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Role of Circulating Tumor Cell (CTC) Monitoring in Evaluating Prognosis of Triple-Negative Breast Cancer Patients in China

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Background: Breast cancer (BC) is the most common malignant tumor in females. This study investigated the role and utility of CTC monitoring in evaluating the prognosis of triple-negative breast cancer patients.

Material/Methods: We enrolled 286 female triple-negative breast cancer patients who were diagnosed at and received radical resection surgery in our hospital. Peripheral venous blood samples were collected preoperatively and at 3 and 7 days postoperative, and the Cell Search system was used to detect CTC in peripheral blood. We analyzed the relationship between preoperative CTC level and clinical pathological characteristics of patients. Kaplan-Meier method was used to establish progression-free survival curves and overall survival curves, we used the log-rank test to compare the survival rate, and we explored the effects of preoperative and postoperative CTC levels on patient survival.

Results: Compared with preoperative levels, the average CTC content in peripheral blood of breast cancer patients was significantly increased at 3 days after surgery, and then decreased to the preoperative baseline level by 7 days after surgery. The 3-year overall survival rate and progression-free survival rate in patients with CTC >5/7.5 mL peripheral blood were significantly lower than in patients with CTC <5/7.5 mL peripheral blood detected preoperatively and at 3 and 7 days postoperatively.

Conclusions: Dynamic monitoring of preoperative and postoperative CTC levels can accurately predict recurrence and progression of disease, and is important in postoperative monitoring and prognosis evaluation.

MeSH Keywords: Breast • Neoplastic Cells, Circulating • Triple Negative Breast Neoplasms

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Background

Breast cancer is the most common malignant tumor in female and has the highest incidence rate among female malignant tumors. Breast cancer accounts for about 25–30% of female malignant tumors; furthermore, it has increased at an average annual rate of 2%, and has become the leading cause of death among women [1,2]. In both developed and developing countries, breast cancer is the leading cause of death from malignant tumors [3]. About 1.3 million people are diagnosed with breast cancer each year world-wide, and about one-third of them die due to the disease [4], in which recurrence and metastasis are the leading cause of deaths [5,6] of patients with breast cancer. Most patients who were newly diagnosed have early non-metastatic breast cancer. Therefore, early diagnosis of the metastasis and the monitoring of postoperative metastasis for breast cancer patients are of great significance to enhance the therapeutic effects and improve the prognosis of patients. Hematogenous spread is the main means and pathway for distant metastasis of breast cancer, and micrometastasis of breast cancer cells entering the peripheral blood is the main mechanism for distant metastasis. Breast cancer cells in peripheral blood can reach a variety of tissues and organs through blood circulation, in which bone [7] and lung [8] are the main sites of distant metastasis.

Circulating tumor cells (CTCs) refer to the tumor cells circulating in the peripheral blood; they either spontaneously or as a result of clinical operations spread from the solid tumor's primary focus or metastatic focus [9]. Studies have shown that CTCs correlate with metastatic lymph nodes and can help to show prognosis of various cancers [10–12]. Tumor cells divide from tumor tissue and enter the blood circulation, and then form tumor embolisms through migration, adhesion, and aggregation in the blood circulation. The above process is the main type of distant metastasis of breast cancer [13], and is also an important factor that affects the survival and prognosis of patients [14]. Therefore, the detection of circulating tumor cells in peripheral blood of breast cancer patients plays an important role in breast cancer diagnosis, prognosis assessment, selection of treatment regimen, and prediction of metastasis and recurrence [15]. Triple-negative breast cancer (TNBC) refers to a special type of breast cancer, in which the expressions of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) are all negative [16,17]. TNBC accounts for about 10~17% of all pathologic types of breast cancers, and possesses the characteristics of high malignant degree, easy recurrence, and distant metastasis [18]. The purpose of this study was to investigate the role and values of preoperative and postoperative CTC monitoring in the prognosis of TNBC patients.

Material and Methods

Clinical data

A total of 286 female TNBC patients were enrolled, who were diagnosed and underwent radical resection in our hospital from January 2013 to September 2015. These patients were ages 35.7 to 68.5 years old, with an average age of 48.2±15.3 years. All patients were diagnosed and underwent no preoperative chemotherapy, immune therapy, biological therapy, or other treatments prior to the study. All patients provided informed consent to participate in the study. The detection of 3 markers – ER, PR, and HER-2 – were used in the diagnosis of TNBC. According to the clinical practice guidelines of the American Society of Clinical Oncology and the American Association of Pathologists [19,20], the results of ER- and PR-positive cell numbers <1% is defined as negative and HER2-positive cells numbers <10% is defined as negative. All the patients underwent chest CR and abdominal ultrasound examination to ensure that there was no pulmonary or hepatic metastasis, and underwent systemic bone scan to ensure that there was no bone metastasis. The general conditions of patients were good. Their physical status was 0~1 points according to the evaluation standard of the United States Eastern Cooperative Oncology Group (ECOG) (0 points means the patient has completely normal activities of daily living and the condition is not different from before the onset of disease; 1 point means the patient can move around freely and engage in light physical activities such as general household or office work, but cannot engage in heavy physical activity; 2 points means the patient can move around freely and perform self-care but has lost the ability to work, and can be up for more than half of the daytime hours; 3 points means the patient can perform some but not all self-care activities, and needs to be in bed or in a wheelchair for more than half of the daytime hours; 4 points means the patient cannot get out of bed and cannot perform self-care activities; and 5 points means the patient is dead). We excluded patients with history of other malignant tumors, pregnant or lactating women, patients with severe coagulopathy (prothrombin time <30%, international normalized ratio >2.5, platelet count $<40\times10^9$/L). The Bloom-Richardson grading standard was used for histological grading of breast cancer, while TNM staging of breast cancer was in accordance with the TNM Staging Standards, Seventh Edition (2010) of the American Joint Commission on Cancer (AJCC) and the International Union Against Cancer (UICC). The present study was approved by the Ethics Committee of our hospital.

Main reagents and materials

We used the CellTracks and AutoPrep® System circulating tumor cell detector system contained in the Cell Search system,

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CellTracks® analyzer II, with matched supplies and reagents purchased from Veridex (United States).

CTC detection

Peripheral blood CTC was detected by Cell Search system. We collected 7.5-mL fasting venous blood samples before the operation (baseline level) and at 3 days and 7 days after the operation, and placed them into Cell Save storage tubes; 6.5 mL dilution buffer was added into the tube, reverse mixed for 5 times, and centrifuged at 800×g for 10 min. Then, the samples were processed using the CellTracks® AutoPrep® system. Firstly, the anti -EpCAM ferrofluid and buffer were added, magnetic incubated for 15 min to capture immunomagnetic particles and enrich the CTC cells that expressed EpCAM antigen. Liquid and un-bound magnetic particles were sucked out, the cytokeratin 8/18(CK8/18) was recognized by PE-marked cytokeratin antibody, the nuclei were marked by DAPI nuclear dye, and white blood cells were recognized by APC-labeled CD45 antibody. After treatment, the samples were transferred into the sample box for analysis and detection using a CellTracks® analyzer II, and the detection results were finally interpreted and counted by operation personnel. The CTC interpretation standard was [21]: the enriched cells were processed by dying, the blank control was assigned as negative color standard, leukocyte antigen CD45 fluorescence antibody was used to exclude the interference of white blood cells, and cells with negative CD45 staining and positive DAPI and CK staining were determined as CTC. CTC numbers detected in 7.5 ml peripheral blood were defined as units, which was assigned as not detected (0) and positive (more than or equal to 1), and the CTC-positive detection rate was calculated.

Evaluation of efficacy

According to the Response Evaluation Criteria In Solid Tumors (RECIST), the curative effect was divided into Complete Response (CR): the tumor disappeared completely in clinical examination; Partial Response (PR): the product of the largest diameter of the tumor and its maximum vertical diameter was reduced by more than 50%; Stable Disease (SD): the product of the largest diameter of the tumor and its maximum vertical diameter was reduced by less than 50% or increases by less than 25%; Progressive Disease (PD): the product of the largest diameter of the tumor and its maximum vertical diameter was increased by more than 25%. Objective Response Rate (ORR)=(CR+PR)/total number of cases ×100%; Disease Control Rate (DCR)=(CR+PR+SD)/total number of cases ×100%.

Follow-up

Patients were followed-up through telephone or letters. The survival times of all the patients were begun to be calculated since the surgical resections were completed, and the progression-free survival (PFS) and overall survival (OS) were adopted as the endpoints. The follow-up period lasted for 3.2~37.6 months, and the effects of CTC baseline level and postoperative CTC level on PFS and OS were compared. PFS is defined as the time from surgical treatment to diagnosis with recurrence for the first time or follow-up cut-off, while OS is defined as the time from surgical treatment to death or the end of the follow-up.

Statistical analysis

SPSS 18.0 was used for the statistical analysis of data. The measurement data are expressed as mean ± standard deviation, the count data are expressed in the form of percentage, the measurement data among groups were compared with the *t* test or variance of analysis, and the count data between groups were compared using the chi-square test. The survival curves of the patients were plotted and analyzed by Kaplan-Meier method and the survival rates were compared by the log-rank test. $P<0.05$ was considered as a statistically significant difference.

Results

Baseline data

In this study, a total of 286 cases of TNBC patients were enrolled, whose clinical pathological features and CTC baseline data are shown in Table 1. The 286 TNBC patients were divided into 3 groups according to the clinical staging: 129 patients were in stage I, in which 30 were detected with CTC and, the positive detection rate was 23.3%; 81 patients were in stage II, in which 30 were detected with CTC and the positive detection rate was 37.0%; and 76 patients were in stage III, in which 43 were detected with CTC and the positive detection rate was 56.6%. With the increase of TNM stage, CTC-positive detection rate gradually increased ($\chi^2=23.097$, $P<0.001$). In addition, as the stage of TNM (I~III) increases, the number of detected CTCs also increases, which was 2.13±1.72, 4.56±3.28, 6.53±4.71/7.5 mL peripheral blood sample ($F=46.93$, $P<0.001$), respectively. The CTC-positive detection rate (26.5%) of the patients with lymph node metastasis was much higher than in those without lymph node metastasis (40.9%) ($\chi^2=5.818$, $P=0.016$). Furthermore, the number of detected CTCs (3.17±2.34) in patients with lymph node metastasis was also significantly higher than in those without lymph node metastasis (5.88±4.56) ($t=5.514$, $P<0.001$). The CTC-positive detection rate exhibits no significant relationships with age, tumor size, menstrual status, or type and histological pathological grading of tumors ($P>0.05$).

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Table 1. Clinical pathological characteristics and CTC baseline data of TNBC patients.

Clinical characteristics	Number of cases	CTC detection		χ^2	P
		Number of positive cases	Positive rate (%)		
Age				0.645	0.422
≤50 years old	120	40	33.3		
>50 years old	166	63	37.9		
Menstrual status				1.933	0.164
Premenopause	121	38	31.4		
Postmenopause	165	65	39.4		
Tumor size				4.069	0.131
<2 cm	136	42	30.9		
2~5 cm	110	42	38.2		
>5 cm	40	19	47.5		
Tumor type				0.595	0.743
Ductal carcinoma	169	59	34.9		
Lobular carcinoma	68	24	35.3		
Lobular/ductal carcinoma	49	20	40.8		
Histological pathological grading				0.286	0.867
I	142	49	34.5		
II	74	28	37.8		
III	70	26	37.1		
TNM staging				23.097	0.001
I	129	30	23.3		
II	81	30	37.0		
III	76	43	56.6		
Lymph node metastasis				5.818	0.016
Without	98	26	26.5		
With	188	77	40.9		

Pre- and post- operative CTC changes

Pre- and post-operative CTC absolute value changes of patients were compared and analyzed. On the third day after the operation, the level of CTC decreases in 58 patients (accounting for 20.3%), remained unchanged in 103 patients (accounting for 36.0%), and increased in 125 patients (accounting for 43.7%). On the seventh day after the operation, the level of CTC decreased in 80 patients (accounting for 27.9%), remained unchanged in 116 (accounting for 40.6%), and increased in 90 (accounting for 31.5%). By comparing the results on the third day after the operation and on the seventh day after the operation, the proportions of decreased, unchanged, and increased CTC levels showed significant differences, χ^2=9.977, P=0.007 (Table 2). In terms of absolute numbers in CTC contents in 7.5-mL peripheral blood samples taken before the operation, and at 3 days and 7 days after the operation were 4.42±2.81, 55.48±52.67, and 6.34±5.21, respectively. The results showed that, compared with conditions before the operation, the average content of CTC in peripheral blood of breast

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Table 2. Variation of CTC level before and after operation.

Variation of CTC value	3 days after operation		7 days after operation		χ^2	P
	Number of cases	Percentage (%)	Number of cases	Percentage (%)		
Reduced	58	20.3	80	27.9	9.977	0.007
No change	103	36.0	116	40.6		
Increased	125	43.7	90	31.5		

Table 3. Effect of CTC level on the therapeutic effect of patients.

CTC	Before operation		3 days after operation		7 days after operation	
	≤5 (224)	>5 (62)	≤5 (205)	>5 (81)	≤5 (219)	>5 (67)
ORR (%)	161 (71.88%)	34 (54.84%)*	145 (71.22%)	49 (60.49%)*	167 (76.25%)	27 (40.30%)*
DCR (%)	182 (81.25%)	39 (62.90%)*	162 (79.02%)	59 (72.83%)*	189 (86.30%)	32 (47.76%)*
Recurrence rate (%)	21 (9.38%)	9 (14.52%)*	18 (8.78%)	12 (14.81%)*	15 (6.85%)	15 (22.39%)*

* Indicates that compared with CTC ≤5, P<0.05.

cancer patients increased significantly on the third day after the operation (P<0.05), and decreased to the baseline level on the seventh day after the operation (P>0.05).

Effect of CTC level on the therapeutic effect of patients

A multicenter study by Banys et al. [22] showed that the survival and prognosis of breast cancer patients whose CTC level in 7.5-ml blood samples were greater than or equal to 5 were significantly worse than in those with CTC level less than 5. Therefore, in this study, the peripheral blood of patients with CTC level of 5 was regarded as the cut-off value, and all of the patients were divided into group CTC level less than or equal to 5 and group CTC level greater than 5, and the effects of CTC levels on ORR, DCR, and recurrence rate of the 2 groups before the operation and at 3 days and 7 days after the operation were observed. We found that the ORR, DCR, and recurrence rate of TNBC patients with CTC level greater than 5 were significantly lower than in those with CTC level less than or equal 5, as shown in Table 3.

Relationship between CTC level versus survival and prognosis of patients

A multicenter study carried out by Banys et al. [22] demonstrated that the survival and prognosis of breast cancer patients with the CTC level greater than 5 in 7.5-ml blood samples are significantly worse than in patients with CTC level less than 5. Therefore, the patients in this group were divided into 2 groups using 5 CTCs in the peripheral blood as a cut-off value, and the effects of CTC level on the survival and prognosis of patients with breast cancer before the operation and at 3 days and 7 days after the operation were discussed. Before the operation, the survival curves of TNBC patients with the CTC level greater than 5 were significantly steeper compared with those patients of with CTC level less than 5. The shortest OS was 8.3 months for the former, while the shortest OS was 11.4 months for the latter. The shortest PFS for the former was 3.2 months, while the shortest PFS for the latter was 5.6 months. The log-rank test results show that the 3-year OS rate (χ^2=12.71, P=0.005) and PFS rate (χ^2=14.27, P=0.003) of patients with CTC level greater than 5 were significantly lower than in those with CTC level less than 5, as shown in Figure 1A and 1B. For the 2 groups of TNBC patients, who were divided according to the CTC detection results 3 days and 7 days after the operation, the 3-year OS rate and PFS rate of patients with the CTC level greater than 5 were also lower than in patients with CTC level in less than 5, as shown in Figure 1C–1F.

Discussion

China has a high incidence of breast cancer. In recent years, the incidence and mortality of female breast cancer in China have increased year by year, and breast cancer is now the most common malignant tumor of females [23]. TNBC is a special type of breast cancer and accounts for approximately 10–20% of breast cancers. Due to the lack of a series of receptors such as estrogen receptor, progesterone receptor (PR), and human epidermal growth factor receptor, as well as specific molecular

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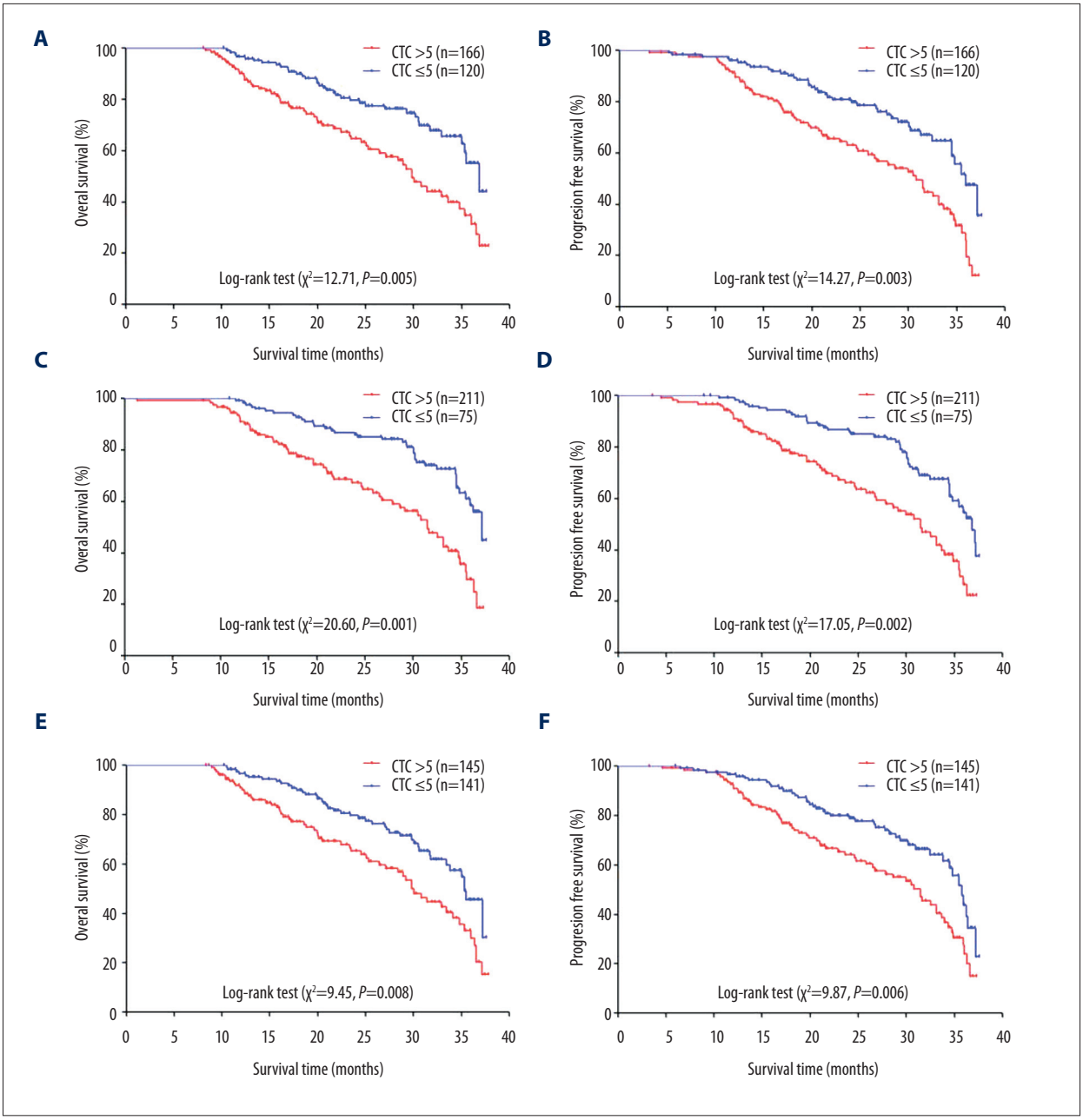

Figure 1. Analysis of survival curves of patients with different CTC levels. (**A**) Preoperative OS rate compared in patients with different CTC levels; (**B**) Preoperative PFS rate compared in patients with different CTC levels; (**C**) OS rate 3 days after operation compared in patients with different CTC levels; (**D**) PFS rate 3 days after operation compared in patients with different CTC levels. (**E**) 7 days after operation OS rate comparison in patients with different CTC levels. (**F**) PFS rate 7 days after operation compared in patients with different CTC levels.

target, TNBC cannot benefit greatly from endocrine- and biological-targeted treatment strategies [24]. At present, surgery and radiochemotherapy are commonly used in the treatment of TNBC, but the curative effects are still not ideal. TNBC still is characterized by high invasiveness, high recurrence rate, poor prognosis, and high mortality [25]. For most tumors, once distant metastasis occurs, the difficulty of treatment greatly increases and the efficacy and prognosis are worse. More than 90% of deaths in patients with malignant tumors are caused by distant metastasis and recurrence of tumor cells [26]. Hematogenous dissemination is an important mode of distant metastasis of breast cancer. The distant metastasis of tumor cells can occur even in the early stage of breast cancer. The spreading of breast cancer cells from the primary focus and then entering

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the blood circulation to form CTC are the first links in distant metastasis. Detection of changes in CTC number and dynamic states can reflect tumor loading, provide early prediction of the recurrence and metastasis of non-metastatic breast cancer, monitor the development of the disease, and help clinicians to choose treatment options and take effective intervention measures to block the metastatic focus formation, and thus is important in controlling the disease, reducing recurrence, providing high curative effect, and improving prognosis. Therefore, the diagnostic and predictive value of CTC and its role in the transformation of medical research have attracted more and more attention from medical science researchers, and are now popular topics in the field of cancer research.

Compared with the traditional examination methods, such as sampling of bone, histologic pathological examination, and imaging examination for disseminated tumor cells detection, CTC detection has many advantages, such as the convenient and almost noninvasive sampling, repeatability, real-time dynamic monitoring, and high sensitivity [27]. There are a variety of CTC separation and detection methods and techniques, mainly including the immunomagnetic separation method, density gradient centrifugation, reverse transcription polymerase chain reaction, laser scanning cytometry measurement technique, and flow cytometry counting. Cell Search is currently the only CTC detection method approved by the U.S. Food and Drug Administration, and has been applied in a number of clinical studies [21]. Many clinical trial studies have confirmed that CTC is an independent predictor for PFS and OS of patients with breast cancer, and the positive CTC detection results at any timepoints indicate a high risk of disease progression [28]. Therefore, in this research, a CTC detection system (Cell Search) was used to analyze the relationship between preoperative and postoperative CTC levels versus the survival and prognosis of TNBC patients. The analysis results of baseline data showed that the observed positive detection rate of CTC in patients with breast cancer in this study was 36%. Foreign studies have demonstrated that the positive detection rate of CTC in patients with breast cancer was between 10.6% and 50.0% [29–31], and the present results fell into this range. With increased TNM stage, the positive CTC detection rate and average detection quantity also increase gradually, which indicates that the positive detection rate of CTC is closely related to the TNM stage. Specifically, the higher the stage, the higher the positive detection rate of CTC. This agrees well with the fact that the breast cancer patients with higher stage are more prone to suffering from distant metastasis. Whether the lymph node metastasis occurred or not, CTC can be detected in the peripheral blood in some patients with breast cancer; however, the positive CTC detection rate and the detection numbers of the patients with lymph node metastasis are significantly higher than in those without lymph node metastasis. According to related reports, cancer cells can also be detected in the regional lymph nodes in patients with primary treatment whose CTCs are not detected in the peripheral blood, indicating breast cancer cell metastasis towards lymph nodes4[32]. However, in some non-lymph node metastasis patients, the distant spread of breast cancer cells can bypass the lymphatic pathway and directly enter the blood circulation, suggesting that the detected CTCs in non-lymph node metastasis patients are still indicative of the risks of recurrence and metastasis. The CTC detection rate and numbers in patients with lymph node metastasis may be greater, which is similar to the results observed in this study [33]. Compared to the preoperative result, on the third day after the operation, some patients showed an elevated CTC level in the peripheral blood, while some patients showed a decreased CTC level; however, the proportion of patients with increased CTC level was larger than that with decreased CTC level. Furthermore, on the seventh day after the operation, the proportion of patients with increased CTC level was reduced greatly, while the proportion of the patients with decreased CTC level increased. In addition, compared to the preoperative results, the average detected CTC numbers in patients with breast cancer increases significantly on the third day after the operation, and decreased to the preoperative level on the seventh day after the operation. Camara et al. [34] found that 3~4 days after the operation, the CTC levels of more than 80% of the patients increased up to 1000 times that of the preoperative results, and then fell to the preoperative baseline level; however, CTC may persist in peripheral blood of some patients, and may aggregate and transfer into metastatic focus under certain conditions. Qiao et al. [35] believed that surgical treatment could increase the possibility of tumor cells shedding and consequently entering the peripheral blood. This research suggests that the CTC number and its dynamic changes should be detected before and after the operation for monitoring the disease conditions. Therefore, we further explored the effects of CTC levels on survival and prognosis at 3 different timepoints: before the operation, and 3 days and 7 days after the operation. The results show that the average CTC levels of the abovementioned 3 timepoints affect ORR, DCR, recurrence rate, OS, and PFS times, in which the survival and prognosis of the patients with a 7.5-mL sample CTC blood level greater than 5 were worse than for patients with the CTC level less than 5, and the recurrence rate were also higher. The use of 5 CTC as the boundary value, which was set by the Cell Search system, has positive predictive values for the judgment of prognosis of patients with breast cancer. Jansson et al. [36] confirmed that survival and prognosis of patients with the CTC level less than 5 in 7.5-mL blood samples were better than those with greater than 5. Tsai et al. [37] also found that the distant metastasis of the tumor of patients with the CTC level less than 5 in 7.5-mL blood samples is only one-eighth as likely as those with CTC level greater than 5, and the prognosis was better than the latter.

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In addition, the results of this study show that predicting the prognosis and survival of patients by CTC levels at 7 days after the operation was more valuable than at other timepoints. Dynamic monitoring of CTC levels can provide a basis for follow-up treatment and prognosis.

A recent domestic multicenter prospective study [38] confirmed that CTC also has important prognostic judgment value in Chinese triple-negative metastatic breast cancer patients, which is consistent with the results of this study.

Conclusions

CTC numbers and TNM stage of the patients with breast cancer are correlated with lymph node metastasis to a certain degree, and preoperative and postoperative dynamic monitoring of CTC can effectively predict disease recurrence and progression, which are helpful and have high values in judging and improving the prognosis.

Disclosure of conflict of interest

All authors declared no conflict of interest.

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