Non-Colorectal Non-Neuroendocrine Liver Metastases: Management and Prognostic Factors Analysis in a Third Level Hospital

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ABSTRACT

Introduction: Treatment of non-colorectal non-neuroendocrine (NCRNNE) liver metastases is controversial. This study analyses the surgical approach to this pathology in a third level hospital.

Material and Methods: Sociodemographic variables, primary tumor and metastatic disease characteristics, variables linked to the treatment and Adam score have been evaluated as possible prognosis factors.

Results: Twenty patients were included, 50% of each sex. The most common primary tumors were ductal carcinoma of the breast and GIST. Fifty percent of patients were treated with major hepatectomy. There were 30% of postoperative complications without deaths. The one-year survival rate after hepatectomy was 85% whereas the three- and five-year survival rates were 55% and 20%. There were no statistically significant differences in survival according to the analyzed variables.

Conclusion: Further studies are necessary to achieve a better knowledge of survival predictive factors to select those patients that can benefit from surgery.

Keywords: Liver metastases; NCRNNE; Surgery; Survival; Adam score

INTRODUCTION

The liver is one of the most affected organs by the metastatic spread of solid tumors. The surgical treatment of colorectal and neuroendocrine liver metastases is widely accepted achieving 5-year survival rates greater than 60%. However, the adoption of this therapeutic approach is controversial for Non-Colorectal Non-Neuroendocrine (NCRNNE) metastases.

Liver metastases associated with colorectal tumors occur either through portal venous drainage or via lymphatic dissemination, but NCRNNE tumors spread by systemic dissemination. Therefore, hepatic resection could be less effective due to the possibility of the primary tumor has spread to other organs. These factors, coupled with the fact of being an unusual situation, have resulted in a lack of consensus about its treatment. Traditionally, palliative chemotherapy has been considered as the treatment of choice for these cases [1], but at present, surgical treatment has become feasible due to the multidisciplinary approach along with the safety improvements in the surgical procedures. However, an appropriate selection of patients is required, which makes the detection of prognostic pre-surgical factors decisive.

The aim of this study is to analyze the patients with NCRNNE liver metastases treated with hepatic resection in the context of a third level hospital and to compare these results to the literature.

MATERIALS AND METHODS

The scope of analysis is the prospective data collected from patients who have received surgical treatment for NCRNNE hepatic metastases with curative intent in our hospital over the past 20 years. Sociodemographic variables, variables that describe the primary tumor, variables linked to the metastatic disease and variables related to the treatment are considered.

Adam's score is also included in the analysis as a potential prognostic factor [2]. This risk model validated over different populations was developed by R. Adam based on the results of a study of 1.452 patients.

As shown in Table 1, a score on a scale from 0 to 10 is given to each patient. A 5-year survival rate of 30% for patients having 0 to 3 points is estimated, 10% to 30% of those having 4 to 6 points and less than a 10% survival rate for those with more than 6 points [2].

Table 1: Adam score.

Factor	Value	Score
Extrahepatic metastases	Yes	1
	No	0
R2 resection	Yes	1
	No	0
Major hepatectomy	Yes	1
	No	0
Patient age	>60	2
	30-60	1
	<30	0
Disease-free interval	<12	2
	12-24	1
	>12	0
Primary tumour	Melanoma	3
	Squamous	2
	All others	1
	Breast	0
Highest score		10

The statistical analysis has been performed using an R programming language (R version 3.5.0 within RStudio IDE). Kaplan-Meier survival curves have been determined using R package survival for calculations and R package survminer for graphical representations. These curves have been calculated to represent the overall survival of the population analyzed and to perform the univariate analysis of prognostic factors. In the case of the Adam Score, instead of representing all the possible values, only two groups have been considered (low/high score) setting the cut-off point in the median (5 points) to simplify the representation. Univariate analyses of prognostic factors were performed using Cox proportional hazards regression model.

RESULTS

Patient and tumour characteristics

During the last 20 years, 20 patients have been treated with surgical resection. As shown in Table 2, the mean age was 60 years (range 33-80 years) 50% of each sex. The most common primary tumors were ductal carcinoma of the breast (30%), GIST (20%) and melanoma (10%, including one choroid melanoma).

Table 2: Clinical features of patients.

Mean age	60 (33-80)
Gender	
Male	10 (50%)
Female	10 (50%)
Neoadjuvant chemotherapy	5 (25%)
Liver metastases	
Synchronous	4 (20%)
Metachronous	16 (80%)
Size >1 cm	17 (85%)
LHL1	9 (45%)
RHL2	8 (40%)
Both lobes	3 (15%)
Resection	
Major	10 (50%)
Minor	10 (50%)
Primary tumor	
Ductal carcinoma of the breast	6 (30%)
GIST	4 (20%)
Melanoma	2 (10%)
Adenoid cystic carcinoma of the parotid gland	1 (2%)
Clear cell renal cell carcinoma	1 (2%)
Ewing sarcoma	1 (2%)
Embryonic testicular tumor	1 (2%)
Epidermoid carcinoma of the pyriform sinus	1 (2%)
Fallopian tube adenocarcinoma	1 (2%)

Endometrial adenocarcinoma	1 (2%)
Gastric adenocarcinoma	1 (2%)

1) Left Hepatic Lobe; 2) Right Hepatic Lobe

Regarding metastases characteristics, they were metachronous in 80% of patients. The mean time from diagnosis of the primary tumor to that of the liver metastases was 100 months (range 16-252 months). Twenty-five percent of the patients presented more than one hepatic lesion and the size of the metastases was larger than 1 cm in 85% of patients. Forty-five percent of the metastases affected the left hepatic lobe, 40% the right lobe and 15% both.

There were no statistically significant differences in the overall survival according to the Adam Score or the variables considered in its calculation. Nor were the rest of the variables related to the patient, the treatment and the tumor-associated to greater or less survival; as it is shown in Table 3. However, the female gender is associated with increased survival.

Treatment of the primary tumor and metastases

In terms of oncology treatment, 25% of the patients received neoadjuvant chemotherapy after diagnosis of the primary tumor. Sixty percent of these patients received presurgical treatment due to the presence of synchronous metastatic disease.

Adjuvant chemotherapy between the treatment of the primary tumor and the surgical treatment of metastases was received by 45% of patients.

All patients except one received surgical treatment for the primary tumor. The exception was a patient with breast cancer, who was treated with radiotherapy and hormonotherapy.

Regarding the treatment of hepatic metastatic disease, a major hepatectomy (resection of three or more liver segments) was performed in 50% of patients. Surgical treatment was carried out through laparoscopy by 10%. The average hospital stay was 14 days (range 2-52 days). Thirty percent of patients suffered some post-operative complications, three of Grade I and one of Grade II according to the Clavien-Dindo classification. Two presented a Grade III complication requiring surgical reintervention, one of them due to bleeding and the other as a result of a biliary fistula. None of the patients died in the post-operative period.

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Survival and prognostic factors

As shown in Figure 1, the one-year survival rate after hepatic surgery is 85% whereas the three and five-year survival rates are 55% and 20% respectively, after a mean follow-up of 48 months (range 2-187 months). The primary tumor and complications related to it or its metastases were the cause of death in 85% of dead patients. The remaining 15% died due to other reasons.
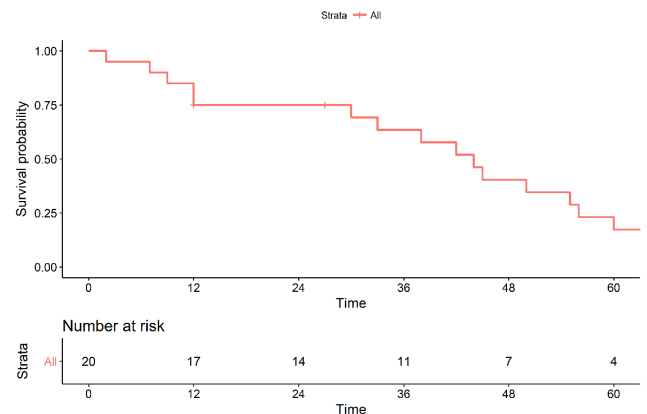

Figure 1: Kaplan-Meier overall survival.

During post-hepatectomy follow-up, the disease recurred in 45% of patients with a mean recurrence-free interval of 36 months (range 7-168 months). Two patients presented recurrence in soft tissues, two in lungs, two in liver, and lungs and one in the peritoneum. Three patients with hepatic recurrence underwent a second hepatectomy. One of them, with a parotid carcinoma as a primary tumor, was also treated with thoracic surgery due to lung metastases. This patient also received radiofrequency treatment due to subsequent recurrences in the liver and lungs and a second thoracic surgery to treat chest wall metastases.

There were no statistically significant differences in the overall survival according to the Adam Score or the variables considered in its calculation. Nor were the rest of the variables related to the patient, the treatment and the tumor-associated to greater or less survival; as it is shown in Table 3. However, the female gender is associated with increased survival with a P value close to statistically significance (p-value ≤ 0.05).

Table 3: Univariate analysis of predictors of survival (Cox regression).

Variable	Overall Survival	
	HR (95% CI)	p-value
Age	0.996 (0.9565-1.036)	0.83
Gender (Female)	0.356 (0.1199-1.055)	0.062
Breast primaries	0.9659 (0.3102-3.007)	0.952
Adjuvant chemotherapy	1.2355 (0.471-3.241)	0.667
Major hepatectomy	2.4126 (0.7884-7.383)	0.123
Metachronous metastases	0.8217 (0.2619-2.578)	0.736
Adam Score	1.2377 (0.45-3.404)	0.68

DISCUSSION

The surgical treatment of NCRNNE liver metastases remains controversial. There are increasing retrospective studies that analyze presurgical variables as predictors of hepatectomy

outcomes. In this respect, no associations between presurgical variables and patients' prognosis have been found in our study but it must be noted that obtaining significative results is very limited by the small number of patients considered.

Considering the studies of the literature over a larger number of patients, the three-year survival rate is 34%-57% decreasing to 19%-42% in 5 years, postsurgical mortality varies between 0 and 5% and morbidity between 18% and 29%. Regarding the primary tumor, breast [2,3,], genitourinary system [4] and digestive tract [5] are the most common origins. These values match those found in our study.

Furthermore, factors more frequently associated with bad prognosis according to the literature are positive resection margins [4], extra hepatic disease [2,3,4] and a short interval between the treatment of primary tumor and the treatment of the metastases [2,3,4]. In terms of primary tumors types, patients with liver metastases from breast tumors present better prognosis [2,4], whereas those with melanoma experience worse survival rates [2,3]. Regarding these factors, no statistically significant relations have been found in our study but a connection nearly to statistical significance between female sex and good prognosis has been noted.

As it is the most prevalent primary tumor type both in the literature and in our study, surgical treatment of liver metastases from breast carcinoma will be review in depth. Studies from the literature report 3-year survival rates from 49% to 68% and 5-year survival rates that vary from 27% to 53% [2,8,10]. In our series, this primary tumor site is associated with a 3-year survival rate of 50% and a 5-year survival of 17%, which is below the range found in the literature. Predictive factors associated with a bad evolution are short disease-free interval [4,5], absence of hormone receptors expression [4], bad response to preoperative chemotherapy [5] and positive resection margins in hepatectomy [3]. Other studies have also found negative associations to treatments with Trastuzumab [5]. Some of these factors are specific to ductal carcinoma of the breast and may indicate that overexpression of HER2 and the presence of positive hormone receptors help increase patients' survival when targeted therapies complement the surgical treatment of hepatic metastases [4]. In our series two of six patients with breast carcinoma presented HER2-positive and received targeted treatment. In addition, one of them presented positive hormone receptors. The four patients with HER2-negative and the other patient with HER2-positive do not present hormone receptors. In contrast to the literature, the results found in our series point out that patients with hormone receptors and HER2-negative present lower survival than the rest, although conclusions cannot be drawn due to the small number of patients.

CONCLUSION

A better knowledge of presurgical predictive factors must help us to select those patients that can benefit from aggressive treatment as hepatectomy. For this reason, it is necessary to conduct further studies both observational and experimental in order to achieve the goal of offering the best treatment to every patient.

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