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• *BRIEF REPORTS* •

Treatment for liver metastases from breast cancer: Results and prognostic factors

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Abstract

AIM: Liver metastases from breast cancer (BCLM) are associated with poor prognosis. Cytotoxic chemotherapy can result in regression of tumor lesions and a decrease in symptoms. Available data, in the literature, also suggest a subgroup of patients may benefit from surgery, but few talked about transcatheter arterial chemoembolization (TACE). We report the results of TACE and systemic chemotherapy for patients with liver metastases from breast cancer and evaluate the prognostic factors.

METHODS: Forty-eight patients with liver metastases, from proved breast primary cancer were treated with TACE or systemic chemotherapy between January 1995 and December 2000. Treatment results were assessed according to WHO criteria, along with analysis of prognostic factors for survival using Cox regression model.

RESULTS: The median follow-up was 28 mo (1-72 mo). Response rates were calculated for the TACE group and chemotherapy group, being 35.7% and 7.1%, respectively. The difference was significant. The one-, two- and three-year Survival rates for the TACE group were 63.04%, 30.35%, and 13.01%, and those for the systemic chemotherapy group were 33.88%, 11.29%, and 0%. According to univariate analysis, variables significantly associated with survival were the lymph node status of the primary cancer, the clinical stage of liver metastases, the Child-Pugh grade, loss of weight. Other factors such as age, the intervals between the primary to the metastases, the maximal diameter of the liver metastases, the number of liver metastases, extrahepatic metastasis showed no prognostic significances. These factors mentioned above such as the lymph node status of the primary cancer, the clinical stage of liver metastases, the Child-Pugh grade, loss of weight were also independent factors in multivariate analysis.

CONCLUSION: TACE treatment of liver metastases from breast cancer may prolong survival in certain patients. This approach offers new promise for the curative treatment of the patients with metastatic breast cancer.

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Key words: Liver neoplasms; Secondary; Breast cancer; Transarterial chemoembolization; Chemotherapy; Prognosis

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INTRODUCTION

Breast carcinoma is the most common malignancy-affecting women in the US and China, and it is the most common cause of cancer mortality in their population[1]. Approximately 50% of all women diagnosed with breast carcinoma develop metastatic disease and for these patients, the average survival-time from the time of diagnosis of metastatic breast carcinoma ranges from approximately 18-30 mo. Liver metastases developed in approximately half of all women with metastatic breast cancer and are typically associated with poor outcome[2]. In these circumstances, the primary goal of therapy is palliation and treatment usually involve chemotherapeutic agents or TACE (transarterial chemoembolization), but the management remains controversial[3]. Some groups had used aggressive approaches including liver resection and achieved good results, but the patients are highly selective and the patients who can receive surgery are rare[4-8]. Metastatic breast cancer, even if it appears to be limited to a single organ, is generally considered to be a disseminated disease that requires systemic, rather than local therapy[9]. Nevertheless, a substantial number of patients have irresectable disease confined to the liver and this has led to the most widespread use of local TACE treatment. Regional TACE treatment for liver tumors has several theoretic advantages[3,10-12].

TACE has been developed as a palliative treatment for unresectable liver tumors, because anatomic studies in a variety of animal species including humans have demonstrated that hepatic tumors derive most of their blood supply from the hepatic artery as opposed to the portal vein. In chemoembolization, embolization of the hepatic artery reduces the blood flow, creates ischemia, and increases local concentrations of a chemotherapeutic agent, allows prolonged drug exposure to the tumor cells and thus potentially increase the cell-kill fraction. Subsegmental chemoembolization enhances the local effect on the neoplasms while it minimizes further

damage to the surrounding liver tissue. Extensive clinical experience with TACE of hepatic tumors has been reported since it was described in 1964[13,14].

TACE is used in a variety of clinical settings today and has been reported to be effective in prolonging survival for patients with liver metastases. However, these results have not been confirmed in liver metastases from breast cancer. We hypothesized that TACE, used as a palliative treatment, might improve the survival of patients with hepatic metastases from breast cancer. In this article, we reviewed our experience with 28 patients who received TACE and discuss the survival benefit of this procedures.

MATERIALS AND METHODS

Data for this study were retrieved from the Cancer Hospital, Fudan University. The survey involved 48 patients from January 1995 to December 2000. In 2003, all the clinical records of these patients were retrospectively examined. The mean age at the time of diagnosis of breast cancer was 54.07±12.6 years. All patients underwent radical mastectomy or modified radical mastectomy after the initial diagnosis. Most patients received 3-6 cycles of postoperative chemotherapy and 19 patients received radiotherapy. Estrogen receptor assay was positive in 29.2% of cases (n = 14), HER-2/neu assay was positive in 10.4% of cases (n = 5), and the receptor status was unknown in 15 cases. At diagnosis there was one radiographic evidence of liver metastasis on computerized tomography. In nine patients, liver metastases were diagnosed at 1 year intervals after the initial diagnosis were resected, 22 patients at 2-3 year intervals and 16 patients were diagnosed exceeding 3 years interval. Diagnosis of liver metastasis was made by the ultrasound-guided transcutaneously fine-needle aspiration and subsequent cytological examination in 42 cases and for the other cases, the diagnosis was made by a combining consideration of the history, physical examinations, tumor mark levels and noninvasive imaging procedures. The BCLM was solitary in 5 cases (10.4%), two lesions were present in 10 cases (20.8%), three lesions were present in 12 cases (25%) and more than three lesions were present in 21 cases (43.8%). These BCLM were solitary and isolated in 29 of cases (60.4%) and associated with a second metastatic site in 19 of cases (39.6%), essentially bone metastases, which were always controlled. The mean diameter of the largest BCLM for each patient was 2.84±2.47 cm (range: 1-8 cm). The BCLM were situated in the left lobe of the liver in 10 cases (20.8%), in both lobes in 29 cases (60.4%) and in the right lobe in 9 cases (18.8%).

As treatment for liver metastases, 28 patients received transcatheter arterial chemoembolization (TACE), 20 received chemotherapy. TACE was performed with infusion of Fludrouracil or 5-FUDR (1.0 g), cisplatin (40-60 mg), followed by chemoembolization with a mixture of iodized oil and doxorubicin (40-60 mg), or with gelatin-sponge particles for the embolization. Most systemic chemotherapy were administered on an anthracycline based scheme. Nine patients received cyclophosphamide 500 mg/m^2 as 1-h infusion combined with epirubicin 60 mg/m^2 and 5-FU 500 mg/m^2, six patients were treated with navelbine 25 mg/m^2 on the 1st day and then on the 8 th day at the same dosage, epirubicin lowered to 50 mg/m^2, five patients received Taxotere 80 mg/m^2 and DDP 40 mg/m^2. Treatment was held on wk 4, if the absolute neutrophil count was 2 000 or more or the platelet count was less than 100 000. Treatment was given for a minimum of 3 cycles. Patients, with complete response, were treated for 4 cycles past the response. Patients with a partial response or stable disease (SD) were treated with 2-4 cycles past the response. Additional treatment given was at the physician's discretion.

Effects of the treatments were evaluated based on serial CT scans 4-6 wk following completion of the therapies and then every 1 to 3 mo. The complete disappearance of the tumor was regarded as complete remission (CR), a decrease over 50% in tumor size as partial remission (PR), the decrease of less than 50% or no change as SD, and progression as progressive disease (PD). Response rate was calculated for CR or PR and the SD cases were considered non-responsive. Survival was estimated from the starting date of diagnosis of liver metastases according to the Kaplan-Meier method.

After the procedures as described above, the outcome of patients was investigated by visiting patient's families or over telephone. Follow-up was carried out for all subjects regularly for more than 6 mo, with the median follow-up period being 28 mo. The follow-up program included measurement of serum tumor mark and ultrasonography or CT scan for every 3 mo. Patients with recurrence were managed with various therapeutic method including TACE, chemotherapy and/or biotherapy.

Statistical analysis

The data collected are presented as mean±SD. Continuous laboratory values were clustered to obtain two samples of approximately equal size. Statistical comparison between groups was performed using the χ^2 test with the Yates' correction for nominal data, and the Student's t test for numerical data. Kaplan-Meier survival plots were built to evaluate the prognostic values of individual indices and compared using the log rank test. The same method was used for univariate analysis of survival. The univariate analysis was also carried out with age, etiology and liver function parameters measured at the beginning of the observation to establish their predictive value for survival. Baseline variables included in the univariate analysis were also analyzed by multivariate analysis using the step-wise forward Cox regression model to assess their predictive value with respect to survival. To check proportionality of risk factors with time, we have plotted the log of cumulative hazards against time, demonstrating parallel behaviors in the two groups of patients separately with low- and high-risk values of selected prognostic covariates. All statistical analyses were computerized using the soft package SPSS 10.0 (SPSS Inc., Chicago, IL). P<0.05 was considered statistically significant.

RESULTS

Various patient characteristics are summarized in Table 1. There were no significant differences between the two groups regarding age, the type of primary breast cancer, the intervals between the primary sites to the metastases, symptoms, carcinoembryogenic antigen (CEA), lactic dehydrogenase

Table 1 Basic clinical data between the two groups

Factors	A group	B group	*P*
Age (yr)	53.13±9.23	55.65±12.32	0.412
The type of primary breast cancer infiltrating ductal carcinoma/simple carcinoma/adenocarcinoma	26/0/2	18/2/0	0.120
Method of treatment for primary tumor surgery/postoperative radiotherapy/postoperative chemotherapy	28/10/27	20/9/20	0.911
Interval time between the primary tumor and metastasis (mo)	31.21±24.56	27.23±22.97	0.110
Number of liver metastasis single/multi	9/19	5/15	0.591
Stage of liver metastasis			
I/II/III/IV	10/10/6/2	10/6/3/1	0.794

Criteria of liver metastasis staging see Gennari's staging system[15]. A group: TACE group; B group: systemic chemotherapy group.

(LDH), alkaline phosphatase, the number of liver metastases, the stage of liver metastases.

Response rates were calculated for the TACE group and chemotherapy group, being 35.7% and 7.1%, respectively. The difference was significant ($P<0.05$; Table 2). The 1-, 2- and 3-year Survival rates for the TACE group were 63.04%, 30.35% and 13.01%, and those for the systemic chemotherapy group were 33.88%, 11.29%, and 0%, Median survival times of these two groups were 28.00±2.77 and 18.00±1.83 mo, respectively. Figure 1 shows the overall cumulative survival after treatment.

Table 2 Comparison of treatment responses between the groups

	A group (n = 28)		B group (n = 20)	
	No of patients	%	No of patients	%
Overall response	10	35.7	2	10
Complete response	2	7.1	0	0
Partial response	8	28.6	2	10
Stable disease	13	46.4	7	35
Progressive disease	5	17.9	11	55

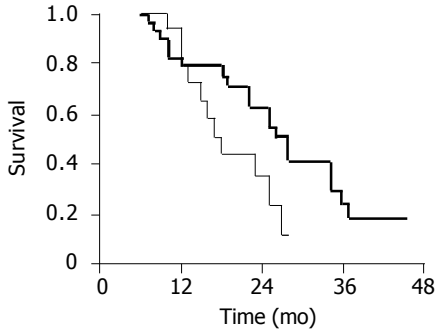

Figure 1 Kaplan-meier survival curves for BCLM patients with TACE (dashed line) and chemotherapy (solid line).

The majority of patients experienced at least 1 adverse events that was considered possibly, or most likely related to treatment. However, the intensity of treatment-related adverse events was mild to moderate in the majority of these patients. The incidence of the adverse events included in this survey are summarized in Table 3. GI side effects (e.g., nausea, emesis, and stomatitis) were the most common treatment-related adverse events. Leukopenia and thrombocytopenia were also seen during the therapies. There was more patients developed myelosuppression in the systemic chemotherapy group, but there was no significant difference between the two groups. The post-embolization syndrome consisted of abdominal pain, fever apparently unrelated to the tumor, and nausea, slight or severe, was seen in almost all patients. Narcotics, anti-emetics and acetaminophen were given to relieve the symptoms. One patient died due to chronical hepatic and renal failure after TACE, one died of hepatic encephalopathy.

Prognostic factors

Univariate analysis for TACE group Significant differences in survival were recognized for the following factors: (1) the lymph node status of the primary cancer: N0 *vs* N1+N2 ($P<0.05$); (2) the clinical stage of liver metastases: I+II stage *vs* III+IV stage ($P<0.01$); (3) the Child-Pugh grade: A grade *vs* B or C grade ($P<0.01$); (4) loss of weight: yes *vs* no ($P<0.01$). Other factors such as age, the intervals between the primary to the metastases, the maximal diameter of the liver metastases, the number of liver metastases, extrahepatic metastasis showed no prognostic significances.

Multivariate analysis Multivariate analysis was performed by using four prognostic factors that were shown to be significant ($P<0.05$; the lymph node status of the primary cancer, the clinical stage of liver metastases, the Child-Pugh grade, loss of weight) and considered to be important ($P<0.1$; intervals between the primary to the metastases) in the univariate analysis. As shown in Table 4, the Child-Pugh grade, the clinical stage of liver metastases, the lymph node status of the primary cancer, loss of weight had prognostic significances in decreasing order. As indicated by the regression coefficient, the following findings were associated with poor prognosis: the poor Child-Pugh grade, the terminal stages of liver metastases, the presence of lymph node metastases of the primary cancer, loss of weight.

DISCUSSION

Breast cancer is generally thought to be more easily metastasis to visceral organs. Zinser *et al*[16], reported that survival in breast cancer patients with liver only metastases (19 mo) or those with liver and bone metastases (17 mo) was longer than that in patients with metastases to other sites(12 mo). The authors, therefore, concluded that the presence of isolated liver metastases may not indicate as poor a prognosis as previously believed.

Systemic polychemotherapeutic regimens are usually considered first for such patients. Systemic treatment of liver metastases with intravenous chemotherapy has been

Table 3 Side effects between the two groups

Side effects	A group		B group	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Leukopenia	3	0	6	3
Hypochromia	3	0	4	1
Thrombocytopenia	2	0	4	1
Reaction of GI system	1	0	3	1
Impairment of liver function	5	0	2	0
Impairment of renal function	0	0	1	0

Table 4 Multivariate analysis of prognostic factors of patients with BCLM

Factors	Gradings	Regression coefficient	Standard error	Chi-square	*P*
Child-Pugh grade	A gradeB or C grade	2.283	0.712	10.683	0.0010
Clinical stage of liver metastases	I+II stageIII+IV stage	-0.452	0.273	9.118	0.0054
Lymph node status of the primary cancer	N0 N1+N2	0.177	0.080	4.548	0.0287
Loss of weight	Yes No	0.435	0.210	4.297	0.0392
Intervals between the primary to the metastases	≤48 mo >48 mo	0.012	0.158	0.024	0.8860

employed extensively when surgery has been rendered inappropriate, either because of extent of the disease or because of the poor condition of the patient[17-19]. The use of 5-fluorouracil-based or anthracycline-based regimens, such as cyclophosphamide, doxorubicin/epirubicin, and 5-FU, as first-line or adjuvant chemotherapy is widespread [20]. Other agents such as the taxanes (e.g., paclitaxel and docetaxel) and vinorelbine have demonstrated considerable activity in the treatment of metastatic breast carcinoma. Taxanes and anthracyclines are used by many physicians as first-line chemotherapy, with response rates ranging from approximately 20 to 40% when used as monotherapy to as high as 80% when used in combination regimens in selected patient populations[17,18,21]. For tumors that overexpress HER-2/neu, trastuzumab has become an increasingly important treatment[22]. Response rates to salvage chemotherapy regimens, once hormonal and first-line chemotherapy have been exhausted, are extremely poor and short-lived. This necessitates the development of new and better treatment strategies. One strategy that may hold promise is high-dose chemotherapy with hematopoietic stem cell support[23]. When high-dose chemotherapy is used for response consol-idation, CR rates ranging from 47% to 80% have been reported with some lasting longer than 24 h. But some authors reported that this didn't influence the long-, term survival of these patients. Although occasional high response rates with such chemotherapy regimens have been reported, the responses have been invariably short-lived, and the outlook has remained bleak. The prognosis of non-responders, who comprise the majority of patients, is much worse. Stehlin *et al*[24], reported that the survival duration of nonresponders was only 3 mo and no patients survived longer than 18 mo.

Adjuvant systemic chemotherapy has succeeded in delaying relapse and prolonging survival in patients with operable breast cancer. On the other hand, chemotherapy for patients with metastatic breast cancer has not succeeded in conferring a long term survival benefit or cure, although a substantially high response rate can sometimes be achieved, its use in treating metastatic disease is usually limited to palliative rather than curative purposes. This complexity underlies the heterogeneous nature of the response to chemotherapy and is a major barrier to improve the outcome of chemotherapy for metastases from breast cancer discovered clinically.

Local therapies have proved valuable in patients with isolated liver metastases from colorectal and other primary tumors, principally because of the tendency of these tumors to metastasize exclusively or primarily to the liver and because liver metastases have a dominant influence on survival in these patients[25]. In the case of colorectal metastatic disease, the liver is the only metastatic site in 20-30% of patients[26]. This hepatic involvement is a life threatening prognostic indicator; therefore, early local or regional treatments, which may improve survival, are viable options. One possible local therapeutic option for unresectable liver metastases is TACE, which is the selective administration of chemotherapy that usually is combined with embolization of the vascular supply to the tumor, and this treatment results in selective ischemic and chemotherapeutic effects on liver metastases. The rationale for TACE is based on the concept that the blood supply to hepatic tumors originates predominantly from the hepatic artery. In contrast, normal liver parenchyma obtains the majority of its blood supply from the portal vein. Therefore, embolization of the hepatic artery can lead to selective necrosis of the liver tumor, while it leaves normal liver parenchyma virtually unaffected. It has been shown that anoxic damage increases vascular permeability and thereby promotes penetration of chemotherapeutic agents into the tumor[3].

It remains to be proved whether the treatment of liver metastases from breast cancer-even if successful-can be result in the same survival benefit. In our surveys, response rates were calculated for the TACE group and chemotherapy group, being 35.7% and 7.1%, respectively. The difference was significant ($P<0.05$). The better results also achieved in TACE group in prolonging the survival time. The 1-, 2- and 3-year survival rates for the TACE group were

63.04%, 30.35%, and 13.01%, and those for the systemic chemotherapy group were 33.88%, 11.29%, and 0%. Patients who underwent TACE lived at least two times longer than those given standard systemic chemotherapy. These data suggest that TACE prolongs the life of at least some patients. But the nine patients in TACE group had single liver metastasis and the liver is the only metastatic site, this may helps to explain the good efficacy achieved in TACE group. We should also note that the inconsistency regimens in chemotherapy group and the lower rates of the new regimens. So the actual benefit of systemic chemotherapy can not be deduced from our series. Lately, we have started to administer chemotherapy by taxotere, and further studies are required to elucidate the efficacy of these chemotherapy regimens.

The real impact on patient- survival is very difficult to evaluate in the absence of randomization. Age, the initial stage of the breast cancer (TNM), histological results, type of treatment, disease-free interval, other associated extrahepatic metastases, number of cycles of chemotherapy or interventional therapy have their prognostic value in terms of survival. Reports about the prognostic factors for BCLM are not rarely, but most focused on the patients who can receive surgery. Pocard *et al*[8], showed that the time to onset of BCLM to be predictive factors, Selzner *et al*[26], also found that patients in whom liver metastases were found more than 1 year after resection of the primary breast cancer had a significantly better outcome than those with early metastatic disease. But our results failed to reach significance, probably because the number of patients in our studies was small or the method of treatment was used. The opinions about the lymph node status at the time of the primary breast cancer resection are still controversial, but our results was affirmative. The presence of symptoms relating to the metastases such as pain or weight loss has correlated with survival in both Cady and Finan's [27,28] studies of untreated liver metastases patients. Finan *et al*, have reported a median survival of 6.2 mo if the patient had weight loss >3 kg *vs* 13.0 mo without weight loss. Indeed, the clinical manifestation of weight loss was an adverse prognostic factors for our surveys. Some factors, especially clinical stages of liver metastases were prognostic in our studies. But our criteria of liver metastasis staging was from Gennari's staging system, which is based on colorectal cancer liver metastases, so the results still need further studies to confirm it. Other factors such as age, the maximal diameter of the liver metastases, the number of liver metastases, extrahepatic metastasis showed no prognostic significances, the reason most likely is the small number of patients.

In order to improve the prognosis of patients with hepatic metastases, early diagnosis is essential. No treatment is available for patients who display specific symptoms and signs, such as hepatomegaly, jaundice and abdominal pain, and their prognosis is extremely poor. The most efficient diagnostic modality is periodic abdominal US, followed by CT scanning and tests for tumor markers, such as CEA and CA153[29]. Metastatic liver tumors from the breast usually show hypoechogenic nodular pattern on US examination[30] and they are relatively easy to detect. After treatment for the primary lesion, patients usually undergo routine US examinations every 6 mo and tumor marker tests every 2 mo, as well as chest roentgenography and bone scintigraphy. When a hepatic metastasis is detected, CT scans, magnetic resonance imaging and sometimes angiography are necessary. We believe that our follow-up regime is sufficiently rigorous to detect liver metastases at an early stage, enabling many candidates suitable for TACE treatment to be selected. We stress that the precise diagnosis is essential for determining the necessity for TACE.

There have been recent reports of improved survival in patients undergoing surgical resection of limited liver metastases from breast cancer. This has given rise to the hypothesis that surgical mass reduction of metastatic tumors such as liver metastases can help to reduce the extent of cancer cells heterogeneity, thus leading to easier disease control and longer patient survival. Elias *et al*[6], and Schneebaum *et al*[25], reported median survival in patients undergoing hepatic resection that were at least three times those in comparable patients treated with standard nonsurgical therapies. Some patients described in these series remain alive and free of disease up to 5 years after resection. However, these reports describe only small patient cohorts, and all investigators noted considerable heterogeneity in the presentation and progression of metastatic disease. Thus, despite initially promising results, most patients with metastatic breast cancer continue to be treated with systemic chemotherapy or TACE.

Vogl *et al*[3], also carried out a survey to evaluate a treatment protocol with repeated TACE before laser-induced thermotherapy (LITT) in patients with unresectable liver metastases that are too large for LITT alone and achieved good results. Reduction in size of primary unresectable hepatic metastases is achieved in 50.6% of cases and allows local ablative treatments such as MR imaging-guided LITT. Compared to surgery, RF ablation offers the advantages of being less expensive and considerably less invasive[31]. The use of RF ablation does not prevent the simultaneous or subsequent use of other, potentially complementary treatments. Hormonal therapy, systemic chemotherapy and intraarterial infusion chemotherapy, each can be given before or after RF ablation, according to local preferences and practice guidelines[32].

In conclusion, TACE appears to be a safe, relatively simple, and effective treatment for liver metastases from breast cancer. The absence of major complications and the high rate of local control achieved in this series suggest that TACE may be a valid alternative to chemotherapy in patients with BCLM. It therefore appears to be important to include the possibility of TACE in multicenter treatment protocols for BCLM. The quality of the responses obtained with new chemotherapy protocols, especially those using taxanes, could extend the indications for remission consolidation strategies, with future randomized controlled trials, one arm with prolonged chemotherapy, one with TACE.

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