

# Does Liver Resection Provide Long-Term Survival Benefits for Breast Cancer Patients with Liver Metastasis? A Single Hospital Experience

Jee Ye Kim,<sup>1</sup> Joon Seong Park,<sup>1</sup> Seung Ah Lee,<sup>2</sup> Jae Keun Kim,<sup>1</sup>  
Joon Jeong,<sup>3</sup> Dong Sup Yoon,<sup>1</sup> and Hy-De Lee<sup>3</sup>

<sup>1</sup>Pancreaticobiliary Cancer Clinic, <sup>2</sup>Breast Cancer Clinic, Department of Surgery,  
Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;

<sup>3</sup>Department of Surgery, Eulji General Hospital, Eulji University College of Medicine, Seoul, Korea.

Received: June 28, 2013

Revised: October 4, 2013

Accepted: October 7, 2013

Corresponding author: Dr. Dong Sup Yoon,  
Department of Surgery,  
Gangnam Severance Hospital,  
Yonsei University College of Medicine,  
211 Eonju-ro, Gangnam-gu,  
Seoul 135-720, Korea.  
Tel: 82-2-2019-2444, Fax: 82-2-3462-5994  
E-mail: yds6110@yuhs.ac

The authors have no financial conflicts of interest.

**Purpose:** Liver resection with colorectal liver metastasis widely accepted and has been considered safe and effective therapeutic option. However, the role of liver resection in breast cancer with liver metastasis is still controversial. Therefore, we reviewed the outcome of liver resection in breast cancer patients with liver metastases in a single hospital experiences. **Materials and Methods:** Between January 1991 and December 2006, 2176 patients underwent breast cancer surgery in Gangnam Severance Hospital. Among these patients, 110 cases of liver metastases were observed during follow-up and 13 of these patients received liver resection with potential feasibility to achieve an R0 resection. **Results:** The median time interval between initial breast cancer and detection of liver metastasis was 62.5 months (range, 13-121 months). The 1-year and 3-year overall survival rates of the 13 patients with liver resection were 83.1% and 49.2%, respectively. The 1-year and 3-year overall survival rates of patients without extrahepatic metastasis were 83.3% and 66.7% and those of patients with extrahepatic metastasis were 80.0% and 0.0%, respectively ( $p=0.001$ ). **Conclusion:** Liver resection for metastatic breast cancer results in improved patient survival, particularly in patients with solitary liver metastasis and good general condition.

**Key Words:** Breast cancer, liver metastasis, liver resection, prognosis

## INTRODUCTION

Because many doctors consider liver metastasis from malignant cancer as a systemic recurrence rather than a local recurrence, their therapeutic aim is only to improve the quality of life using conservative management. However, liver resection in patients with colorectal liver metastasis has now become widely accepted and has been shown to be a safe and effective therapeutic option in several reports.<sup>1,2</sup> In contrast to metastasis from colorectal cancer, non-colorectal liver metastasis is only considered for surgical resection in selected cases.

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According to the Korea Cancer Center Registry, the rate of breast cancer is rapidly increasing and it ranks sixth in overall cancer incidence and second form of cancer among females in Korea.<sup>3</sup> The prognosis of breast cancer has greatly improved as new medical imaging technologies and various chemotherapeutic drugs have been developed. However, liver metastases occur in 15% of breast cancer patients and these patients have a poor prognosis with an average survival period of less than 24 months, even if they receive aggressive systemic and hormone therapy.<sup>4-6</sup>

Recently, liver resection-related mortality rates have largely declined due to improved anesthesia, progression of surgical techniques, and improvements in postoperative managements. In addition, improved chemotherapy agents may reduce the number or size of liver metastases, resulting in favorable conditions before and after surgery.

Some papers has reported that liver resection shows a tendency to improve prognosis in selected patients.<sup>7-10</sup> However, the role of liver resection in breast cancer with liver metastasis is still debatable. Therefore, we reviewed the outcome of patients with breast cancer with liver metastases after liver resection in a single hospital experiences.

## MATERIALS AND METHODS

### Patients

Between January 1991 and December 2006, 2176 patients underwent breast cancer surgery in Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Among these patients, 110 cases of liver metastasis were observed during follow-up. Of these, 13 patients received liver resection with potential feasibility to achieve an R0 resection. The patients were followed closely until December 30, 2011.

Ambulatory follow-up examinations of all patients were performed every 6 months for 5 years after the surgery and follow-up observation was performed every year subsequently. The following basic examinations were performed every 6 months after surgery: physical examination, radiological examination (chest X-ray, ultrasound, and mammography), and laboratory testing (general blood test, liver function test, and tumor marker test). Abdomen and chest computed tomography, bone scan and PET were routinely performed in all patients to check for systemic metastasis.

### Statistical analysis

All statistical analyses were performed using SPSS soft-

ware, Version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the  $\chi^2$  or Fisher's exact test, and continuous variables were analyzed using either a Student's t-test or Mann-Whitney U rank tests. A *p*-value less than 0.05 was considered statistically significant. Survival curves were constructed and compared by the Kaplan-Meier method and the log-rank test, respectively.

## RESULTS

### Patient characteristics

During the study period, a total of 110 patients were diagnosed with breast cancer with liver metastasis: 91 patients (83%) with multi-organ metastasis, including the liver, and 19 (17%) patients with isolated liver metastasis. Among the 110 patients with liver metastasis, 13 received liver resection with potential feasibility to achieve an R0 resection. The mean age of the 13 patients was 51.0±9.4 years (range 39-64 years) and were all female.

All 13 patients underwent surgery for breast cancer involving either conservative breast surgery or radical mastectomy. The pathology of breast cancer was infiltrating ductal carcinoma in 12 patients (92.3%) and mucinous carcinoma in one patient (7.7%). The histological grade classification of breast cancer was well differentiated in seven patients (53.8%), moderately differentiated in three patients (23.1%), and poorly differentiated in three patients (23.1%). The T stage of breast cancer was T1 in four patients (30.8%), T2 in seven patients (53.8%), T3 in one patient (7.7%), and T4 in one patient (7.7%). The initial N stage of breast cancer was N0 in five patients (38.5%), N1 in two patients (15.3%), N2 in five patients (38.5%), and N3 in one patient (7.7%). The hormone receptor and HER2 status of the breast cancer was available for all patients. Six patients had estrogen (ER) and progesterone (PR) positive tumors, one was ER+/PR-, one was ER-/PR+ and five were ER-/PR-. Five patients were HER2-positive (38.5%). All patients received adjuvant therapy after surgery for breast cancer depending on their hormone receptor status and the stage.

Patients were divided into two groups; solitary liver metastasis and multi-organ metastasis including liver. Single liver metastasis was observed in seven (53.8%) patients, and multi-organ metastasis was detected in six (46.2%) patients. Clinicopathological characteristics of patients in the two groups are listed in Table 1 and 2. The median time interval between initial breast cancer and detection of liver metastasis

**Table 1. Clinical Characteristics of the Seven Patients Treated for Solitary Liver Metastasis from Breast Cancer**

Case	Sex	Age (yrs)	Status of breast cancer					Status of liver metastasis		Postoperative chemotherapy	Survival (months)
			Pathology	HG	TNM	HR (ER/PR)	HER2	Site	Type of liver resection		
1	F	44	IDC	Mod	T2N2M0	-/-	-	S4	Wedge resection	Yes	39.3
2	F	39	IDC	Well	T1N0M0	+/+	-	S4, 7, 8	Wedge resection+RFA	Yes	54.4
3	F	62	IDC	Well	T1N0M0	+/+	-	S6	Wedge resection	Yes	50.2
4	F	61	Mucinous cancer	Well	T2N0M0	+/-	+	S2, 3	Lateral sectionectomy	Yes	15.6
5	F	60	IDC	Well	T2N2M0	-/-	-	S3	Wedge resection	Yes	17.6
6	F	49	IDC	Poor	T4N2M0	+/+	-	S5	Wedge resection	Yes	15.2
7	F	39	IDC	Poor	T1N0M0	-/+	-	S3	Lateral sectinectomy	Yes	57.9

IDC, infiltrating ductal carcinoma; HG, histologic grade; HR, hormone receptor; RFA, radiofrequency ablation; ER, estrogen; PR, progesterone.

**Table 2. Clinical Characteristics of the Six Patients Treated for Extrahepatic and Liver Metastasis from Breast Cancer**

Case	Sex	Age (yrs)	Status of breast cancer					Extrahepatic metastasis	Status of liver metastasis		Postoperative chemotherapy	Survival (months)
			Pathology	HG	TNM	HR (ER/PR)	HER2		Site	Type of liver resection		
1	F	46	IDC	Mod	T2N2M0	-/-	+	Neck node	S4, 5	Wedge resection	Yes	13.1
2	F	45	IDC	Well	T3N3M0	+/+	-	Ovary	S2, 4, 7, 8	Wedge resection	Yes	12.5
3	F	41	IDC	Moderate	T2N2M0	+/+	+	Bone	S6, 7	Right posterior sectionectomy	Yes	25.0
4	F	54	IDC	Well	T2N1M0	-/-	+	Brain	S4	Wedge resection	Yes	7.1
5	F	64	IDC	Well	T2N2M0	+/+	-	Bone	S3, 7, 8	Lateral sectionectomy +RFA	Yes	11.8
6	F	60	IDC	Poor	T1N0M0	-/-	+	Neck node	S5	Lateral sectionectomy	Yes	7.6

IDC, infiltrating ductal carcinoma; HG, histologic grade; HR, hormone receptor; RFA, radiofrequency ablation; ER, estrogen; PR, progesterone.

sis excluding two patients with synchronous metastasis was 62.5 months (range, 13-121 months).

Among patients with multi-organ metastasis, two (33.3%) had bone metastasis, two (33.3%) had metastasis in neck nodes, one (16.7%) had brain metastasis, and one (16.7%) had ovarian metastasis.

### Liver resection

All patients received adjuvant therapy after surgery for breast cancer depending on their hormone receptor status and tumor stage. Two patients had synchronous metastases–liver metastases at the time of the initial breast cancer diagnosis–and after six cycles of neo-adjuvant therapy, the breast cancer and metastatic liver lesions were both operated upon.

Nine patients (69.2%) received an open liver resection and four patients (30.8%) received laparoscopic liver resection. Major liver resection (three segments or more) was performed in one (7.7%) patient, minor resection (fewer than three segments) in four (30.8%) patients, and wedge resection in eight (61.5%) patients. Liver resection was combined with radiofrequency ablation in two pa-

tients.

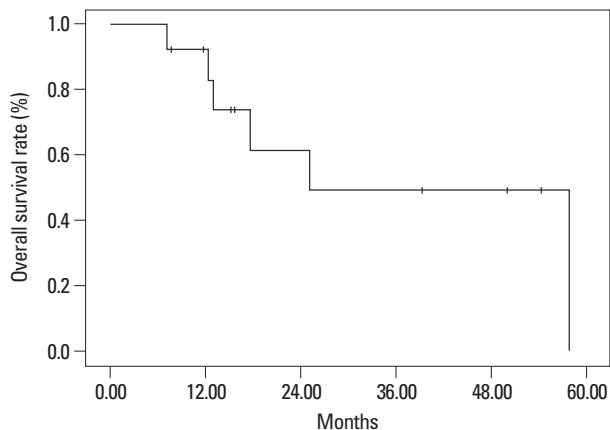
All patients with extrahepatic metastatic disease were treated with curative intent for their extrahepatic metastatic lesions.

All patients received postoperative adjuvant chemotherapy after liver resection.

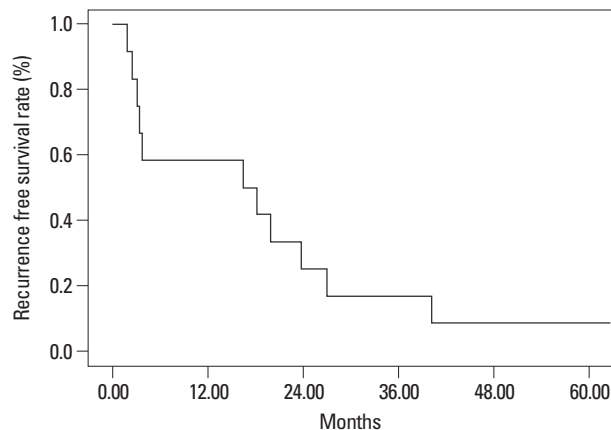
### Surgical outcomes

The 1-year and 3-year overall survival rates of the 13 patients with liver resection were 83.1% and 49.2%, respectively (Fig. 1). The 1-year and 3-year overall survival rates of patients without extrahepatic metastasis were 83.3% and 66.7% and those of patients with extrahepatic metastasis were 80.0% and 0.0%, respectively ( $p=0.001$ ) (Fig. 2).

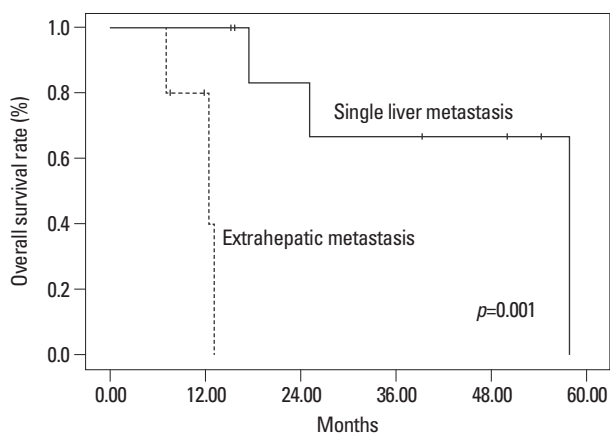
The 1-year and 3-year recurrence free survival rates after liver resection of the 13 patients were 50.0% and 16.7%, respectively (Fig. 3). The 1-year and 3-year recurrence free survival rate after liver resection of patients without extrahepatic metastasis were 83.3% and 33.3% and those patients with extrahepatic metastasis were 33.3% and 0.0%, respectively ( $p=0.023$ ) (Fig. 4).



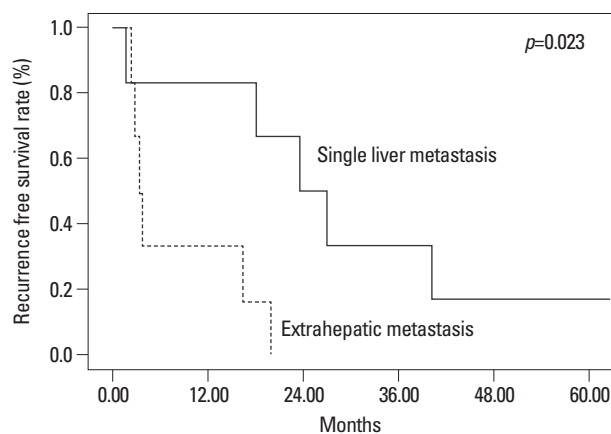
**Fig. 1.** Overall survival rate after hepatic resection for breast cancer patients with liver metastasis.



**Fig. 3.** Recurrence free survival rate after hepatic resection for breast cancer patients with liver metastasis.



**Fig. 2.** Overall survival rate following hepatic resection according to status of extrahepatic metastasis.



**Fig. 4.** Recurrence free survival rates following hepatic resection according to status of extrahepatic metastasis.

## DISCUSSION

Recurrence rates after breast cancer surgery are 30-40%, and mainly involve bone metastases. After bone and lung metastases, liver metastases represent 40% of total breast cancer recurrence;<sup>11</sup> bone metastasis was also the most frequent in this study and liver metastasis ranked third in total recurrences.

Nonetheless, many doctors consider liver metastasis from breast cancer as systemic recurrence. Therefore, their aim is only to improve the quality of the patient's life using alleviation therapy rather than improving survival rates. Recently, patients with liver metastasis from breast cancer have shown improved survival rates due to improvements in anticancer drugs.<sup>12-14</sup> However, these are not satisfactory long-term survival rates and the average overall survival time is reported to be only 15 months.<sup>15</sup>

As surgical techniques for liver resection have improved

and postoperative morbidity and mortality rates have decreased after operation, attempts of liver resection from breast cancer started in the 1980s. Elias, et al.<sup>7</sup> first reported that liver resection in patients with metastatic breast cancer could lengthen patient survival compared with conservative management. Nevertheless, the role of surgical treatment for liver metastasis from breast cancer has not yet been clearly defined.

Many studies have reported that median survival for liver resection in breast cancer ranges between 24 and 60 months and 5-year survival rates are between 21% and 60%.<sup>16-19</sup> In the present study, the average median survival was 57.9 months, and the 3-year survival rate was 59.3%. This represents an improved overall survival rate compared with patients that received systemic chemotherapy treatment.<sup>20-22</sup>

Some reports showed that age, estrogen and HER2 receptor status of the primary tumor, number of metastasis, and resection margins are significant prognostic factors.<sup>9,10,17-19,23</sup> However, we could not analyze the prognostic factors after

liver resection because of the small number of patients in our study.

In this study, the surgical indication of liver metastasis was restricted to cases where an extrahepatic lesion could be controlled by local treatment and no other distant metastases were present. Nonetheless, we demonstrated that the presence of extrahepatic metastasis lesions was a significant prognostic factor after liver resection. In our results, after liver resection of patients with extrahepatic metastasis, the 1- and 3-year survival rates were 60.0% and 20.0%, respectively. Therefore, even when extrahepatic metastasis is present, if the systemic condition of the patient is satisfactory and if cure of the extrahepatic lesion is possible, we think that surgical treatment of the liver lesions should be considered.

It is possible that the treatment outcome of patients with liver metastasis may have been overestimated in this study because it is a retrospective study with a limited number of cases. Nonetheless, although this study contains a small number of patients and has limitations, it suggests that surgery in patients with solitary liver metastasis results in a promising good prognosis.

In conclusion, liver resection for metastatic breast cancer results in improved patient survival, particularly in patients with solitary liver metastasis and good general condition.

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