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Original article

Role of resection surgery in breast cancer liver metastases. Experience over the last 10 years in a reference hospital☆

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A B S T R A C T

Introduction: Breast cancer liver metastases (BCLM) are considered as a systemic disease which is mainly treated with chemotherapy, while the role of surgical resection still remains to be well defined.
The aim of the study is to analyse the survival and prognostic factors predictive of mortality in patients with BCLM treated by liver resection.
Material and methods: A total of 21 patients were operated on between 1998–2008, with liver resection being performed on 12. We retrospectively collected several variables.
Results: The mean age was 48 years. The most frequent stage was I, with curative surgery in all cases, and the majority (66.7%) received adjuvant treatment. The BCLM were mainly meta metachronic (83.3%). The majority (66.7%) received neoadjuvant treatment. The liver resection was R0 in all cases with no morbidity and a mortality in the long term of 8.3%. Two-thirds received chemotherapy. The estimated survival at one year was 67% and 23% at 5 years. A disease free period of less than 24 months between the primary tumour and the appearance of metastasis was associated with a worse survival.
Conclusions: Resection of BCLM within a multimodal treatment is safe in selected patients.
(ISRCTN Number: 50105150).

Papel de la resección quirúrgica en las metástasis hepáticas de carcinoma de mama: experiencia en los últimos 10 años en un hospital de referencia

Palabras clave:
Metástasis hepáticas de carcinoma de mama

R E S U M E N

Introducción: Las metástasis hepáticas de carcinoma de mama (MHCM) se consideran una enfermedad sistémica cuyo tratamiento principal está basado en la quimioterapia, mientras que el papel de la resección quirúrgica sigue sin estar bien definido.

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Resección hepática
Supervivencia a enfermedad metastásica

El objetivo de este estudio fue analizar la supervivencia y los factores pronósticos predictivos de mortalidad en las pacientes con MHCM tratadas con resección hepática.
Material y métodos: Entre 1998-2008 intervinimos a 21 pacientes, realizando resección hepática en 12. Recogimos distintas variables retrospectivamente.
Resultados: La edad media fue de 48 años. El estadio más frecuente del tumor primario fue el i, con cirugía curativa en todos los casos, y recibió tratamiento adyuvante la mayoría (66,7%). Las MHCM fueron fundamentalmente metacrónicas (83,3%). Recibió tratamiento neoadyuvante el 66,7%. La resección hepática fue R0 en todos los casos con una morbilidad nula y una mortalidad a largo plazo del 8,3%. Recibió quimioterapia adyuvante el 66,7%. La supervivencia estimada fue del 67% al año y del 23% a los 5 años. Un periodo libre de enfermedad entre el tumor primario y la aparición de metástasis menor de 24 meses se asoció a peor supervivencia.
Conclusiones: La resección de las MHCM dentro del manejo multimodal es un tratamiento seguro en pacientes seleccionadas.

Introduction

Although the liver is a common site for metastasis, the development mechanisms for it are different, and depend on the location of the primary tumour. In patients with primary gastrointestinal tumours, the liver acts as a filter and liver metastases (LM) lodge in it via the portal veins or the abdominal lymph channels, which is not considered as a systemic disease. It is currently accepted that the best treatment for LM from colorectal cancer (LMCRC) is a combination of surgical resection and chemotherapy (CT), estimating that the survival of non-resected patients is zero at five years, while in patients treated with hepatic resection, it is 35%-58% in series in the last 10 years.[1,2]

In addition, LM from extra-abdominal primary tumours owe their development to systemic tumour spread, so liver resection in these cases is controversial. Among them are the LM from breast cancer (LMBC), which will develop in 5%-12% of patients diagnosed with breast cancer.[3,4] Most receive only chemotherapy, with a median survival of 22-27 months.[3]

Studies evaluating the effectiveness of liver resection in extra-abdominal primary tumours have reached no clear conclusions, due to the heterogeneity of these primary tumours, the limited number of patients, and the association of surgical treatment with CT.[5-8] However, in recent years, and probably encouraged by the good results obtained with surgical resection in patients with LMCRC, there have been several studies. They show that this treatment option is safe in selected patients and can provide increased survival when compared with treatment based solely on CT, which is administered in most cases.[9-11]

The aim of this study was to analyse the results and prognostic factors associated with poor survival in our series of patients with LMBC where liver resection was indicated, and thus to be better able to select those that may benefit from this therapy.

Material and method

Between November 1998 and November 2008, 21 patients diagnosed with LMBC underwent surgery at the *Unidad de Cirugía y Trasplante Hepático del Hospital Universitario La Fe* (Liver Transplant and Surgery Department, La Fe University Hospital), 12 of them underwent liver resection.

Surgery was proposed in those patients who met two criteria: good clinical health not contraindicating a liver resection and the possibility of R0 resection, according to additional preoperative imaging tests. A CT scan and/or MRI was performed in all patients and, in cases selected with a greater risk of occult peritoneal or liver disease, positron emission tomography was also used in the last stage of the testing process. A complete scan of the abdominal cavity was performed in all cases during surgery, to exclude carcinomatosis and locoregional adenopathy; intraoperative liver ultrasound was also performed. Some patients, for whom it was considered impossible to make a R0 resection during surgery, did not undergo hepatectomy and were excluded from the final statistical analysis.

The CT regimes were different, being Taxol®, cyclophosphamide, epirubicin and methotrexate the agents most commonly used.

The variables analysed are shown in Table 1.

Statistical analysis was performed using SPSS® software, version 11.0. Kaplan Meier curves were used for the survival analysis and the logrank method used for the univariate survival analysis. This analysis studied the influence of age; disease-free interval (DFI), with a cut-off point of 24 months, following the trend of the latest publications,[9,10] breast cancer stage and hormonal status for breast cancer and LMBC (which were considered positive if oestrogen and/or progesterone receptors were expressed, and negative if the expression of both receptors was negative); the number and size of metastases and type of hepatectomy (with major

Table 1 – Data collected from patients

Primary tumour	Liver metastases
Stage	Disease-free period (months)
Neoadjuvant chemotherapy regimen and number of cycles	Presence of other synchronous metastases
Type of surgery (conservative/mastectomy)	Neoadjuvant chemotherapy regimen and number of cycles
Adjuvant chemotherapy regimen and number of cycles	Neoadjuvant treatment response (complete/partial/none)
Postoperative radiotherapy	Relapse (yes/no)
Tumour hormonal status (positive/negative)	Type of hepatectomy (major/minor)
	Size of metastases
	Metastases, n
	Type of resection (R0/R1/R2)
	Morbidity
	Hospital stay, days
	Adjuvant chemotherapy regimen and number of cycles
	Hormonal status of metastasis (positive/negative)
	Disease-free survival, months
	Recurrence location
	Follow-up period, months

hepatectomies being those which included the resection of 3 or more liver segments). A P=.05 was considered statistically significant.

Results

Patient characteristics

Of the 21 patients who underwent surgery, unresectable lesions were found in 9 cases due to multiple liver diseases or the presence of unresectable extrahepatic disease. In these patients, surgery was limited to exploratory laparotomy. In the 12 remaining patients, R0 liver resection was performed and these are the cases included in this study series.

The resection rate was therefore 57.1%. Analysing the number of exploratory laparotomies per year (Figure 1), we found that the number decreased progressively from 2002 to the present. The average age of these patients was 47.6 years (35-67).

Primary tumour characteristics

Breast carcinoma was diagnosed at stage I in 36.4% of cases (n=4), stage II in 16.7% (n=2), stage IIIa in 9.1% (n=1), stage IIIb in 9.1% (n=1) and stage IV in 27.3% (n=3). Stage IV consisted of two patients with liver disease and one with extrahepatic disease, and this was not yet known in one of the patients. The 3 patients in stage II and IIIa received neoadjuvant chemotherapy. The CT regimens were different in the three cases, where 2-4 cycles were received. R0 resection of the primary tumour was performed in all patients. 66.7% (n=8) received adjuvant chemotherapy with an average of 5 cycles (range 4-6). Different CT regimens were administered, with the most frequent being cyclophosphamide, methotrexate and 5FU in 25% of cases (n=3). Radiotherapy was given to 50% of patients (n=6), mainly those who underwent breast-conserving surgery (lumpectomy/quadrantectomy). 25% (n=3) of the patients were treated with hormone therapy.

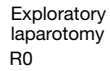

Figure 1 – Liver resection and exploratory laparotomy by year.

The treatment followed by patients according to the primary tumour stage is shown in Table 2.

Liver metastasis characteristics

The average time between mastectomy and diagnosis of LM, disease-free interval (DFI), was 34 months (range 0-73), being synchronous in 2 cases (16.7%) and metachronous in the rest (83.3%).

Eight patients received neoadjuvant chemotherapy (66.7%) with different regimens. The most frequent agent administered was Taxol® (16.7%) and the average number of cycles administered was 6 (range 2-9). A complete response was found in 12.5% (n=1), a partial response in 75% (n=6), and disease stabilisation in 12.5% (n=1). The patient who had complete response relapsed after two years.

LMBC surgery consisted of major liver resection in 58.3% of cases (n=7) and a minor resection in the remainder (n=5). The average size of metastasis was 4.8 cm (range 1.5-8), with an average of 2 (range 1-6) being resected. R0 resection was performed in all cases. No patient had postoperative complications and the average hospital stay was 5.4 days (range 3-8).

Table 2 – Treatment of primary tumour by stage

Primary tumour stage	Neoadjuvant CT, n	Operation	Adjuvant CT, %	RT, n	HT, n
I (n=4)	0	M: 2 CS: 2	4	1	1
II (n=2)	2	M: 1 CS: 1	1	1	1
IIIa (n=1)	1	M: 1	1	0	0
IIIb (n=1)	0	M: 1	1	1	1
IV (n=3)	0	M: 1 CS: 2	0	1	0

CS, conservative surgery; CT, chemotherapy; HT, hormone therapy; M, mastectomy; RT, radiotherapy.

Table 3 – Patient characteristics and monitoring

P	Age	TAM	DFI, months	Neoadjuvant CT	M, n	Adjuvant treatment	Relapse	DFS, months	OS, months	CS
1	43	Stage I	70	0	6	CT		46	46	DF
2	35	Stage I	45	0	1	CT	Liver	68	111	AD
3	42	Stage I	28	Yes	2	CT+HT		84	84	DF
4	38	Unknown	40	0	1	CT+HT		17	17	DOF
5	51	Stage IV	0	Yes	1	CT		6	6	DF
6	50	Stage II	12	Yes	1	CT+HT	Bone	6	12	AD
7	54	Stage IV	1	Yes	1	HT	Liver	6	18	DF
8	50	Stage I	73	0	1	CT+HT		6	6	DF
9	40	Stage II	41	Yes	1	HT		13	13	DF
10	51	Stage IV	4	Yes	1					DD
11	67	Stage IIIa	41	Yes	4			1	1	DF
12	50	Stage IIIb	53	Yes	1	CT		27	27	AD

AD indicates alive with disease; CS, current status; CT, chemotherapy; DD, death due to disease; DF, disease-free; DFI, disease-free interval; DFS, disease-free survival; DOF, dropped out during follow-up; HT, hormone therapy; M, metastasis; OS, overall survival; P, patient; TAM, tumour, adenopathy, metastasis.

Eight patients (66.7%) received adjuvant chemotherapy, with an average of 6 cycles (range 3-9), where the CT regimen was different in each of them. Hormone therapy was administered in 50% of cases.

The mean follow-up period was 31 months (range 1-111). Disease recurrence was seen in 33.3% of cases (n=4), with 2 patients having liver recurrence, 1 bone recurrence and another brain recurrence. The mean DFI after liver resection was 25.5 months (range 1-84). The current rate of patients living free of disease is 58.3% (n=7), while those alive with the disease are 25% (n=3), with a death rate of 8.3% (n=1) because of the disease. One of the patients with hepatic recurrence responded completely to chemotherapy. Operative mortality was zero and long-term mortality was 8.3% (1 case).

The patient characteristics and disease follow-up is shown in Table 3. One patient dropped out during the follow-up period.

Survival analysis

Patients were followed for a mean of 31 months and a median of 12.5 months, one patient dropped out and one died. Actuarial survival was 67% per year and 23% at 5 years (Figure 2), with a mean of 33.8 months and median of 17 months. Of the living patients controlled (n=10), 70% are disease-free.

Analysis of risk factors

The results of the univariate analysis of the variables included are shown in Table 4. The only factor with a statistically significant difference regarding survival is the DFI. Therefore, if the patient sample is split between those with less than 24 months DFI and those with a DFI greater than or equal to 24 months, there is a statistically significant difference for patients with the greater DFI.

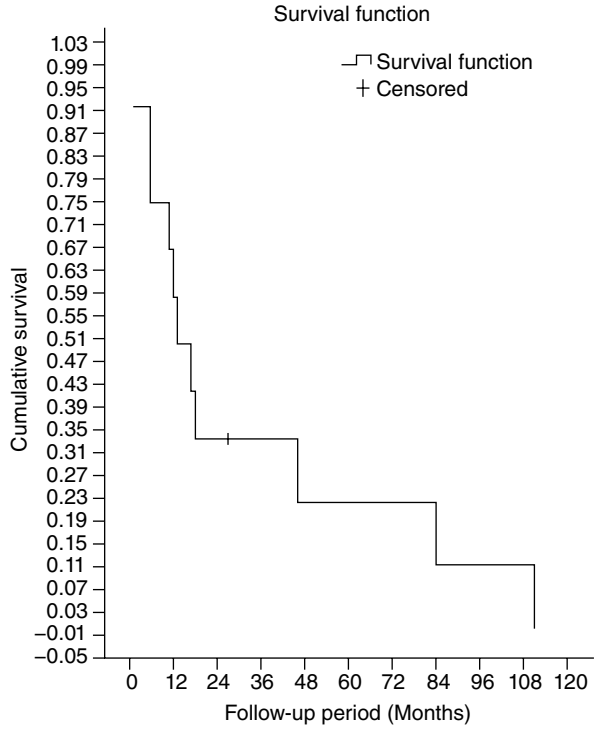

Figure 2 – Kaplan-Meyer survival curve after liver metastases resection.

Table 4 – Univariate analysis of variables

Variables	Median survival, months	P
Age		
≥50	46	.109
<50	12	
Primary tumour stage		
I-IIb	13	.45
IIIa-IV	18	
Hormonal status of breast carcinoma		
Negative (O and P)	84	.66
Positive (O and/or P)	17	
Hormonal status of liver metastases		
Negative (O and P)	13	.12
Positive (O and/or P)	46	
Disease-free period		
<24 months	12	.003
≥24 months	84	
Number of liver metastases		
1	13	.7
>1	46	
Size of liver metastases		
≤5 cm	18	.4
>5 cm	13	
Type of hepatectomy		
Minor	46	.16
Major	12	

O indicates oestrogen receptors; P, progesterone receptors.

Discussion

It is generally considered that metastatic breast cancer is a disease that spreads, and many oncologists are reluctant to include surgery in the multimodal treatment strategy for these patients. Although systemic treatments can achieve about 60% of response in the metastatic recurrence of breast cancer, long-term survival is rare with only medical treatment. Without liver resection, the average survival reported after the first occurrence of LM can range from 1-15 months.[3] However, most of these patients received palliative care.

In recent years, buoyed by the encouraging results of some pioneering groups, surgery in LMBC is being increasingly integrated as a resource within a multimodal treatment strategy. At present, liver resection is the only chance for a cure for these patients, offering an increase in survival.[10] To improve the selection of surgery candidates, the analysis of risk factors associated with poor survival must be analysed as well as identifying patients who will not benefit from liver resection.

In analysing our results, we obtained an average estimated survival of 33.8 months, exceeding that achieved with chemotherapy only.[3] Our results support the current trend of integrating surgery in the treatment of these patients, and of advocating its use in selected patients in combination with an adjuvant at all times. The most important aspect to consider for liver resection of LMBC is the selection of patients. And following current criteria for liver resection in LMCRC, we considered all patients in good clinical condition with lesions allowing complete resection with a safe resection margin as candidates. Still, the resection rate achieved (57.1%) was probably low and less than that obtained with LMCRC in the same medium.[2] However, as discussed in the "Results" section, the number of exploratory laparotomies has decreased steadily since 2002, which can be explained by the improvement in preoperative diagnostic imaging methods (computed tomography, magnetic resonance imaging, positron emission tomography), which have led to better patient selection.[12,13]

Another point to consider is that the majority of oncologists believe that extrahepatic metastases contraindicate liver resection. However, some studies[6,11,14] have found no statistically significant differences in terms of long-term survival after hepatic resection among patients who had other metastases and those who, at the time of diagnosis, did not. If we analyse the studies, we see that most patients with extrahepatic metastases had lesions on the bone and

were treated with CT and/or radiotherapy before the surgery, and that these were not considered a contraindication for liver resection. In our study, the presence of extrahepatic metastasis was not an exclusion criterion. We were aware of the presence of extrahepatic metastases in three patients when surgery was indicated (2 patients with bone metastases, one also with lung metastasis and another patient with axillary metastases). However, the liver disease was not resectable in any of them, with the surgery consisting of exploratory laparotomy without liver resection, and so these were not included in the statistical analysis of the results. Given the sensitivity of this type of tumour to chemotherapy and the long survival times achieved while maintaining the disease stable, liver resection may become the adjuvant treatment for increasing survival even in the presence of unresectable extrahepatic disease.

Regarding the survival analysis, actuarial survival was 67% at one year and 23% at five years. Disease recurrence after surgery was observed in 33.3% of patients (n=4); these results are similar to those found in other studies.[9-11]

In the univariate analysis of risk factors, the only parameter showing statistically significant differences was the DFI between the primary tumour and the appearance of metastases, with worse survival for those patients with a DFI of less than 24 months. This confirms that DFI is one of the most important factors to consider for patients with metastatic breast cancer.[15]

Among the risk factors analysed is the hormonal status of the primary tumour. We observed wide differences in median survival among patients with positive and negative hormonal status (17 vs 84 months), with a longer survival in patients with a negative hormonal status. However, this difference was not statistically significant. Our results are consistent with those of other authors,[9,11] who also observed a difference in median survival for a negative hormonal status of the primary tumour. The difference was statistically significant in the Lubrano[9] study, while in the Adam[11] study it was not. Currently, the role of hormonal status in both the primary tumour and the LM is not clear from the medical literature.[7,10,16]

For the other variables analysed (Table 4), no statistically significant differences for survival were found, in accordance with the results of other studies,[10,11] despite having a larger patient sample than ours. However, the Lubrano[9] study, with a slightly higher sample (16 patients), showed statistically significant longer survival in patients over 50 years, with only 1 having LM, who underwent minor hepatectomy. These results can be explained by having a sample of patients with better prognosis (higher average age, higher DFI) than the patients included in our series.

The results in our study are in keeping with those obtained in other series,[9-11] which support LMBC surgery as a safe treatment in selected patients, when associated with systemic treatment. To maximise the benefits of surgery, the key point is the selection of patients, while a risk factor analysis can also be helpful. In our study, a DFI of less than 24 months was the only negative prognostic factor with a statistically significant difference. Patients with negative hormone receptors in the primary tumour had higher median survival than patients with positive receptors, although these differences were not statistically significant.

We think that currently surgical resection of LMBC should always be offered to all patients with a clinical condition good enough to allow liver resection, with lesions that can be completely resected (R0) and where the DFI is great. Surgeons should work together with oncologists in treating these patients to offer them longer survival and perhaps the possibility of a cure.

Conflicts of interests

The authors affirm that they have no conflicts of interests.

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