgical margin of more than 1 cm[7,10,14,21].

Over the last decade, however, there has been a change of paradigm regarding the selection of patients with resectable tumors. Instead of dogmatic criteria based on the characteristics of the metastatic disease, attention was drawn to a new criterion based on clinical judgment regarding the possibility of complete resection of the metastatic hepatic and extrahepatic lesion. In addition, emphasis was placed on the amount and quality of the remaining liver parenchyma[23].

With this conceptual shift, the importance of safety margins (the distance between the resected metastatic tumor and the surgical margin of transaction) has become an ever-recurring issue. Some authors reported a survival benefit for patients with a resection margin greater than 1 cm[2,7,18]. In contrast, other publications documented that subcentimeter surgical margins (between 0 to 9 mm, yet tumor-free) would have no negative impact on the survival of those patients[18,24,26].

Furthermore, surgeons are frequently faced with multiple metastases, which mandate local resections or enucleations and makes it difficult to obtain margins of more than 1 cm. Therefore, it is of great relevance to assess the relationship of surgical margins of hepatic resections for colorectal metastases and disease free survival.

Therefore, the aim of this study was to evaluate the surgical margins in hepatic resections for colorectal metastases and their correlation with local recurrence and survival.

METHODS

The present retrospective, analytical study was based on the review of the medical records of the patients who underwent hepatic resection for colorectal metastases between January 2000 and December 2009. Preoperative data, as well as those concerning the surgical procedure and postoperative follow-up were examined. The study included all the patients undergoing hepatectomy for colorectal metastasis during the period of interest who had previously been treated with curative intent for the primary neoplastic disease and had not undergone any other surgical treatment for intra- or extrahepatic metastases. The exclusion criteria comprised patients who had incomplete macroscopic resection (R2 surgery), early deaths (up to 30 days after surgery), patients with extrahepatic metastasis concomitantly or previously to liver resection, or cases with unavailable specimen slides and/or paraffin blocks for pathological review.

The following variables were examined for each patient: gender, age, resection date and TNM stage of the primary tumor, neoadjuvant systemic chemotherapy or local radiotherapy in the treatment of the primary lesion, date of diagnosis of the liver metastasis, number of nodules identified, site of the hepatic lesions, adjuvant chemotherapy after hepatectomy, date and type of the hepatic resection, size of the largest nodule, number of lesions on pathological assessment, surgical margin width, histological grade of the metastatic tumor, length of hospital stay, immediate and long-term postoperative follow-up, pre- and postoperative imaging studies, presence of recurrence, site of recurrence, and survival.

Pathological review

Slide review was performed for all the cases selected for analysis. During the histopathological review, the closest distance was measured between the tumor edge and the transection surface of the liver parenchyma (surgical margin). Microscopically positive margins (R1) were defined when the tumor was in contact with the surgical margin; widths of less than, or equal to, 1 mm were considered to be coincidental, yet tumor-free (R0). Other widths were stratified as greater than 1 mm to 4 mm; 5 mm to 10 mm, and greater than 1 cm.

Statistical analysis

The data were analyzed for recurrence rate evaluation. Disease-free survival intervals and overall survival were also examined.

Univariate logistic regression analysis was performed across the cohort to evaluate risk factors for recurrence using Fisher's exact test. Multivariate logistic regression was conducted for factors with clinical or statistical relevance (variables with a p-value <0.20 on univariate analysis). The analyses were performed using the Hosmer-Lemeshow test. Risk prediction was reported as p-values, odds ratios (ORs) and 95% confidence intervals (95% CIs). The descriptive level (p) of 0.05 (which corresponds

to 95% confidence) was adopted to determine the statistical significance of the differences. The Kaplan-Meier curves were used to evaluate the recurrence rates, and the log-rank test was used for comparisons between groups.

The statistical analysis and percent values were computed with the aid of the SPSS 19.0 software (Chicago, IL).

RESULTS

The inclusion criteria were fulfilled by 117 patients who underwent hepatic resection of metastases. However, only 91 patients could be included in the statistical analyses, since seven patients showed extrahepatic metastasis at the time of surgery, three died in the immediate postoperative period, two underwent R2 resection, and in 14 cases, the material was unavailable for pathological review.

The study demographics, the characteristics of the metastatic liver disease and surgical procedure are outlined in Table 1. Seven patients underwent concurrent ablative therapy (radiofrequency) in addition to the hepatic resection.

TABLE 1 - Patient demographics, characteristics of the hepatic metastatic disease and surgical procedure.

Characteristic	Value
Male	41 (45%)
Age	59 (28 – 81) anos
Synchronous tumor	44 (49%)
Bilobar metastasis	30 (33%)
Number of hepatic nodules	
Solitary	40 (44%)
Two	22 (24%)
Three or more	29 (32%)
Nodule diameter	5.18 (0.5 – 23.5) cm
Anatomic resection	60 (66%)
Two-stage resection	7 (8%)
Length of hospital stay	(2-70) days

*Metric variables are represented by means and ranges.

TABLE 2 - Distribution of patients according to surgical margin in relation to recurrence site

Surgical margin	RECURRENCE SITE							
	No recurrence		Extrahepatic recurrence		Intrahepatic		At surgical margin	
	n	%	N	%	n	%	N	%
Positive	1	(4)	3	(10)	5	(18)	1	(10)
≤ 1 mm (coincidental)	7	(28)	7	(24)	4	(15)	5	(50)
> 1 mm to 4 mm	8	(32)	8	(27)	9	(37)	1	(10)
5 mm to 10 mm	4	(16)	6	(20)	5	(19)	2	(20)
> 10 mm	5	(20)	5	(17)	4	(11)	1	(10)
Total	**25**	**(100)**	**29**	**(100)**	**27**	**(100)**	**10**	**(100)**

TABLE 3 - Results of the statistical analyses of surgical margin size in relation to incidence and site of tumor recurrence after hepatectomy

Factor	Post-hepatectomy recurrence		
	Yes or no (p)	Hepatic recurrence (p)	Recurrence at the margin (p)
Positive margin	0.274	0.305	0.999
Margin ≤ 1 mm*	0.999	0.999	0.109
Margin >1 mm to 4 mm*	0.999	0.810	0.259
Margin 5 mm to 10 mm*	0.765	0.785	0.999
Margin >1 cm*	0.748	0.549	0.999

*in these calculations, the patients with positive margins were not considered.

TABLE 4 - Disease-free survival analysis of the R0 patients according to the distance from the surgical margin

Variable		Disease-free survival			p
		1 year	3 years	5 years	
Distance from margin	< 1 mm	48.1	25.9	22.2	0.21
	> 1 mm	63.7	36.6	31.5	

For 42 (46.2%) patients, systemic chemotherapy was employed as adjuvant therapy following hepatectomy. Twenty-two of these underwent a chemotherapy regimen consisting of 5-fluorouracil and leucovorin; 13 patients received 5-fluorouracil, oxaliplatin and leucovorin (FLOX regimen); four patients, 5-fluorouracil, oxaliplatin and leucovorin (Nordic FLOX regimen); two patients, irinotecan; and one patient, oxaliplatin alone.

The mean length of follow-up was 34 months (range, 12 to 126 months). The mean disease-free survival was 28.9 months, with a median of 14.5 months. The mean overall survival was 41.3 months, with a median of 33.5 months. The overall 5-year survival and 5-year disease-free survival rates of the study population were 40.3% and 28.7%, respectively.

Regarding surgical margin status, 81 (89.1%) patients had negative margins, and in 10 (10.9%) were microscopically positive (R1 surgery). Histological review categorized 23 (25%) patients as coincidental margins; 26 (28%) with margins greater than 1 mm to 4 mm; 17 (19%) with margins of 5 mm to 1 cm; and 15 (17%) with margins greater than 1 cm.

Regarding tumor grade, 88 patients had moderately differentiated metastatic adenocarcinomas, while three patients had poorly differentiated tumors.

Tumor recurrence developed in 65 (71.4%) patients and was diagnosed 12.8 months on average (median 10 months) after liver resection. Among patients with tumor recurrence, 28 (43%) showed extrahepatic recurrence, exclusively. Intrahepatic recurrence was found in 37 (57%) patients; only 10 (15%) of these showed local recurrence (close to the margin of resection).

The correlation of surgical margin status with site of recurrence yielded no statistically significant difference between the groups (p=0.531). Table 2

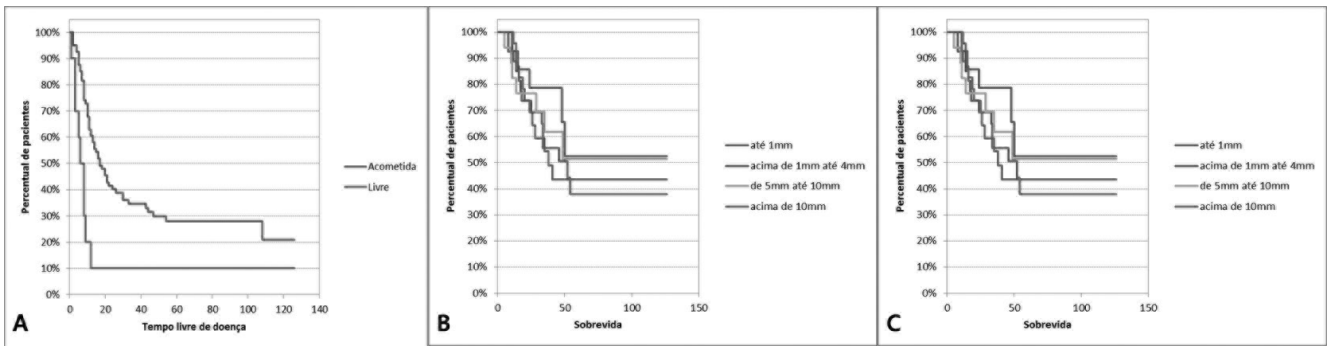

FIGURE 1 - A) curve for disease-free survival among patients with microscopically free surgical margins (R0) and affected (R1), B) Disease-Free Survival curve vs. distance between tumor and resection margin C) overall survival curves in relation to the distance between tumor and resection margin.

depicts the distribution of the patients included in this analysis.

The individual analysis of the surgical margins stratified by width in relation to tumor recurrence showed no significant difference between tumor recurrence and surgical margin width, as illustrated in Table 3.

The incidence of recurrence in R1 versus R0 patients showed no statistically significant difference (p=0.274); the same was true for overall survival (p=0.057). In contrast, disease-free survival was significantly lower for R1 patients (p=0.002, Figure 1A).

There was no statistically significant difference between the stratification of surgical margin size in relation to the disease-free survival and overall survival curves (p=0.728 and p=0.833, respectively), as seen in Figure 1B and 1C.

Among the patients with negative margins (R0), no significant difference was found between coincidental margins and wider (>1 mm) margins with regard to disease-free survival (p=0.612, Table 4). Surgical margins of less than 1 mm and R1 post-surgery margin status represented no risk factors for recurrence (p=0.74 and p=0.27, respectively), even when only the patients with intrahepatic recurrence were evaluated (p=0.15 and p=0.48, respectively).

DISCUSSION

Surgical margins of hepatic resection of colorectal metastases are a constant debate. Studies have shown controversial results, with some groups recommending a minimum margin width of 1 cm[12,18,22], while others report comparable outcomes, even for negative subcentimeter margins[5,28,29].

A meta-analysis evaluated 18 published articles with a total of 4821 patients who underwent hepatectomy for colorectal metastasis, which compared surgical margins of greater *versus* lesser than 1 cm[1]. The overall analysis revealed a 5-year survival benefit for patients with margins greater than 1 cm (46% versus 38%). However, a careful assessment of the methodology employed in this study raises doubts over the validity of the analysis[3,9].

In 2007, Are *et al.*[2] published the first study with a significant number of patients that demonstrated, on multivariate analysis, greater survival of patients who underwent hepatectomy with a margin of more than 1 cm. Those authors further stressed that a resection margin of less than 1 cm, despite showing a decreased survival rates, provides better outcomes than patients with positive margin or those who had no surgical treatment, with mean survival of 42, 30, and 20 months, respectively.

Figueras *et al.*[13] studied prognostic factors for recurrence in 663 patients who underwent hepatectomy for colorectal metastasis. Despite the fact that they observed greater likelihood of long-term recurrence in patients with a surgical margin of less than 1 cm, the multivariate analysis failed to show subcentimeter surgical margins as an independent risk factor for recurrence[16].

Haas *et al.*[15], in a large French study, suggested that the survival of patients who had R1 resection was similar to those who underwent R0 resection, despite a higher recurrence rate[15]. Likewise, Martí *et al.*[19] investigated 182 patients who underwent hepatectomy with curative intent in a retrospective single-center analysis and found no significant differences in the recurrence and survival rates of the patients with surgical margins of less than 1 cm, and even between the patients with microscopically positive margins (R1)[19] In a similar study, Bodingbauer *et al.*[4] obtained the same results.

In the present study, R1 surgery was defined as complete macroscopic excision of the tumor but with histologically detection of tumor in the transection plane, as proposed by a number of authors[13,15,19]. Was found that free surgical margin, independently of its dimension, was not a significant prognostic factor for survival or recurrence. The

stratification of surgical margin widths yielded the same results even when coincidental margins (up to 1 mm) were taken into account. The patients with microscopically positive (R1) margins showed statistically inferior disease-free survival compared with the R0 surgery patients; however, overall survival was identical. These controversies regarding the width of surgical margins indicate that other biological factors could be involved in the physiopathology of recurrence[4].

One possible bias in these results could be the favorable interference of adjuvant chemotherapy after hepatectomy. The perioperative administration of systemic chemotherapy drugs is associated with improved survival rates[8,25]. However, in these data the use of adjuvant chemotherapy following hepatectomy showed no benefit in disease-free survival and overall survival rates; this was probably due to the small number of patients who underwent that treatment.

Another point concerns the use of devices for parenchyma transection or cauterization of the raw area of the liver. Elias *et al.*[11] conducted preoperative imaging studies using the middle hepatic vein as a landmark for the expected surgical margin, and compared these with the margins obtained in the surgical specimen of the liver resection without the use of energy devices (Kelly clamp-crushing technique). Their study demonstrated that 5 to 8 mm of liver parenchyma are destroyed by the surgical procedure[27]. A similar loss of parenchyma occurs with the use of an ultrasonic surgical aspirator that suctions the liver tissue close to the margins[19]. The cytological study of the aspirate collected by an ultrasonic aspirator was suggested as a parameter for surgical margins[11]. Besides, the use electronic devices for hemostasis of the raw area with electric cautery, argon beam or bipolar coagulator would extend the hepatic surgical margin by approximately 2 mm[13]. However, it is difficult to fully understand the actual influence of these factors on the surgical margins and their role in the long-term outcomes of these patients[6].

The present study shows a few limitations. Firstly, it is a retrospective review. Secondly, the number of patients was relatively small in relation to some of the variables, e.g., the microscopically positive margins (R1). Nevertheless, in an attempt to minimize this bias, the data were obtained through a prospective and thorough review of the pathological specimens.

CONCLUSION

The resections of liver metastases with negative margins, independently of the margin width, had no impact on tumor recurrence (intra- or extrahepatic) or patient survival.

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