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Residual tumor thickness at the tumor-normal tissue interface predicts the recurrence-free survival in patients with liver metastasis of breast cancer☆

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ABSTRACT

Tumor response to neoadjuvant therapy is a significant predictive indicator of recurrence-free survival. We measured tumor response using residual tumor thickness at the tumor-normal tissue interface (TNI) and evaluated its association with outcome in patients with liver metastasis of breast cancer. We included 48 patients who underwent neoadjuvant therapy followed by partial liver resection at MD Anderson Cancer Center between 1997 and 2010. The hematoxylin-eosin–stained tumor sections were evaluated for both pathologic response and the residual tumor thickness at the TNI by 3 pathologists who were blinded to the clinical information, treatment regimen, and patient outcome. The residual tumor thickness at the TNI was correlated with recurrence-free survival using Kaplan-Meier method and log-rank test. Cox proportional hazard model was used to identify predictors of recurrence-free survival. All patients were women with a median age of 43 years. The median duration of follow-up was 52.1 months. Residual tumor thickness less than or equal to 3 mm at the TNI correlated with major pathologic response and was associated with longer recurrence-free survival in both univariate and multivariate analyses. Residual tumor thickness at the TNI predicts recurrence-free survival and provides an objective outcome end point in patients who underwent neoadjuvant therapy and liver resection of metastatic breast cancer. We suggest using both the pathologic response and the residual tumor thickness at the TNI to measure tumor response to therapy to improve accuracy.

1. Introduction

Liver metastasis of breast cancer (LMBC) develops in more than 50% of breast cancer patients [1], and one-third of patients with metastatic breast cancer have metastases only in the liver [2]. Liver metastasis of breast cancer usually portends a poor prognosis. However, neoadjuvant therapy followed by partial liver resection to remove the residual metastatic tumor has been shown to provide survival benefit for these patients [2], and the tumor response to neoadjuvant therapy is a significant predictive indicator of recurrence-free survival [2,3].

Tumor response to neoadjuvant therapy is measured by the pathologic response, defined by estimating the percentage of residual tumor cells in the resected tumor. This method of measuring tumor response is useful, but estimating the percentage of residual tumor cells is prone to interobserver and intraobserver variations. A new method of defining tumor response to neoadjuvant therapy by measuring the residual tumor thickness at the tumor-normal tissue interface (TNI) was shown to be a significant predictive indicator of recurrence-free survival in patients with resected liver metastases of colorectal cancer [4]. We have observed that the patterns of residual tumor cells and fibrocollagenous proliferation in resected LMBC after neoadjuvant therapy are similar to those in resected liver metastases of colorectal cancer. We hypothesized that the residual tumor thickness at TNI can predict recurrence-free survival in patients with LMBC as well. We measured the tumor response to neoadjuvant therapy using the residual tumor thickness at TNI and percentage of residual tumor cells in resected liver metastases of breast cancer and evaluated its association with recurrence-free survival.

☆ Disclosure: None.

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2. Materials and methods

2.1. Patient selection

This retrospective study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. We identified 89 patients with LMBC who underwent partial liver resection at MD Anderson Cancer Center between 1997 and 2010 by searching the databases of the Departments of Surgical Oncology and Pathology. Twenty patients were excluded because they did not undergo neoadjuvant therapy for the metastatic tumor, and 21 others were excluded because the pathology slides were not available for review. We included the remaining 48 patients in the study.

The electronic medical records of these patients were reviewed. The relevant clinical data were abstracted, including patient's age, size, histologic grade of tumor, status of lymph node metastasis, status of hormonal and Her2/neu receptors of the tumor, whether liver metastasis was synchronous or metachronous, number of cycles of preoperative chemotherapy, whether liver resection was major or minor, status of surgical margins, and clinical follow-up.

2.2. Assessment of pathologic response by percentage of residual tumor cells

Two pathologists (JZ and DR) who were blinded to the clinical information, treatment regimen, and outcome evaluated the hematoxylin-eosin–stained slides of metastatic tumor nodules. The third pathologist (DM), who was also blinded to the clinical information, treatment regimen, and outcome resolved any discrepancy between the 2 pathologists. The percentage of residual tumor cells was assessed as described by Blazer et al [5]. All hematoxylin-eosin–

Table
Predictors of recurrence-free survival

Variable	No. of patients	Recurrence-free survival					
		Univariate analysis			Multivariate analysis		
		P	HR	95% CI	*P*	HR	95% CI
Age							
<50 y	36						
≥50 y	12	.188	1.75	0.76-4.00	NS		
Pathologic response							
Major	19	.01	0.32	0.133-0.758	NS		
Minor	29						
Tumor thickness at TNI							
≤3 mm	23						
>3 mm	25	.004	3.02	1.37-6.65	.001	4.11	1.76-9.61
No. of tumor nodules							
<2	28	.467	1.32	0.62-2.79			
≥2	40						
Tumor size							
≤5 cm	43						
>5 cm	5	.006	4.24	1.51-11.94	NS		
Liver resection							
Major	30	.851	1.07	0.51-2.26			
Minor	18						
Surgical margin							
Positive	4	.009	5.20	1.50-17.97	.002	8.3	2.20-31.28
Negative	44						
Tumor type							
Ductal type	44	.920	1.06	0.32-3.57			
Lobular type	3						
Mixed type	1						
Estrogen receptor status							
Positive	31	.340	0.66	0.28-1.54			
Negative	14						
No data	10						
Progesterone receptor status							
Positive	23	.882	0.94	0.43-2.06			
Negative	21						
No data	4						
ER and PR status							
Positive	14	.340	1.51	0.647-3.53			
Negative	31						
No data	3						
Her2/neu status							
Positive	20	.583	0.795	0.35-1.81			
Negative	21						
No data	7						
Synchronous liver disease							
Yes	16	.443	0.71	0.30-1.67			
No	32						
Primary neoadjuvant chemo							
Yes	17	.244	1.63	0.74-3.56			
No	31						
Neoadjuvant chemotherapy for liver metastasis >6 cycle							
Yes	32	.349	0.67	0.29-1.55			
No	16						

Abbreviations: *HR*, hazard ratio; *NS*, not significant; *ER*, estrogen receptor; *PR*, progesterone receptor; *chemo*, chemotherapy.