RESEARCH ARTICLE

Clinical Characteristics and Survival Analysis of Breast Cancer Molecular Subtypes with Hepatic Metastases

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Abstract

Background: The liver is one of the most common metastatic sites of breast cancer, hepatic metastases developing in 6%-25% of patients with breast cancer and being associated with a poor prognosis. The aim of this study was to analyze the survival and clinical characteristics of patients with hepatic metastases from breast cancer of different molecular subtypes and to investigate the prognostic and predictive factors that effect clinical outcome. Methods: We retrospectively studied the charts of 104 patients with breast cancer hepatic metastases diagnosed at Sun Yat-sen University Cancer Center from December 1990 to June 2009. Subtypes were defined as luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) enriched, triple-negative (TN). Prognostic factor correlations with clinical features and treatment approaches were assessed at the diagnosis of hepatic metastases. Results: The median survival time was 16.0 months, and the one-, two- three-, four-, five-year survival rates were 63.5%, 31.7%, 15.6%, 10.8%, and 5.4%, respectively. Median survival periods after hepatic metastases were 19.3 months (luminal A), 13.3 months (luminal B), 18.9 months (HER2-enriched), and 16.1 months (TN, P=0.11). In multivariate analysis, a 2 year-interval from initial diagnosis to hepatic metastasis, treatment with endocrine therapy, and surgery were independent prognostic factors. Endocrine therapy could improve the survival of luminal subtypes (P=0.004) and was a favorable prognostic factor (median survival 23.4 months vs. 13.8 months, respectively, P=0.011). Luminal A group of patients treated with endocrine therapy did significantly better than the Luminal A group of patients treated without endocrine therapy (median survival of 48.9 vs. 13.8 months, P=0.003). Conclusions: Breast cancer subtypes were not associated with survival after hepatic metastases. Endocrine therapy was a significantly favorable treatment for patients with luminal subtype.

Keywords: Breast cancer - hepatic metastases - subtypes - prognostic variables - survival analysis

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Introduction

Breast cancer is the most common cancer in women in the world (Shibuya et al., 2002). Despite improvement in treatment, 20%-30% of patients with early breast cancer will experience metastatic disease (Early Breast Cancer Trialists' Collaborative Group, 2005). Meanwhile, 6%-10% of patients were to be ill with metastatic disease at the initial diagnosis of breast cancer (Miller et al., 1999). Hepatic metastasis is the one of the most frequency distant metastasis of breast cancer (Shibuya et al., 2002). Survival rate for patients with hepatic metastasis breast cancer was poor, with a median survival time about 14 months (Zinser et al., 1987).

Breast cancer has different molecular subtypes which may be defined by gene expression profiles (Perou et al., 2000; Parker et al., 2009) or immunohistochemical biomarkers (Nielsen et al., 2004; Cheang et al., 2008). It is reported that human epidermal growth factor receptor 2 (HER2)-enriched subtype breast cancers aggressively spread to the liver (Harrell et al., 2012). Endocrine therapy is indicated for estrogen receptor (ER) and/or progesterone receptor (PgR) patients with long survival interval. Major treatments for hepatic metastasis breast cancers include chemotherapy, surgery, and intervention therapy.

The aim of this study was to analyze the clinic-pathological characteristics and detect prognostics of different molecular subtypes of breast cancer patients with hepatic metastases.

Materials and Methods

One hundred and four female patients with hepatic metastases breast cancer diagnosed and treated at Sun Yat-sen University Cancer Center from December 1990 to June 2009 were selected in this analysis. All the patients with no evidence of distant metastasis at the time of primary diagnosis with breast cancer were followed. In this study,

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we took into consideration only the initial metastatic site that could be liver. If death was not due to breast cancer, data were censored at the date of their last known contact. If main patient clinico-pathologic characteristics, treatment strategies and outcomes were incomplete, cases were not included in this study. Clinical characteristics included normal information, pathologic subtype, disease stage, treatment, location and time of metastasis and ER, PgR and HER-2 expression. The TNM Cancer Staging Manual 7th edition of the American Joint Committee on Cancer (AJCC) (Sinn et al., 2010) was used to classify the cancer stages. Breast cancers were classified into four molecular subtypes according to a gene expression profile-validated immunohistochemical surrogate panel as follows: luminal A (ER positive and/or PgR positive and HER-2 negative), luminal B (ER positive and/or PgR positive and HER-2 positive), HER-2 enriched (ER negative and PgR negative and HER-2 positive), and triple-negative (TN) (ER negative and PgR negative and HER-2 negative).

After initial surgical treatment, patients had follow-up including clinical examination, laboratory tests, ultrasound every six months, and an annual mammography during the first 5 years. Hepatic metastases were diagnosed according to liver ultrasound, computed tomography or magnetic resonance imaging. Ethics approval had been obtained from the Ethical Review Committee, Sun Yat-sen University Cancer Center, and informed consent had been obtained from all patients.

Treatment

Of the 104 patients included in the study and presenting no evidence of metastases at the time of initial diagnosis, all had undergone tumor resection with axillary lymph node dissection: 97.6% patients had undergone mastectomy and 2.4% patients had lumpectomy. Patients treated with new adjuvant chemotherapy as initial treatment were not included in the study. Adjuvant chemotherapy was given in 84.3% patients. 49.4% patients had undergone local regional radiotherapy associated with surgery. Adjuvant endocrine therapy was given to 42.3% patients. After diagnosed hepatic metastases, 88 patients had received chemotherapy with drugs as: anthracycline-based (31 cases, 35.2%), paclitaxel-based (46 cases, 52.3%), and platinum-based (11 cases, 12.5%). Adjuvant endocrine therapy was given to 25 patients: tamoxifen was given to 21 patients; aromatase inhibitor was given to 4 patients. 3 patients had undergone surgery. 5 patients were given to targeted gene therapy with trastuzumab.

Definition of survival time and survival rate

Follow-up began after first diagnosed and ended on May 31, 2012 for the patients in the study. Survival time and survival rate, stated at the time of diagnosed of hepatic metastases, was the interval between hepatic metastases and death due to breast cancer.

Statistics

All data was analyzed by SPSS version 17.0 software. Survival analysis was estimated using the Kaplan-Meier method including number of patients, median survival time and a 95% confidence interval (CI). Survival was compared across subtypes using the log-rank test. Statistical comparisons were carried out using T test or analysis of variance (ANOVA) for quantitative variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables. Multivariate analysis was estimated by creating a Cox proportional hazards regression model. P-value < 0.05 was considered statistically significant.

Results

Hepatic metastases patients' characteristics

The age interval of the patients was 21-82 years, with a median of 49 years. 52 cases (50%) were pre-menopausal. 99 cases (95.1%) were invasive ductal carcinoma, 4 cases (3.9%) were adenocarcinoma and 1 case (1%) was invasive lobular carcinoma. The cancer stages were classified as follows: stage I, 2 cases; stage II, 39 cases; stage III, 63 cases. Among 104 cases 30 (28.9%) were luminal A, 35 (33.6%) were luminal B, 21 (20.2%) were HER-2 enriched, 18 (17.3%) were TN. Median disease free interval after first diagnosed with breast cancer was 16.0 months (0.0-163.6 months). Median interval from initial diagnosis to hepatic metastasis was 13.5 months (0.0-77.1 months). 2 (1.9%) stage I patients developed hepatic metastases with median interval of 37.4 months (95% CI: 31.4-43.4 months); 39 (37.5%) stage II patients developed hepatic metastases with median interval of 27.4 months (95% CI: 0.03-163.6 months); 63 (60.6%) stage III patients developed hepatic metastases with median interval of 14.6 months (95% CI: 0.2-59.3 months).

Overall survival of hepatic metastases patients

Of the 104 patients included in the study, all had undergone a follow-up interval from initial diagnosis of breast cancer to May 31, 2012 with a median follow-up interval 36.4 months (4.4-190.8 months). Median survival interval after hepatic metastasis diagnosis was

Table 1. Analysis of Clinical Characteristics and Survival of 4 Subtypes of Breast Cancer with Hepatic Metastases in 104 Patients

Group	Patient No.	Age at initial diagnosis (years)	Disease free interval (months)*	Interval from initial diagnosis to HM (months)	Survival after HM (months)	Overall survival (months)
Luminal A	30	47.0	16.0	25.5	19.3	51.2
Luminal B	35	44.4	15.1	19.1	13.3	33.4
HER-2 enriched	21	46.8	21.0	33.0	18.9	54.0
TN	18	50.2	12.4	14.1	16.1	36.4
Overall	104	46.6	16.1	22.9	15.9	43.2
P		0.338	0.371	0.111	0.110	0.026

*excluding patients of stage IV at initial diagnosis. HM, hepatic metastasis; TN, triple negative

Table 2. Univariate and Multivariate Prognostic Analysis of 104 Patients

Prognostic factor	Patient No.	Median survival (months)	95% CI	P Univariate	P Multivariate
Age (years)					
>35	85	16.3	12.7-19.9	0.543	
≤35	19	9.2	7.1-11.3		
Menstrual status					
premenopausal	52	14.7	11.9-17.5	0.976	
postmenopausal	52	16.0	11.2-20.8		
Stage					
I-II	41	16.3	11.0-21.6	0.708	
III	63	15.3	11.2-19.4		
Subtype					
Luminal A	30	19.3	12.3-26.3	0.110	
Luminal B	35	13.3	11.2-15.4		
HER-2 enriched	21	18.9	12.3-25.5		
TN	18	16.1	12.8-19.4		
HM after initial diagnosis					
>1 year	66	13.9	9.3-18.5	0.078	
≤1 year	38	21.1	6.6-35.6		
HM after initial diagnosis					
>2 years	35	12.3	6.5-18.1	0.016	<0.001
≤2 years	69	17.2	12.8-21.6		
HM after initial diagnosis					
>5 years	4	18.9	1.4-36.4	0.615	
≤5 years	100	15.9	13.2-18.6		
Number of HM sites					
Isolated	20	14.9	12.3-17.5	0.634	
Multiple	84	16.0	11.5-20.5		
Endocrine therapy(first line)					
Yes	44	19.0	15.1-22.9	0.756	
No	60	14.5	11.7-17.3		
Chemotherapy					
Yes	88	15.9	13.1-18.7	0.875	
No	16	16.1	0.0-35.3		
Anthracycline					
Yes	31	15.3	12.2-18.4	0.879	
No	73	17.0	8.5-25.5		
Paclitaxel					
Yes	46	15.3	13.3-17.3	0.359	
No	58	16.1	11.1-21.0		
Platinum					
Yes	32	16.3	11.7-20.9	0.171	
No	72	15.9	12.5-19.3		
Target therapy					
Yes	5	21.2	4.2-38.2	0.897	
No	99	15.9	13.2-18.6		
Endocrine therapy					
Yes	25	23.4	16.7-30.1	0.025	0.001
No	79	14.5	11.5-17.5		
Surgery					
Yes	3	7.3	1.7-12.9	0.018	0.002
No	101	16.1	12.7-19.5		

HM, hepatic metastasis

16.0 months (0.5-119.7 months, 95% CI: 12.9-18.9 months), 1-year survival was 63.5%, 2-year survival was 31.7%, 3-year survival was 15.6%, 4-year survival was 10.8%, and 5-year survival was 5.4% (Figure 1). Survival after hepatic metastases between luminal A and other subtypes was not significantly different (P=0.154) (Figure 2). Overall survival among different subtypes was significantly different (P=0.026), however survival after hepatic metastases was also not significantly different

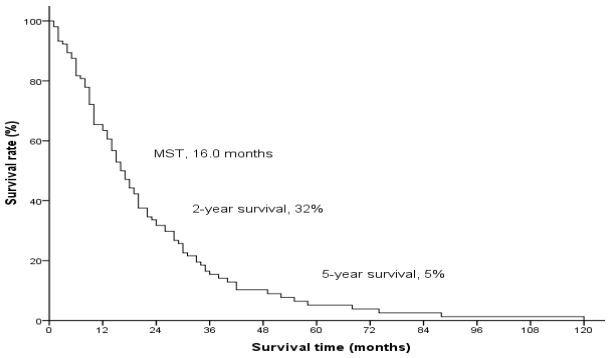

Figure 1. Survival for All Patients of Hepatic Metastases from Breast Cancer

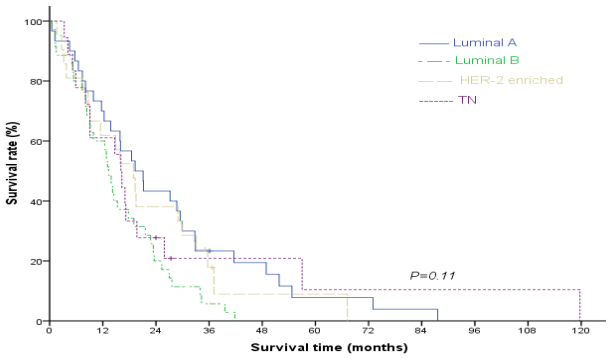

Figure 2. Survival for Patients with Different Subtypes of Breast Cancer

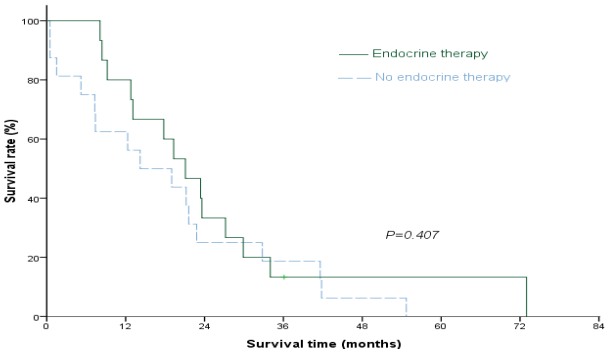

Figure 3. Survival for Patients of Luminal Subtypes of Breast Cancer with Hepatic Metastases Previously Treated with Endocrine Therapy

(P=0.110) (Table 1).

Univariate analysis

Univariate analysis for survival after hepatic metastases showed the following parameters as significant prognostic factors: hepatic metastases diagnosis period, presence of endocrine therapy, and surgery. In addition, treatment with surgery after hepatic metastatic diagnosis was also associated with poor survival. Nevertheless, patients had a favorable survival if treatment with endocrine therapy after hepatic metastasis (Table 2).

Multivariate analysis

Multivariate analysis was performed including 2 years-interval from initial diagnosis to hepatic metastasis, treatment with endocrine therapy, and surgery. Hepatic metastatic diagnosis interval>2 years and treatment without endocrine therapy, and the presence of surgery were carried out to be unfavorable independent prognostic

Table 3. Prognostic Analysis of Clinical Characteristics and Treatment in Luminal Subtypes of Breast Cancer with Hepatic Metastasis in 65 Patients

Prognostic factor	Patient No.	Median survival (months)	95% CI	P Univariate
Age (years)				
>35	51	15.9	10.7-21.1	0.589
≤35	14	9.9	0.7-19.1	
Menstrual status				
premenopausal	30	16.0	8.6-23.4	0.854
postmenopausal	35	14.2	10.0-18.4	
Stage				
I-II	28	18.5	9.6-27.4	0.571
III	37	13.8	10.8-16.8	
HM after initial diagnosis				
>1 year	42	13.1	4.7-21.5	0.538
≤1 year	23	16.0	6.9-25.1	
HM after initial diagnosis				
>2 years	23	12.3	4.9-19.7	0.070
≤2 years	42	16.0	9.0-23.0	
Number of HM sites				
Isolated	13	15.9	6.6-25.2	0.921
Multiple	52	14.5	9.0-20.0	
Endocrine therapy(first line)				
Yes	31	19.3	11.7-26.9	0.548
No	34	13.8	10.8-16.8	
Chemotherapy				
Yes	54	14.2	11.1-17.3	0.544
No	11	27.0	4.9-49.1	
Anthracycline				
Yes	15	15.9	1.8-30.0	0.711
No	50	14.5	9.9-19.1	
Paclitaxel				
Yes	31	15.3	6.6-24.0	0.674
No	34	14.2	7.8-20.6	
Platinum				
Yes	19	13.3	10.3-16.3	0.944
No	46	15.9	10.3-21.6	
Endocrine therapy				
Yes	19	23.4	17.3-29.5	0.011
No	46	13.8	11.4-16.2	
Surgery				
Yes	2	7.3	None	0.142
No	63	15.9	10.8-21.0	

HM, hepatic metastasis

factors to predict survival after hepatic metastasis (Table 2).

Survival analysis of luminal subtype patients

Endocrine therapy was a significant treatment to hormonal receptor positive patients. In this study, we analyzed more particularly the survival and prognostic factors of luminal A and luminal B subtypes. Endocrine therapy was a favorable prognostic factor for luminal subtype patients with hepatic metastases (Table 3).

Of 65 luminal subtype patients, 31 had received endocrine therapy after initial diagnosis of breast cancer (Figure 3). When analyses were performed between patients, who received adjuvant endocrine therapy after hepatic metastases diagnosis, and patients, who did not received endocrine therapy, the results showed endocrine therapy was not a significantly favorable prognostic factor for luminal subtype patients, who initial treated with endocrine therapy (Table 4).

Table 4. Prognostic Analysis of Clinical Characteristics and Treatment in Patients with Hepatic Metastases of Luminal Subtypes with Previously used Adjuvant Endocrine Therapy

Prognostic factor	Patient No.	Median survival (months)	95% CI	P Univariate	P Multivariate
Age (years)					
>35	23	21.2	17.6-24.8	0.665	
≤35	8	9.2	1.2-17.2		
Menstrual status					
premenopausal	15	17.8	4.2-31.4	0.771	
postmenopausal	16	19.3	15.2-23.4		
Stage					
I-II	14	21.2	20.3-22.1	0.377	
III	17	13.1	5.7-20.5		
HM after initial diagnosis					
>1 year	26	19.3	14.6-24.0	0.417	
≤1 year	5	8.1	1.9-14.3		
HM after initial diagnosis					
>2 years	13	19.3	11.1-27.5	0.844	
≤2 years	18	17.8	1.2-34.4		
Number of HM sites					
Isolated	7	19.0	15.9-22.1	0.534	
Multiple	24	19.3	9.6-29.0		
Chemotherapy					
Yes	28	17.8	9.8-25.8	0.113	
No	3	41.6	None		
Anthracycline					
Yes	6	21.1	0.0-44.0	0.867	
No	25	19.0	10.7-27.3		
Paclitaxel					
Yes	16	21.1	5.2-37.0	0.742	
No	15	19.0	12.6-25.4		
Platinum					
Yes	10	17.8	4.6-31.0	0.494	
No	21	19.3	9.0-29.6		
Endocrine therapy					
Yes	11	21.1	14.0-28.2	0.407	
No	20	14.2	1.1-27.3		
Surgery					
Yes	2	7.3	None	0.084	
No	29	21.1	17.2-25.0		

HM, hepatic metastasis

Discussion

Breast cancers could be classified by using complementary DNA microarrays and hierarchical clustering techniques into five molecular subtypes: luminal A, luminal B, HER2-enriched, basal-like, and normal breast-like (Perou et al., 2000; Sorlie et al., 2001; Sorlie et al., 2003; Fan et al., 2006; Hu et al., 2006). Because of the different clinical outcomes of subtypes of breast cancers, numerous studies had analyzed the association between breast cancer subtypes and prognosis (Sorlie et al., 2001; Sorlie et al., 2003; Hu et al., 2006). Owing to limited fresh specimens and slashing technique, complementary DNA microarrays could not been used in normal clinical medicine. In this study, we used a gene expression profile-validated immunohistochemical surrogate panel to distinct subtypes of breast cancers. Previous study has reported that HER2-enriched subtype

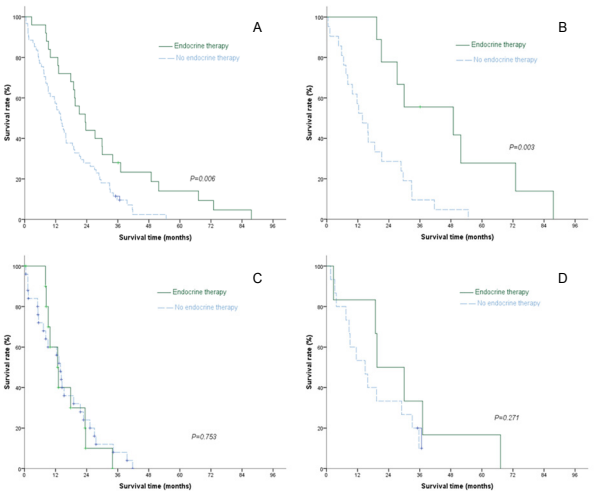

Figure 4. Survival from the Time of Diagnosis of Hepatic Metastases for Patients of Different Subtypes of Breast Cancer Treated with Endocrine Therapy after Diagnosis of Hepatic Metastases. A: all patients; B: Luminal A subtype; C: Luminal B subtype; D: HER2-enriched subtype

tumors vigorously spread to the liver, while TN subtypes transfer to the brain and lung (Harrell et al., 2012). TN subtype has been reported previously with poor outcomes (Sorlie et al., 2001; Sorlie et al., 2003). In our study, HER2-enriched subtype patients have a better survival time than TN subtype. It may due to the resistance to systemic therapy and/or biological characteristics of the TN subtype breast cancers.

In this study, hepatic metastases from breast cancer had a median survival time of 16.0 months which is similar to the results quoted by Wyld et al. (Zinser et al., 1987; Wyld et al., 2003) and better than the findings of other studies (Patanaphan et al., 1988; O'Reilly et al., 1990; Hoe et al., 1991). On multivariate analysis in this study, hepatic metastatic interval after initial diagnosis, treatment with surgery, and endocrine therapy, which for hepatic metastases, were the independent prognostic factors for hepatic metastases breast cancer. In our study, patients with hepatic metastatic interval after initial diagnosis greater than 2 years had significantly lower survival time. It may explain that patients had a higher rate of other sites of metastases in the initial two years. Surgery for hepatic metastasis appears to be an unfavorable independent prognostic factor. Less cases and cross-sectional study may explain this bias. In our study, patients treated with chemotherapy had a median survival time of 15.9 months after hepatic metastasis. We found chemotherapy was not an independent prognostic factor which was similar to the results of previous studies.

Endocrine therapy was of limited use to patients with hepatic metastases from breast cancers at initial diagnosis. In the present study, endocrine therapy was an independent predictor of survival for hepatic metastases patients. Those patients receiving endocrine therapy had a relatively good overall prognosis, with responders surviving for a median of 23.4 months. This was better than the outcome of previous study (Wyld et al., 2003). Interestingly, we found that endocrine therapy could improve the survival time of luminal subtype patients regardless of endocrine therapy to give patients at initial diagnosis of breast cancer whether or not. Generally, chemotherapy, surgery, and interventional therapy were the major treatments for patients with hepatic metastases. Endocrine therapy commonly was given to patients with higher sensitivity to treatment and better general health. However, non-endocrine-therapy-treated patients with lower sensitivity to major treatment frequently had a lower survival rate. Consequently, endocrine therapy might not use to treat patients with a short survival interval after hepatic metastases. Otherwise, small sample with 19 cases in our study might be a bias influencing the outcomes of statistics. Furthermore, we detected the effect of endocrine therapy on Luminal A, Luminal B, and HER2-enriched subtypes. Because of none triple negative group of patients receiving endocrine therapy, we could not explore endocrine therapy was a prognostic factor for TN subtype patients or not. Luminal A group of patients treated with endocrine therapy did significantly better than patients treated without endocrine therapy (median survival of 48.9 vs. 13.8 months, P=0.003, Figure 4B). Unfortunately, there were not significantly differences of Luminal B group (P=0.753) and HER2-enriched group (P=0.271). However, we found a good tendency of survival time of HER2-enriched group of patients treated with endocrine therapy (Figure 4D). One explanation to this observation might be the genetically and biologically heterogeneous between primary tumor of breast cancer and hepatic metastatic site from breast cancer. It would expect prospective study with large samples to validate the relation of HER2-enriched breast cancer with hepatic metastasis and endocrine therapy.

The clinico-pathologic characteristics of the primary tumor of patients with hepatic metastasis had no influence on the outcome for patients. In our study, age was not an independent prognostic factor. However, age smaller than 35 years had a tendency of short survival time after hepatic metastases. It may due that tumors of younger patients were commonly associated with a high propensity of proliferation, intravasation, and angiogenesis and young age at diagnosis was relative poor survival from diagnosis.

In conclusion, We demonstrated that breast cancer patients with hepatic metastases have a poor prognosis. It is presently shown that hepatic metastatic interval after initial diagnosis, treatment with surgery, and endocrine therapy for patients of hepatic metastases are the most relevant prognostic factors for predicting survival time initial hepatic metastases. Endocrine therapy can improve the survival time and appear to be a reasonable treatment for patients with hepatic metastases from breast cancer. As our study is limited by its small samples and retrospective trial, future clinical study with large samples and a prospective design are expected to validate the hypothesis and findings.

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