Cancer antigen 153: A risk factor for ocular metastases in patients with breast cancer

QIAN-MIN GE*, QIAO-HAO HU*, JIA-XIANG LIU*, YOU-LAN MIN, RONG-BIN LIANG, BIAO LI, WEN-QING SHI, QI LIN, QING YUAN, QIU-YU LI and YI SHAO

Department of Ophthalmology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

Received September 27, 2019; Accepted December 19, 2022

DOI: 10.3892/etm.2024.12710

Abstract. Ocular metastasis (OM) in breast cancer (BC) always predicts poor prognosis. The present study explored differences in tumor markers in patients with BC with and without OM, and attempted to determine risk factors for OM in patients with BC. This study involved 629 patients with BC. Patients' clinical features were tested using χ^2 test, unpaired Student's t-test and Mann-Whitney U. These parameters were analyzed using binary logistic regression to obtain risk factors for OM. A receiver operating characteristic curve was then established to determine the diagnostic value for OM. There were no significant differences in age, sex, menopausal state, and pathological type between the two groups. Significantly more axillary lymph node metastases were observed in the OM group compared with the non-ocular metastases group. Cancer antigen 153 (CA153) was revealed to be a significant independent risk factor for OM in patients with BC. The cutoff CA153 value for diagnosis of OM was 43.00 u/ml, the sensitivity was 96.15% and the specificity was 96.02%. In conclusion, CA153 was demonstrated to be a risk factor for OM in patients with BC. High levels of CA153 were associated with OM in patients with BC.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women globally in addition to being the leading cause of cancer mortality in women in >100 countries, with a continuously increasing incidence (1). Moreover, >1/3 of patients with BC will develop distant metastases such as lung, liver, bone and brain metastases (2-5).

Ocular metastasis (OM), an uncommon distant metastasis, is easily neglected because of its obscure clinical symptoms in the early stage (6). When it develops to an advanced stage, OM causes ocular pain, foreign body sensation, vision loss, visual field defects and other symptoms, thus seriously affecting patients' quality of life (7). Currently, positron emission computed tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI) and ultrasonic testing are often used in clinical practice for diagnosis of OM (8,9). However, these approaches have obvious disadvantages, including their expense and damage from high-dose radiation (10). Thus, it is important to explore improved methods for predicting OM in breast cancer. Serum testing for clinical parameters is a practical method to assess the possibility of distant metastases, as it can shed light on the progress of tumors. Among the various parameters that have been used in clinical practice, tumor markers are considered to be reliable indices to predict distant metastases in patients with cancer (11).

A cancer biomarker is a substance or process that indicates the presence of cancer in the body (12). Measured either in the tumor or in blood, tumor biomarkers can be used to evaluate tumor condition and thus predict the possibility of developing distant metastases (11). Traditional cancer biomarkers include embryonic antigens, as well as protein, carbohydrate, enzyme and hormonal markers (13).

Cancer antigen 153 (CA153) is used to detect Mucin 1 (MUC-1), a transmembrane protein consisting of two subunits (14). MUC-1 is expressed at the apical plasma membrane in normal secretory epithelial cells (15). However, it is released into the serum when metastatic BC occurs (16). Numerous other advanced types of cancer, including ovarian, pancreatic, gastric and lung cancer, also result in elevated CA153 levels (17-20). High levels of C153 can also be observed in a number of benign diseases, including chronic active hepatitis, liver cirrhosis, sarcoidosis and metaplastic anemia (17,21,22). Owing to its low specificity, the use of CA153 in diagnosing early BC has been limited, although it provides useful prognostic information. Numerous studies have demonstrated that high preoperative levels of CA153 are

Correspondence to: Dr Yi Shao, Department of Ophthalmology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, 17 Yongwaizheng Street, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: freebee99@163.com

*Contributed equally

Key words: breast cancer, tumor markers, diagnostic value, ocular metastases

Table I. Clinical features of patients with breast cancer.

Characteristic	OM	NOM	Whole	P-value
Age, years±SD[a]	45.85±7.76	48.31±10.58	48.21±10.48	0.241
Sex, n[b]				
Women	26	601	627	1.000
Men	0	2	2	
Menopausal status, n[c]				0.248
Premenopausal	19	373	392	
Postmenopausal	7	230	237	
Histopathology, n[c]				0.656
Invasive ductal carcinoma	20	440	460	
Other types	6	163	169	
Axillary lymph node metastases, n[c]				<0.001
0	4	259	263	
1-4	7	210	217	
>4	15	134	149	

[a]Unpaired Student's t-test was used; [b]Fisher's exact test; [c]χ^2 test was used. OM, ocular metastases; NOM, non-ocular metastases.

associated with shorter disease-free and overall survival times in patients with BC (23,24).

Other cancer biomarkers have also been used in diagnosing tumors and metastases. In patients with colorectal cancer and liver metastasis, higher carcinoembryonic antigen (CEA) level is associated with shorter median progression-free survival and median liver progression-free survival (25). In Zhao's study (26), the sensitivity and specificity of cancer antigen 125 (CA125) for diagnosing ovarian cancer were 88.2 and 67.4%, respectively. Cancer antigen 199 (CA199) level >300 mg/ml is an independent prognostic factor for postoperative survival in Zheng's study (hazard ratio, 3.76; 95% CI, 2.18-6.49) (27). Alkaline phosphatase (ALP) is used to diagnose bone metastases in BC with a high specificity (93.96%) but a low sensitivity (65.14%) (28).

A number of studies have reported altered levels of CA153 in patients with cancer with metastases at various sites and investigated their diagnostic value. However, whether CA153 levels could be used to detect OM in patients with BC remains unknown. The present retrospective study analyzed levels of CA153 and other common tumor biomarkers of patients with BC to determine their value in diagnosing OM.

Materials and methods

Study design. This study was designed to determine the associations between levels of cancer biomarkers and OM in patients with BC. The data range of sample collection is Jan 2005-Jan 2019. All BC were diagnosed pathologically, and the pathologist was independent from the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval no. CDYFY-2015-112; date, 2015-05-06; Nanchang, China). All the methods complied with relevant guidelines and regulations. Breast tissues from patients were resected during surgery and the diagnosis of BC was made on the basis of pathological biopsy. CT and MRI were used to make the OM diagnosis. Inclusion criteria were all patients who were diagnosed with BC based on the pathologically. Exclusion criteria were primary ocular malignant tumor, primary ocular benign tumor and secondary BC. As this is a retrospective study, informed consent of the patients was waived, which was approved by the Ethics Committee at The First Affiliated Hospital of Nanchang University.

Data collection. Age, sex, histopathological subtype and menopausal status were recorded as basic information and analyzed for differences among patients (Table I). As well as CA153, axillary lymph node metastasis (ALNM), CEA, CA125, CA199, ALP and calcium were analyzed as these parameters are frequently used in clinical practice and reflect the condition of tumors in patients with cancer. All clinical indices were collected from medical records when patients were first diagnosed with BC. Consecutive data are represented as mean ± standard deviation.

Statistical analysis. First, basic clinical features including age, sex, histopathological subtype, menopausal status and ALNM number were compared using Fisher's exact test, χ^2 test and unpaired Student's t-test. Then, clinical parameters of the ocular metastases (OM) group and non-ocular metastases (NOM) group were compared across different subgroups using the Mann-Whitney U test. Binary logistic regression was carried out to determine independent risk factors for OM. A receiver operating characteristic (ROC) curve was constructed with MedCalc 18.2.1 (MedCalc Software, Ltd.), and the cutoff value, area under the curve (AUC), sensitivity and specificity were obtained. Measurement data are presented as mean ± standard deviation (SD). $P<0.05$ was considered to indicate a statistically significant difference.

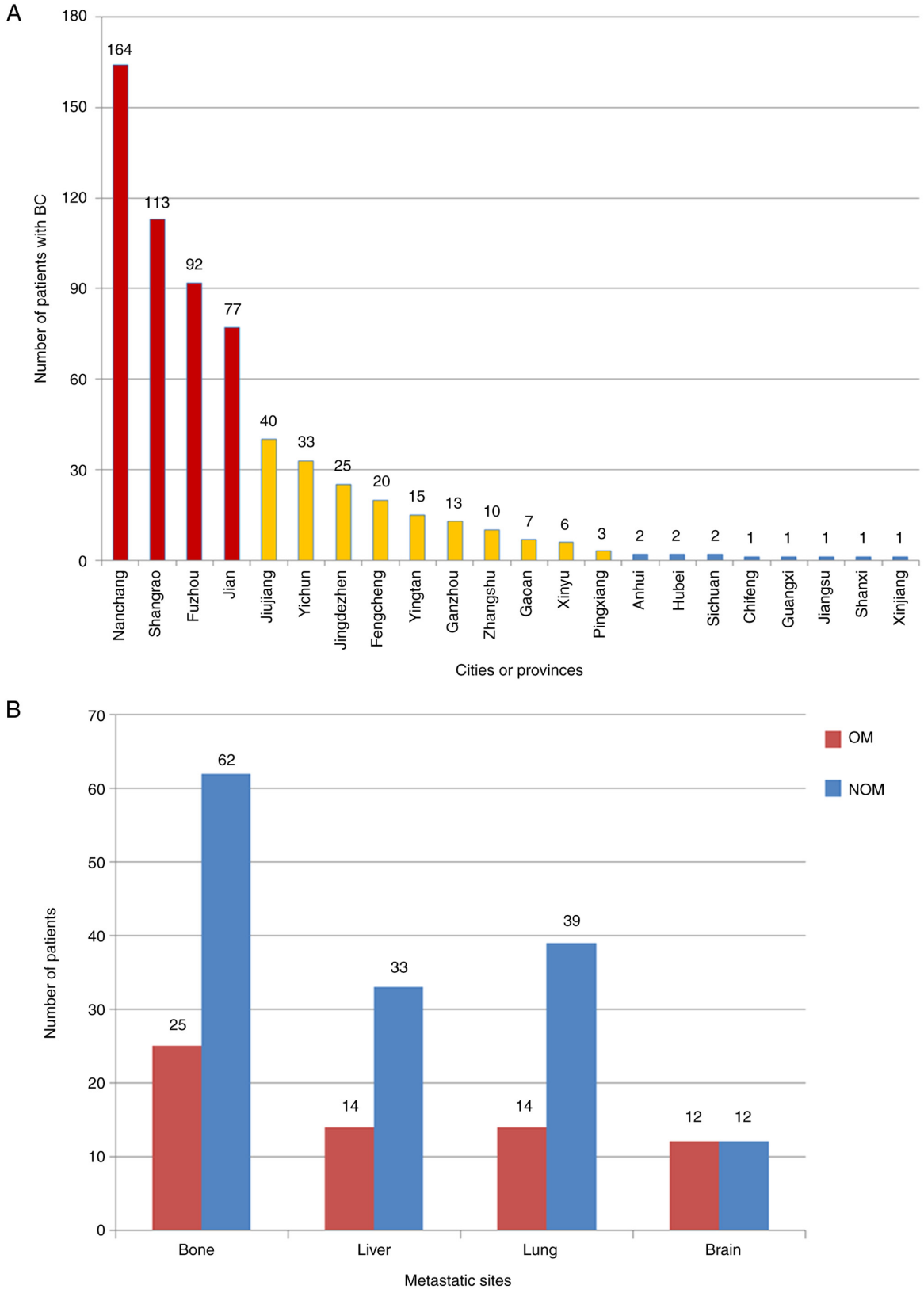

Figure 1. Distributions of patients with BC and conditions of distant organs metastases. (A) Distributions of patients with BC were counted. (B) Other distant metastases of patients with BC were counted. OM, ocular metastases; NOM, non-ocular metastases.

Results

Clinical features of patients with BC. There were 629 patients with BC in total (627 female and two male), of which 26 patients had OM and 603 had NOM. There were no differences in age (P=0.241), sex (P=1.000), menopausal status (P=0.248), or histopathology (P=0.656) between the OM and NOM groups. The average age of patients in the OM group

Table II. Subgroup analysis.

A, Premenopausal

Clinical features	OM (n=19)	NOM (n=373)	P-value
CEA (ng/ml)	39.59±107.83	2.93±9.99	<0.001
CA125 (μ/ml)	57.23±103.74	22.86±67.94	<0.001
CA153 (μ/ml)	158.59±129.37	17.16±26.55	<0.001
CA199 (μ/ml)	30.89±50.44	13.28±13.76	0.375
ALP (μ/l)	134.32±101.45	59.60±24.64	<0.001
Calcium (mmol/l)	2.30±0.42	2.32±0.55	0.688

B, Postmenopausal

Clinical features	OM (n=7)	NOM (n=230)	P-value
CEA (ng/ml)	43.56±72.41	39.45±531.00	0.009
CA125 (μ/ml)	138.19±203.30	24.63±174.47	0.002
CA153 (μ/ml)	147.14±72.26	19.55±32.91	<0.001
CA199 (μ/ml)	8.37±4.55	27.50±216.90	0.350
ALP (μ/l)	107.29±59.49	82.15±42.56	0.391
Calcium (mmol/l)	2.12±0.60	2.32±0.15	0.622

C, NALNM

Clinical features	OM (n=4)	NOM (n=259)	P-value
CEA (ng/ml)	53.01±101.07	2.39±4.27	0.079
CA125 (μ/ml)	118.43±209.20	14.84±31.73	0.213
CA153 (μ/ml)	217.99±219.97	13.13±9.72	<0.001
CA199 (μ/ml)	11.62±6.95	12.90±11.85	0.920
ALP (μ/l)	97.50±43.61	63.67±22.47	0.053
Calcium (mmol/l)	2.65±0.16	2.31±0.13	<0.001

D, ALNM

Clinical features	OM (n=22)	NOM (n=344)	P-value
CEA (ng/ml)	38.41±99.88	27.75±434.30	<0.001
CA125 (μ/ml)	71.87±126.60	30.08±156.44	<0.001
CA153 (μ/ml)	144.15±89.88	21.79±37.24	<0.001
CA199 (μ/ml)	27.22±47.59	23.08±177.62	0.646
ALP (μ/l)	132.41±97.68	71.61±40.89	<0.001
Calcium (mmol/l)	2.18±0.47	2.33±0.57	0.235

E, Bone metastases

Clinical features	OM (n=25)	NOM (n=62)	P-value
CEA (ng/ml)	42.14±99.88	141.30±1021.78	0.095
CA125 (μ/ml)	81.67±140.05	105.98±365.58	0.019
CA153 (μ/ml)	156.81±117.64	54.64±77.02	<0.001
CA199 (μ/ml)	25.33±44.89	72.86±416.87	0.704
ALP (μ/l)	130.00±92.31	102.05±77.10	0.222
Calcium (mmol/l)	2.26±0.48	2.49±1.30	0.980

Table II. Continued.

F, Liver metastases

Clinical features	OM (n=14)	NOM (n=33)	P-value
CEA (ng/ml)	36.01±56.65	252.70±1400.68	0.009
CA125 (μ/ml)	53.37±109.41	122.59±462.49	0.061
CA153 (μ/ml)	140.13±127.64	36.24±53.15	<0.001
CA199 (μ/ml)	31.53±55.19	117.97±570.94	0.735
ALP (μ/l)	140.36±101.37	93.33±81.60	0.036
Calcium (mmol/l)	2.32±0.42	2.30±0.25	0.761

G, Lung metastases

Clinical features	OM (n=14)	NOM (n=39)	P-value
CEA (ng/ml)	53.26±131.52	8.04±29.49	0.047
CA125 (μ/ml)	78.84±148.35	35.70±90.15	0.023
CA153 (μ/ml)	131.96±125.65	20.37±21.18	<0.001
CA199 (μ/ml)	37.96±57.54	14.28±17.47	0.175
ALP (μ/l)	90.50±42.53	70.69±20.57	0.102
Calcium (mmol/l)	2.45±0.26	2.31±0.15	0.068

H, Brain metastases

Clinical features	OM (n=12)	NOM (n=12)	P-value
CEA (ng/ml)	20.99±31.48	6.06±8.68	0.160
CA125 (μ/ml)	77.45±131.97	16.19±12.78	0.012
CA153 (μ/ml)	185.05±151.17	28.40±21.97	<0.001
CA199 (μ/ml)	44.28±60.21	10.18±7.11	0.052
ALP (μ/l)	137.25±105.89	64.42±22.92	0.045
Calcium (mmol/l)	2.41±0.29	2.24±0.12	0.155

I, Whole

Clinical features	OM (n=26)	NOM (n=603)	P-value
CEA (ng/ml)	40.66±98.15	16.86±328.08	<0.001
CA125 (μ/ml)	79.03±137.87	23.53±120.14	<0.001
CA153 (μ/ml)	155.51±115.46	18.07±29.14	<0.001
CA199 (μ/ml)	24.82±44.05	18.71±134.39	0.792
ALP (μ/l)	127.04±91.70	68.20±34.42	<0.001
Calcium (mmol/l)	2.25±0.47	2.32±0.44	0.958

Mann-Whitney U test was used. OM, ocular metastases; NOM, non-ocular metastases; ALNM, axillary lymph node metastases; NALNM, non-axillary lymph node metastases; CA, Cancer antigen.

was 45.85±7.76 years, compared with 48.31±10.58 years in the NOM group. In the OM group, 19 patients had premenopausal status and seven were postmenopausal, whereas in the NOM group the numbers were 373 and 230, respectively. Regarding histopathology, the OM group contained 20 cases of invasive ductal carcinoma and six cases of other types. In the NOM

Table III. Summary of P-values.

Clinical features	PRE	POST	NALNM	ALNM	BM	LIM	LUM	BRM	Whole
CEA	<0.001	0.009	0.079	<0.001	0.095	0.009	0.047	0.160	<0.001
CA125	<0.001	0.002	0.213	<0.001	0.019	0.061	0.023	0.012	<0.001
CA153	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CA199	0.375	0.350	0.920	0.646	0.704	0.735	0.175	0.052	0.792
ALP	<0.001	0.391	0.053	0.000	0.222	0.036	0.102	0.045	<0.001
Calcium	0.688	0.622	<0.001	0.235	0.980	0.761	0.068	0.155	0.958

These were the P-values of all subgroup analyses. PRE, premenopausal; POST, postmenopausal; NALNM, non-axillary lymph node metastases; ALNM, axillary lymph node metastases; BM, bone metastases; LIM, liver metastases; LUM, lung metastases; BRM, brain metastases; CEA, carcinoembryonic antigen; CA, cancer antigen; ALP, alkaline phosphatase.

Table IV. Binary logistic regression analysis.

Factors	B	Exp(B)	Exp(B) 95% CI	P-value
CEA	-0.020	0.998	0.992-1.003	0.458
CA125	0.001	1.001	0.998-1.004	0.464
CA153	0.028	1.029	1.018-1.039	<0.001
CA199	0.002	1.002	0.989-1.015	0.759
ALP	0.001	1.001	0.991-1.010	0.892
Calcium	-0.064	0.938	0.266-3.311	0.921

Enter method was used in the binary logistic regression analysis. CI, confidence interval; CEA, carcinoembryonic antigen; CA, cancer antigen; ALP, alkaline phosphatase.

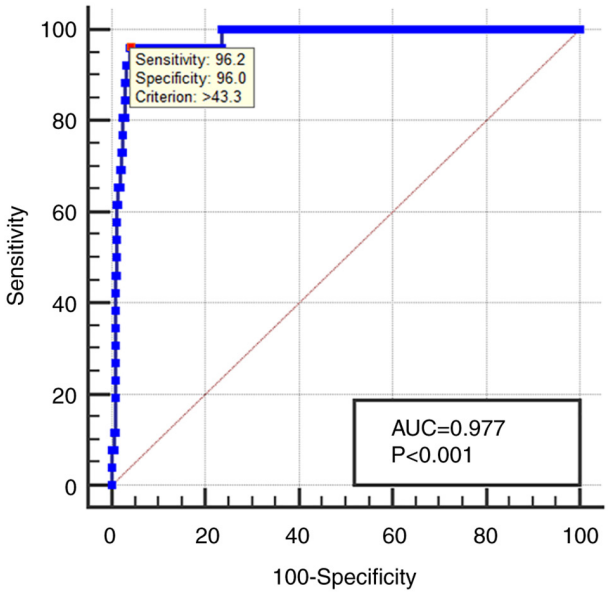

Figure 2. Diagnostic of ocular metastases based on CA153 value. AUC was 0.977 (P<0.001; 95% confidence interval, 0.958-0.995). The cutoff value was 43.3 μ/ml, with a sensitivity of 96.15% and a specificity of 96.02%. AUC, areas under the curve.

group, there were 440 cases of invasive ductal carcinoma and 163 cases of other types. A statistical difference was revealed for ALNM (P<0.001); the OM group contained four cases without ALNM and 22 cases with ALNM, whereas the NOM group contained 259 and 344 cases, respectively. Details are presented in Table I.

Distributions of patients with BC and condition of their distant organ metastases. The top four cities patients came from were Nanchang, Shangrao, Fuzhou, and Jian (marked in red in Fig. 1A). The majority of the patients were from Jiangxi province (marked in red and yellow in Fig. 1A), but there were also 11 patients from other provinces (marked in blue in Fig. 1A). Details of the patient distribution are presented in Fig. 1A.

Numbers of distant organ metastases (bone, liver, lung and brain) in the two groups were counted. Bone was the most common metastatic site for BC, accounting for 25 and 62 cases in the OM and NOM group, respectively (Fig. 1B).

Subgroup analysis and binary logistic regression analysis. To exclude potential confounding by other distant metastases and clarify the diagnostic value of CA153, data were further divided into subgroups. Differences in CA153 levels between the OM group and NOM group were revealed to be statistically significant in each subgroup (Table II). The P-values are summarized in Table III. The binary logistic regression analysis identified CA153 as a risk factor for OM in patients with BC (P<0.001; Table IV).

Sensitivity, specificity, AUC and cutoff value for CA153. A ROC curve for CA153 was established to evaluate its diagnostic value. The AUC for CA153 was 0.977, with a 95% CI of 0.958-0.995. The cutoff value was 43.3 μ/ml, with a corresponding sensitivity of 96.15% and specificity of 96.02% (Fig. 2). Details are presented in Table V.

Discussion

BC has a high incidence of distant metastases and has increased the medical cost burden of our society. Although the widespread use of mammography, PET/CT and MRI has increased the detection rate, there are still some disadvantages (29). Various risk factors and clinical parameters associated with

Table V. Receiver operating characteristic curve analysis.

Variable	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95% CI	P-value
CA153	43.3	96.15	96.02	0.977	0.958-0.995	<0.001

Sensitivity and specificity were obtained at the point of cutoff value. AUC, area under the curve; CI, confidence interval.

Table VI. Literature summary of risk factors for common distant metastases in patients with BC.

Author (Refs.)	Year	Distant metastasis	Risk factors
Slimane *et al* (30)	2004	Brain	Negative hormone receptor status
Cao *et al* (31)	2012	Liver	Lactate dehydrogenase + γ-glutamyltransferase + CA153
Chen *et al* (28)	2017	Bone	Axillary lymph node metastases + CA125 + CA153 + alkaline phosphatase + hemoglobin
Hu *et al* (32)	2017	Lung	CD44v

CA153, cancer antigen 153; CA125, cancer antigen 125.

distant metastases of BC have been taken into consideration to make up for the limitations of these techniques (28,30-32) (Table VI).

Tumor marker serum tests are widely used in patients with cancer to evaluate tumor occurrence and condition. Several studies have already investigated the use of tumor markers in a number of types of cancer. Brand *et al* (33) revealed higher levels of CA199 in patients with pancreatic ductal carcinoma (PDC) compared with healthy controls, indicating that CA199 can be used to diagnose PDC. In Stojkovic's study (34), higher CEA levels are associated with advanced stage in patients with colorectal carcinoma (CRC); the study also demonstrates the use of CEA as a diagnostic factor to predict the severity of CRC. In another study (35), CA125 has been used to diagnose ovarian cancer; the sensitivity and specificity of CA125 according to the ROC curve were 79.6 and 82.5%, respectively. Also, in work by Tang *et al* (36), CA153 has been used in the diagnosis of BC with a sensitivity of 63% and a specificity of 82%.

Notably, tumor markers are also helpful to assess a patient with cancer's risk of distant metastasis. Yuan *et al* (37) observed that CA125 can increase A2780 and OVCAR-3 cell migration, indicating that CA125 may play an important part in tumor metastasis. Moreover, Zhou *et al* (38) revealed CA125 to be an independent risk factor of bone metastases in patients with lung cancer. Cao *et al* (31) revealed that CA153 is useful to predict liver metastasis in patients with BC.

OM is often associated with poor prognosis and low quality of life (39). The incidence of OM in BC has varied among different studies, with rates between 5-30% (40,41). The choroid is the most common site of OM owing to its rich blood supply, followed by the orbit, iris, ciliary body, optic nerve, conjunctiva and eyelid (42). When tumor cells grow in these locations, the substances they produce and release enter the blood and can be tested (43). Thus, tumor markers can well reflect the stage of an OM tumor. However, the diagnostic value of tumor markers in OM of patients with BC remains unclear.

The present study analyzed the differences in basic clinical features and common tumor markers between the OM group and NOM group. Among the basic features, ALNM demonstrated significant differences between the two groups. There were also statistically significant differences in CA153 levels in all subgroups and in the whole group, indicating its diagnostic value as a risk factor for OM in patients with BC.

The present study was the first to evaluate the diagnostic value of CA153 in patients with BC with OM. Compared with patients with NOM, patients with OM had higher CA153 levels. The cutoff value was 43.3 μ/ml, suggesting that patients with BC with CA153 levels higher than this value were at risk of OM. Moreover, the sensitivity and specificity for diagnosing OM in patients with BC were 0.96 and 0.96, respectively. Given the high AUC value (0.977), CA153 represents a relatively high predictive accuracy. As an important specific marker of BC, it is widely used in diagnosis of BC and in assessing prognosis and metastasis (44). In a meta-analysis performed by Tang *et al* (36), the sensitivity and specificity of CA153 in breast secretions for predicting BC were 0.63 and 0.82, respectively. Another meta-analysis conducted by Li *et al* (45), demonstrated that elevated CA153 is associated with shorter disease-free survival times in patients with BC. In a retrospective study performed by Chen *et al* (28), CA153 was revealed to be an independent risk factor for BC bone metastases, with sensitivity and specificity of 0.77 and 0.87, respectively.

Although CA153 is an independent risk factor for both bone metastases and OM, there are differences between the two conditions. First, in the present study, bone metastases were more common, whereas OM was relatively rare. Second,

OM was more likely to occur at an advanced stage, indicating the progression of the disease, whereas bone metastases could be found in early BC. Third, when bone metastases occurred, elevated CA153 and ALP levels were detected, whereas OM was not associated with high levels of ALP. Regarding the diagnostic value of CA153, high levels of CA153 were detected in both metastases, but with some differences. On the one hand, the cutoff values were different. For diagnosing bone metastases, the cutoff value was 25.42 μ/ml, whereas that for OM was 43.3 μ/ml. On the other hand, the sensitivity and specificity for OM were both >95%. Given these differences and clinical symptoms, it is not difficult to distinguish bone metastases from OM.

However, the present study had some limitations. First, as OM is rare, the sample size was relatively small. Second, the majority of participants were from the same province; more studies of patients from different places are needed. Third, although the present study indicated an association between CA153 and OM, it could not identify their causal relationship. Hence, tests from more institutions are necessary to validate the conclusions of the present study. It would also be appropriate to explore the diagnostic value of CA153 in other metastases. Furthermore, associated molecular experiments could be carried out to explore the specific correlations.

The present study clarified CA153 as an independent risk factor for OM in patients with BC. Patients with BC with CA153 >43.3 μ/ml were more likely to have OM. Although CA153 levels had high predictive value for OM according to the present study, CA153 alone was insufficient to diagnose OM in patients with BC. Combining relevant clinical parameters with clinical symptoms would be an improved strategy. However, the present study indicated that physicians should be vigilant when CA153 levels are over the cutoff value. Treatment should be performed in time to avoid severe metastases. These results will help physicians to improve prediction of OM in patients with BC and provide some insight into the specific mechanisms of tumor markers in cancer metastases.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 82160195), Jiangxi Double-Thousand Plan High-Level Talent Project of Science and Technology Innovation (grant no. jxsq2023201036) and the Key R & D Program of Jiangxi Province (grant no. 20223BBH80014).

Data availability and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YS designed the study. QG, QH and JL analyzed and interpreted the patient data. YS and QG confirm the authenticity of all the raw data. QG, QH, JL, QYL and YS made major contributions writing the manuscript. YM, BL, and RL performed the statistical analyses. WS, QL, QY, and QYL collected the clinical data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval no. CDYFY-2015-112). All patients provided written consent to participate.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB, Gerald WL and Massagué J: Genes that mediate breast cancer metastasis to lung. Nature 436: 518-524, 2005.
3. Bacalbasa N, Balescu I, Ilie V, Florea R, Sorop A, Brasoveanu V, Brezean I, Vilcu M, Dima S and Popescu I: The impact on the long-term outcomes of hormonal status after hepatic resection for breast cancer liver metastases. In Vivo 32: 1247-1253, 2018.
4. Oruç Z, Kaplan MA and Arslan Ç: An update on the currently available and future chemotherapy for treating bone metastases in breast cancer patients. Expert Opin Pharmacother 19: 1305-1316, 2018.
5. Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA and Massagué J: Genes that mediate breast cancer metastasis to the brain. Nature 459: 1005-1009, 2009.
6. Liang RB, Yu K, Wu JL, Liu JX, Lin Q, Li B, Zhang YQ, Ge QM, Li QY, Shu HY and Shao Y: Risk factors and their diagnostic values for ocular metastases in invasive ductal carcinoma. Cancer Med 10:824-832, 2021.
7. Georgalas I, Paraskevopoulos T, Koutsandrea C, Kardara E, Malamos P, Ladas D and Papaconstantinou D: Ophthalmic metastasis of breast cancer and ocular side effects from breast cancer treatment and management: Mini review. Biomed Res Int 2015: 574086, 2015.
8. Reddy S, Kurli M, Tena LB and Finger PT: PET/CT imaging: Detection of choroidal melanoma. Br J Ophthalmol 89: 1265-1269, 2005.
9. Razek AA and Elkhamary S: MRI of retinoblastoma. Br J Radiol 84: 775-784, 2011.
10. Shao YH, Tsai K, Kim S, Wu YJ and Demissie K: Exposure to tomographic scans and cancer risks. JNCI Cancer Spectr 4: pkz072, 2019.
11. Martin TA, Ye L, Sanders AJ, Lane J and Jiang WG: Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In: Madame Curie Bioscience Database [Internet]. Landes Bioscience, Austin, TX, 2000-2013.
12. Wagner PD and Srivastava S: New paradigms in translational science research in cancer biomarkers. Transl Res 159: 343-353, 2012.
13. Shimetani N: Status quo of tumor markers and important points in medical practice. Rinsho Byori 51: 1216-1220, 2003 (In Japanese).
14. Kufe DW: Mucins in cancer: Function, prognosis and therapy. Nat Rev Cancer 9: 874-885, 2009.

15. Duffy MJ, Evoy D and McDermott EW: CA 15-3: Uses and limitation as a biomarker for breast cancer. Clin Chim Acta 411: 1869-1874, 2010.
16. Rahn JJ, Dabbagh L, Pasdar M and Hugh JC: The importance of MUC1 cellular localization in patients with breast carcinoma: An immunohistologic study of 71 patients and review of the literature. Cancer 91: 1973-1982, 2001.
17. Hayes DF, Zurawski VR and Kufe DW: Comparison of circulating CA15-3 and carcinoembryonic antigen levels in patients with breast cancer. J Clin Oncol 4: 1542-1550, 1986.
18. Stieber P, Molina R, Chan DW, Fritsche HA, Beyrau R, Bonfrer JM, Filella X, Gornet TG, Hoff T, Jäger W, *et al*: Evaluation of the analytical and clinical performance of the Elecsys CA 15-3 immunoassay. Clin Chem 47: 2162-2164, 2001.
19. Stieber P, Molina R, Chan DW, Fritsche HA, Beyrau R, Bonfrer JM, Filella X, Gornet TG, Hoff T, Jäger W, *et al*: Clinical evaluation of the Elecsys CA 15-3 test in breast cancer patients. Clin Lab 49: 15-24, 2003.
20. Bon GG, von Mensdorff-Pouilly S, Kenemans P, van Kamp GJ, Verstraeten RA, Hilgers J, Meijer S and Vermorken JB: Clinical and technical evaluation of ACS BR serum assay of MUC1 gene-derived glycoprotein in breast cancer, and comparison with CA 15-3 assays. Clin Chem 43: 585-593, 1997.
21. Colomer R, Ruibal A, Genollá J, Rubio D, Del Campo JM, Bodi R and Salvador L: Circulating CA 15-3 levels in the post-surgical follow-up of breast cancer patients and in non-malignant diseases. Breast Cancer Res Treat 13: 123-133, 1989.
22. Symeonidis A, Kouraklis-Symeonidis A, Apostolopoulos D, Arvanitopoulou E, Giannakoulas N, Vassilakos P and Zoumbos N: Increased serum CA-15.3 levels in patients with megaloblastic anemia due to vitamin B12 deficiency. Oncology 67: 359-367, 2004.
23. Molina R, Auge JM, Farrus B, Zanón G, Pahisa J, Muñoz M, Torne A, Filella X, Escudero JM, Fernandez P and Velasco M: Prospective evaluation of carcinoembryonic antigen (CEA) and carbohydrate antigen 15.3 (CA 15.3) in patients with primary locoregional breast cancer. Clin Chem 56: 1148-1157, 2010.
24. Duffy MJ, Duggan C, Keane R, Hill AD, McDermott E, Crown J and O'Higgins N: High preoperative CA 15-3 concentrations predict adverse outcome in node-negative and node-positive breast cancer: Study of 600 patients with histologically confirmed breast cancer. Clin Chem 50: 559-563, 2004.
25. Peng S, Huang P, Yu H, Wen Y, Luo Y, Wang X, Zhou J, Qin S, Li T, Chen Y, *et al*: Prognostic value of carcinoembryonic antigen level in patients with colorectal cancer liver metastasis treated with percutaneous microwave ablation under ultrasound guidance. Medicine (Baltimore) 97: e0044, 2018.
26. Zhao T and Hu W: CA125 and HE4: Measurement tools for ovarian cancer. Gynecol Obstet Invest 81: 430-435, 2016.
27. Zheng BH, Yang LX, Sun QM, Fan HK, Duan M, Shi JY, Wang XY, Zhou J, Fan J, Ma ZY and Gao Q: A new preoperative prognostic system combining CRP and CA199 for patients with intrahepatic cholangiocarcinoma. Clin Transl Gastroenterol 8: e118, 2017.
28. Chen WZ, Shen JF, Zhou Y, Chen XY, Liu JM and Liu ZL: Clinical characteristics and risk factors for developing bone metastases in patients with breast cancer. Sci Rep 7: 11325, 2017.
29. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, Zaguia A, Koundal S and Belay A: Global increase in breast cancer incidence: Risk factors and preventive measures. Biomed Res Int 2022: 9605439, 2022.
30. Slimane K, Andre F, Delaloge S, Dunant A, Perez A, Grenier J, Massard C and Spielmann M: Risk factors for brain relapse in patients with metastatic breast cancer. Ann Oncol 15: 1640-1644, 2004.
31. Cao R and Wang LP: Serological diagnosis of liver metastasis in patients with breast cancer. Cancer Biol Med 9: 57-62, 2012.
32. Hu J, Li G, Zhang P, Zhuang X and Hu G: A CD44v subpopulation of breast cancer stem-like cells with enhanced lung metastasis capacity. Cell Death Dis 8: e2679, 2017.
33. Brand RE, Nolen BM, Zeh HJ, Allen PJ, Eloubeidi MA, Goldberg M, Elton E, Arnoletti JP, Christein JD, Vickers SM, *et al*: Serum biomarker panels for the detection of pancreatic cancer. Clin Cancer Res 17: 805-816, 2011.
34. Stojkovic Lalosevic M, Stankovic S, Stojkovic M, Markovic V, Dimitrijevic I, Lalosevic J, Petrovic J, Brankovic M, Pavlovic Markovic A and Krivokapic Z: Can preoperative CEA and CA19-9 serum concentrations suggest metastatic disease in colorectal cancer patients? Hell J Nucl Med 20: 41-45, 2017.
35. Dayyani F, Uhlig S, Colson B, Simon K, Rolny V, Morgenstern D and Schlumbrecht M: Diagnostic performance of risk of ovarian malignancy algorithm against CA125 and HE4 in connection with ovarian cancer: A meta-analysis. Int J Gynecol Cancer 26: 1586-1593, 2016.
36. Tang S, Wei L, Sun Y, Zhou F, Zhu S, Yang R, Huang Y, Zhang H, Xu H and Yang J: CA153 in breast secretions as a potential molecular marker for diagnosing breast cancer: A meta analysis. PLoS One 11: e0163030, 2016.
37. Yuan Q, Song J, Yang W, Wang H, Huo Q, Yang J, Yu X, Liu Y, Xu C and Bao H: The effect of CA125 on metastasis of ovarian cancer: Old marker new function. Oncotarget 8: 50015-50022, 2017.
38. Zhou Y, Yu QF, Peng AF, Tong WL, Liu JM and Liu ZL: The risk factors of bone metastases in patients with lung cancer. Sci Rep 7: 8970, 2017.
39. Lin Q, Chen XY, Liu WF, Zhu PW, Shi WQ, Li B, Yuan Q, Min YL, Liu JM and Shao Y: Diagnostic value of CA-153 and CYFRA 21-1 in predicting intraocular metastasis in patients with metastatic lung cancer. Cancer Med 9: 1279-1286, 2020.
40. Kreusel KM, Wiegel T, Stange M, Bornfeld N and Foerster MH: Intraocular metastases of metastatic breast carcinoma in the woman. Incidence, risk factors and therapy. Ophthalmologe 97: 342-326, 2000 (In German).
41. Nelson CC, Hertzberg BS and Klintworth GK: A histopathologic study of 716 unselected eyes in patients with cancer at the time of death. Am J Ophthalmol 95: 788-793, 1983.
42. Demirci H, Shields CL, Chao AN and Shields JA: Uveal metastasis from breast cancer in 264 patients. Am J Ophthalmol 136: 264-271, 2003.
43. Tarro G, Perna A and Esposito C: Early diagnosis of lung cancer by detection of tumor liberated protein. J Cell Physiol 203: 1-5, 2005.
44. Lu F, Pan S, Qi Y, Li X and Wang J: The clinical application value of RDW, CA153, and MPV in breast cancer. Clin Lab 67, 2021.
45. Li X, Dai D, Chen B, Tang H, Xie X and Wei W: Clinicopathological and prognostic significance of cancer antigen 15-3 and carcinoembryonic antigen in breast cancer: A Meta-analysis including 12,993 patients. Dis Markers 2018: 9863092, 2018.