http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 13 (4): 175-179, 2010
ISSN 1028-8880

Comparison of Bone Scan with Carbohydrate Antigen 15-3 for Evaluation of Bone Metastasis of Brest Cancer

M. Mohammadzadeh, H. Alikhah and A.G.A. Zareh
Department of Radiology-Radiotherapy-Nuclear Medicine, Imam Khomeini Hospital,
Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: This study aimed at comparing the bone scan and CA15-3 titer in patients with breast cancer for evaluation of bone metastasis. Thirty five patients with definite diagnosis of breast cancer were evaluated in Tabriz Imam Khomeini Hospital from 2007 to 2008. Bone scan (99 mTc-MDP) performed in all patients. The serum CA15-3 was measured by ECLIA method. The increased level was considered as >30 U mL^{-1}. The serum level of CA15-3 was compared between the patients with and without bone metastasis, as well as its correlation with the extent of bone involvement. Thirty five patients with the mean age of 51.69±10.77 (34-81) years were enrolled in the study. According to bone scan results, 24 (68.8%) patients revealed bone metastasis. The mean level of serum CA15-3 was significantly higher in patents with bone metastasis than patients without metastasis (26.37±4.74 U mL^{-1} vs. 19.09±1.99 U mL^{-1}; $p<0.001$). There was not significant relation between the serum level of CA15-3 and the extent of bone metastasis (rho = -0.063, p = 0.769). Coordinates of the curve study yielded a cut-off point > 21.8 U mL^{-1} for the serum level of CA15-3 in our patients, with a sensitivity and specificity of 91.7 and 91%, respectively. Serum level of CA15-3 is higher in the patients with bone metastatic breast cancer; however, the recommended cut-off point might not be suitable for Iranian patients. Further studies with large sample sizes are recommended.

Key words: Metastasis, scintigraphy, tumor marker, oncology

INTRODUCTION

Tumor markers are frequently used for screening and monitoring in oncology. Carbohydrate antigen 15-3 (CA 15-3) is a tumor marker commonly used in the screening, early detection and monitoring of treatment for breast cancers (Velaiutham *et al*., 2008; Agyei Frempong *et al*., 2008; Uehara *et al*., 2008). Significant differences in CA 15-3 expression levels between those in benign tumors and those in stage III and IV disease have been reported. There was a positive correlation between CA 15-3 levels and patient prognosis (Uehara *et al*., 2008).

Breast cancer is a disease that commonly metastasizes to bone, increasing morbidity, mortality and health service costs (Cook and Fogelman, 1999; O'Brien *et al*., 1992; Gedik *et al*., 2006). The 99 m technetium (99 mTc) diphosphonate bone scan historically has played a significant role in the evaluation of skeletal disease and continues to be one of the most clinically used investigations in the staging and follow up of breast cancer patients (Cook and Fogelman, 1999; O'Brien *et al*., 1992). The detection of bone metastasis has both prognostic and therapeutic significance and early detection in the asymptomatic case may alert the clinician to the possible complications inherent in skeletal destruction (O'Brien *et al*., 1992; Gedik *et al*., 2006).

CA15-3 is a circulating human breast tumor associated antigen defined and assayed by two monoclonal antibodies (O'Brien *et al*., 1992; Estrada-Sánchez *et al*., 2003; Ruibal *et al*., 2006). The CA15-3 levels are known to correlate well with the disease stage in breast carcinoma (Estrada-Sánchez *et al*., 2003; Nicolini *et al*., 1999, 2003; Gion *et al*., 2001; Tomlinson *et al*., 1995). However, its value as an indicator or predictor of metastatic bone disease has yet to be fully elucidated. The aim of this study was to evaluate the reliability of CA15-3 as a marker of secondary bony deposits in breast cancer patients.

MATERIALS AND METHODS

A descriptive analytic study was performed on patients with breast cancer presenting to

Corresponding Author: Hossein Alikhah, Tabriz University of Medical Sciences, Post Box 31385-4699, Tabriz, Iran
Tel: 0098 914 315 0150 Tel/Fax: 0098 411 668 8369

Radiology-Oncology Department and Nuclear Medicine Departments of Tabriz Imam Khomeini Hospital from 2007 to 2008. Thirty five consecutive patients with definite histopathologic diagnosis of breast cancer and bone metastasis certified by bone scintigraphy were selected for evaluation of bone scan findings and serum CA15-3 level.

The patients underwent bone scan 3-4 h following intravenous injection of 15-20 mCi of technetium 99 m methylene diphosphonate (99 mTc-MDP) using a gama camera equipped with a low energy, high resolution collimator (General Electric, Infinia and ADAC, Philips). The photopeak was centered at 140 keV with a 20% window. The bone scans were evaluated by 2 experienced nuclear medicine physicians. One milliliter venous blood was sampled from patients and sent to laboratory for measurement of serum CA15-3 by electrochemiluminescence (ECLIA). Bone scintigraphy was considered as gold standard for diagnosis of bone metastasis in patients with breast cancer. Elevated serum level of CA15-3 was considered if more than 30 U mL^{-1}.

All patients signed informed consent and they did not pay any additional cost for participant in this study. The studied variables were age, site of bone involvement, area of bone involvement, serum level of CA15-3 and abnormal levels of CA15-3. New cut-off point for CA15-3 was determined using ROC diagram.

The collected data were expressed as Mean±SD and number and percentage. Statistical analysis was made by SPSS 15 statistical software. The quantitative variables were compared by Student t-test (independent samples) or Mann-Whitney U-test. Also, qualitative (Categorical) variables were compared by Contingency tables using Chi-Square test or Fisher's Exact Test. Correlation was assessed by Spearman's rho coefficient. Suitableness of test was assessed by Hosmer and Lemershow test. New cut-off point was determined using ROC diagram and coordinates of the curve. In all instances, p = 0.05 were considered statistically significant.

RESULTS

We studied 35 patients with breast cancer in two Metastatic (Group Y) including 24 cases (68.6%) and Non-metastatic (Group N) including 11 cases (31.4%). The age range of patients was 34-81 years, with average age of 48.73±8.87 years. These measures for Groups Y and N have been showed in Table 1. The differences between groups were not statistically significant (p = 0.278).

Table 2 shows the distribution of regional involvement of bone metastasis in studied patients.

Table 1: Age groups, age range and average age of studied patients

Age (years)	Group Y	Group N	Total
30-39	3 (12.5%)	2 (18.2%)	5 (14.3%)
40-49	8 (33.3%)	3 (27.3%)	11 (31.4%)
50-59	6 (25%)	5 (45.5%)	11 (31.4%)
60-69	5 (20.8%)	1 (9.1%)	6 (17.1%)
70-79	1 (4.2%)	0	1 (2.9)
≥80	1 (4.2%)	0	1 (2.9)
Age range	53.04±11.45	53.04±11.45	48.73±8.87
Average age	35-81	34-67	34-81

Table 2: Distribution of regional involvement and multifocality of bone metastasis in studied patients

	Involvement			Involvement	
Bone	No.	%	Regional distribution	No.	%
Skull	2	8.3	1 region	8	33.3
Face	1	4.2	2 regions	2	8.3
Spine	24	100	3 regions	5	20.8
Rib	9	37.5	4 regions	4	16.7
Scapula	6	25	5 regions	3	12.5
Stemum	5	20.8	6 regions	1	4.2
Upper limb	3	12.5	7 regions	1	4.2
Pelvis	9	37.5			
Lower limb	10	41.7			

The range of serum CA15-3 in total patients was 16.5-41.3 U mL^{-1}, with average of 24.08±5.30 U mL^{-1}. These measures were 26.37±4.74 (20-41) for Group Y and 19.09±1.99 (16.5-22.5) for Group N. The average level of CA15-3 was significantly more in Group Y than Group N (p<0.001).

Of all patients, 32 (91.4%) had normal and 3 (8.6%) had abnormal (elevated) serum CA15-3 level. In metastatic patients (Group Y, n = 24), 21 (87.5%) had normal and 3 (12.5%) had abnormal (elevated) serum CA15-3 level. These Values for non-metastatic patients (Group N, n = 11) were 11 (100%) and 0 (0%), respectively. However, the difference between the groups were not significant (p = 0.536).

Analysis showed that the relation between serum CA15-3 level and area of bone involvement (number of involved bones) was not statistically significant (p = 0.769, rho = -0.063).

Hosmer and Lemershow test showed that use of serum CA15-3 level for evaluation of bone metastasis was suitable (p = 0.999).

We used ROC diagram for anticipation of presence of bone metastasis of breast cancer. With under curve area of 0.964 and p<0.001 (95%CI: 0.91-1.02), this variable is sufficient for this purpose.

We used also table of coordinates of the curve for determination of new cut-off for anticipation of presence of bone metastasis, which revealed the best cut-off of 21.8 U mL^{-1} for this purpose. The sensitivity and specificity in this cut-off were 91.7 and 91%.

In new cut-off, 12 (34.3%) had normal and 23 (65.7%) had abnormal (elevated) serum CA15-3 level. In metastatic

patients (Group Y, n = 24), 22 (91.7%) had normal and 2 (8.3%) had abnormal (elevated) serum CA15-3 level. These values for non-metastatic patients (Group N, n = 11) were 10 (90.9%) and 1 (1.9%), respectively. The number of cases with abnormal CA15-3 was significantly more in Group Y than Group N ($p<0.001$, OR = 110, 95% CI: 8.90-1359.17).

DISCUSSION

The detection of bone metastasis accurately reflects the prognosis and early detection in the asymptomatic case may alert the clinician to the possible complications inherent in skeletal destruction. Preventive measures may be taken to avert or decrease the related morbidity and mortality (O'Brien *et al*., 1992). Radioisotope bone scintigraphy is the most sensitive and the most common method for screening bony metastatic disease (O'Brien *et al*., 1992). In the present study, the results of bone scan and signs of bone involvement were considered as gold standard of diagnosis.

In agreement with this study, Nicolini *et al*. (1999, 2003) showed that in breast cancer patients the CA15-3 tumor marker panel has a high value in selecting patients with bone metastasis, or at high risk of developing clinically-evident bone metastasis, among the large number of subjects with equivocal bone scan. The study of Estrada-Sánchez *et al*. (2003) on 100 women with breast cancer showed that the mean value of CA 15-3 for the patients without metastatic disease is 16.18 U mL^{-1} and for patients with bone metastasis is 164.02 U mL^{-1}. This study also, is compatible with our findings although, the CA15-3 level in their study very high. However, this high difference may be due the fact that all of their patients were in stages III or IV.

The early cut-off in our study was CA15-3>30 U mL^{-1}, which did not show any significant difference between two groups as elevated levels. However, in new cut-off of CA-15-3>21.8 U mL^{-1}, the elevated levels of CA15-3 was significantly more in patients with bone metastasis (sensitivity of 91.7% and specificity of 91%). Gion *et al*. (2001) suggested that determination of new cut-off value for CA15-3 for prediction of bone metastasis is of great importance. Indeed, the cut-off values for CA15-3 for the best prediction of distant metastasis including bone metastasis, are different in these patients: CA15-3>30 (Tomlinson *et al*., 1995; Wojtacki *et al*., 2001), CA15-3>40 (Ruibal *et al*., 2006), CA15-3>25 (Buffaz *et al*., 1999), CA15-3>35 (Estrada-Sánchez *et al*., 2003), CA15-3>38 (Giai *et al*., 1996), CA15-3>32 (Duncan *et al*., 1991) and CA15-3>10 (Gion *et al*., 2002). This high range of diversity may cause from some reasons including sample size (Petrie and Sabin, 2009) so, that increasing sample size results in more accurate findings. However, the laboratory method used for measurement of CA15-3, is another element that can cause different accuracies and different results. We used ECLIA method.

Tomlinson *et al*. (1995) showed that all patients with a positive bone scan and raised levels of CA15-3 were subsequently confirmed as having bony metastasis; no patient with normal bone scan and normal CA15-3 developed M+ disease. CA15-3 levels were raised in 83% of patients who developed non-bony distant metastasis.

Wojtacki *et al*. (2001) assayed CA15-3 concentrations immuno-enzymatically in 733 women with breast carcinoma. In patients with distant metastasis, mean serum CA15-3 values and the percentage of positive results were significantly higher as compared to cases with locoregional relapse and carcinoma of the contralateral breast and those without clinical evidence of relapse. The highest CA15-3 values were observed in patients with liver and multiple metastasis. The CA15-3 sensitivity rates were higher in patients with bone metastasis (91.4%). The study confirmed the validity of serial CA15-3 assays in the early diagnosis of breast metastatic disease (Wojtacki *et al*., 2001).

O'Brien *et al*. (1992) evaluated 218 patients with breast cancer over a 4-year period. Of these patients, 33 with metastatic breast carcinoma had an elevated tumor marker level at the time of diagnosis of their metastasis; bone metastasis alone (88%), soft tissue metastasis alone (33%), simultaneous bone and soft tissue metastasis (70%). All metastatic bone disease patients demonstrated elevated marker levels, in agreement with previous studies (Nicolini *et al*., 2000, 2006; Arslan *et al*., 2000; Giovanella *et al*., 2002; O'Hanlon *et al*., 1995; Hou *et al*., 1995, 1999). They recommend CA15-3 as a simple, reliable and inexpensive screening method for detecting bone metastasis in the patient with breast carcinoma (O'Brien *et al*., 1992). Inversely, Giai *et al*. (1996) showed the elevated levels of CA 15.3 were mainly related to visceral metastasis. Gion *et al*. (1991) concluded from the present findings that CA15.3 in primary untreated breast cancer is a marker of tumor burden as well as of the tendency of local invasiveness.

Yildiz *et al*. (2004) concluded that although serial tumor marker measurements are an efficient and cost effective method of monitoring disease progression, it does not allow prediction of the bone scan results; so it is not justifiable to reject a bone scan on the basis of these markers.

In agreement with Giai *et al*. (1996), this study revealed no significant relation between serum CA15-3 concentrations and multifocality or regional involvement

of bone metastasis. However, other studies have demonstrated higher sensitivity of the CA15-3 test in detecting multiple bone metastasis (Wojtacki *et al*., 2001; Duncan *et al*., 1991) although, the group of patients was too small to make our observation conclusive.

However, the confounding factors have been considered in this issue: CA15-3 level has been related with tumor size (Ruibal *et al*., 2006; Martín *et al*., 2006) as well as primary untreated tumor (Gion *et al*., 1991) and biological characteristics of tumor such as estrogen or progesterone receptor status (Nishimura *et al*., 2003) although, showed that Duncan *et al*. (1991) there was no association between the CA15.3 concentration and the apparent tumor load. The anatomical type of bone has no any effect on serum tumor marker concentration between patients with normal and elevated levels of tumor markers in metastatic patients (Gedik *et al*., 2006). Also, Gion *et al*. (1991) found no relationships between serum CA15-3 and receptor status, but CA15-3 was significantly higher in medullary than in ductal carcinoma (Gion *et al*., 1991). Gion *et al*. (2001) in another study, showed that the time of CA15-3 measurement during the follow-up period is effective on the achieved results. In patients with metastatic disease and normal CA 15-3, the tumor marker will increase gradually (Estrada-Sánchez *et al*., 2003). Younsi *et al*. (1997) in a retrospective study of the clinical records of 158 women followed for breast cancer, showed that those patients with normal CA 15-3 levels and positive bone scans showed a subsequent rise in CA 15-3 levels which frequently became elevated with a average delay of 15 months.

CA15-3 tumor marker panel can be used as a preliminary screen to select patients who need further radiological investigation, thus, confirming its important role in the postoperative follow-up of breast cancer patients. However, the use of this tumor marker alone in decision making and clinical management is not recommended (Gedik *et al*., 2006; Estrada-Sánchez *et al*., 2003; Tomlinson *et al*., 1995; Wojtacki *et al*., 2001; Nicolini *et al*., 2006; Yildiz *et al*., 2004). The CA15-3 might be assayed alongside a bone scan to confirm positive or negative results. Another role might be screening for breast cancer metastasis in departments with limited access to bone scans and other imaging facilities. The CA15-3 might also be used in monitoring for the development of distant metastasis during follow-up. It is, however, unlikely that CA15-3 can substitute directly for a bone scan or other imaging currently used routinely by clinicians (Tomlinson *et al*., 1995). The early detection of recurrent foci may be accomplished using such highly sensitive tumor marker together with modern imaging technologies (Uehara *et al*., 2008).

On the basis of the present results, before considering CA15-3 for clinical decision-making, further studies should be performed on other independent case series to confirm the observed prognostic relationships. Clinical trials are now necessary to determine the effect of using tumor markers such as CA15-3 on patient morbidity and mortality.

CONCLUSION

In conclusion, CA15-3 tumor marker panel can be used as a preliminary screen to select patients who need further radiological investigation, thus, confirming its important role in the postoperative follow-up of breast cancer patients. This study showed that the serum level of CA 15-3 antigen is higher in the patients with bone metastatic breast cancer; however, the recommended cut-off point might not be suitable for Iranian patients. Further studies with large sample sizes are recommended.

REFERENCES

Agyei Frempong, M.T., E. Darko and B.W. Addai, 2008. The use of Carbohydrate Antigen (CA) 15-3 as a tumor marker in detecting breast cancer. Pak. J. Biol. Sci., 11: 1945-1948.

Arslan, N., M. Serdar, S. Deveci, B. Ozturk and Y. Narin *et al*., 2000. Use of CA15-3, CEA and prolactin for the primary diagnosis of breast cancer and correlation with the prognostic factors at the time of initial diagnosis. Ann. Nucl. Med., 14: 395-399.

Buffaz, P.D., A.S. Gauchez, J.P. Caravel, J.P. Vuillez, C. Cura, C. Agnius-Delord and D. Fagret, 1999. Can tumour marker assays be a guide in the prescription of bone scan for breast and lung cancers? Eur. J. Nucl. Med., 26: 8-11.

Cook, G.J. and I. Fogelman, 1999. Skeletal metastasis from breast cancer: Imaging with nuclear medicine. Semin. Nucl. Med., 29: 69-79.

Duncan, J.L., A. Price and K. Rogers, 1991. The use of CA15.3 as a serum tumour marker in breast carcinoma. Eur. J. Surg. Oncol., 17: 16-19.

Estrada-Sánchez, D.R.G., M.M. Enriquez and N.V. Castaneda, 2003. Reliability of CA 15-3 in the follow up of female patients with breast carcinoma and bone metastasis. Rev. Invest. Clin., 55: 412-418.

Gedik, G.K., P.O. Kiratli, B. Tascioglu and T. Aras, 2006. Comparison of bone scintigraphy with serum tumor markers of CA 15-3 and carcinoembryonic antigen in patients with breast carcinoma. Saudi Med. J., 27: 317-322.

Giai, M., R. Roagna, R. Ponzone, N. Biglia, L. Sgro, M. Perona and P. Sismondi, 1996. TPS and CA 15.3 serum values as a guide for treating and monitoring breast cancer patients. Anticancer Res., 16: 875-881.

Gion, M., R. Mione, O. Nascimben, M. Valsecchi, C. Gatti, A. Leon and G. Bruscagnin, 1991. The tumour associated antigen CA15.3 in primary breast cancer. Evaluation of 667 cases. Br. J. Cancer, 63: 809-813.

Gion, M., L. Peloso, R. Mione, G. Vignati and A. Fortunato *et al*., 2001. Tumor markers in breast cancer monitoring should be scheduled according to initial stage and follow-up time: a prospective study on 859 patients. Cancer J., 7: 181-190.

Gion, M., P. Boracchi, R. Dittadi, E. Biganzoli and L. Peloso *et al*., 2002. Prognostic role of serum CA15.3 in 362 node-negative breast cancers: An old player for a new game. Eur. J. Cancer, 38: 1181-1188.

Giovanella, L., L. Ceriani, G. Giardina, D. Bardelli, F. Tanzi and S. Garancini, 2002. Serum cytokeratin fragment 21.1 (CYFRA 21.1) as tumour marker for breast cancer: Comparison with carbohydrate antigen 15.3 (CA 15.3) and carcinoembryonic antigen (CEA). Clin. Chem. Lab. Med., 40: 298-303.

Hou, M.F., T.J. Huang, J.S. Hsieh, Y.S. Huang and C.J. Huang *et al*., 1995. Comparison of serum CA15-3 and CEA in breast cancer. Gaoxiong Yi Xue Ke Xue Za Zhi., 11: 660-666.

Hou, M.F., Y.L. Chen, T.F. Tseng, C.M. Lin and M.S. Chen *et al*., 1999. Evaluation of serum CA27.29, CA15-3 and CEA in patients with breast cancer. Kaohsiung J. Med. Sci., 15: 520-528.

Martín, A., M.D. Corte, A.M. Alvarez, J.C. Rodriguez and A. Andicoechea *et al*., 2006. Prognostic value of pre-operative serum CA 15.3 levels in breast cancer. Anticancer Res., 26: 3965-3971.

Nicolini, A., P. Ferrari, A. Sagripanti and A. Carpi, 1999. The role of tumour markers in predicting skeletal metastasis in breast cancer patients with equivocal bone scintigraphy. Br. J. Cancer, 79: 1443-1447.

Nicolini, A., A. Carpi, P. Ferrari, L. Anselmi, C. Spinelli, M. Conte and P. Miccoli, 2000. The role of tumour markers in improving the accuracy of conventional chest X-ray and liver echography in the post-operative detection of thoracic and liver metastasis from breast cancer. Br. J. Cancer, 83: 1412-1417.

Nicolini, A., A. Carpi, P. Ferrari and L. Pieri, 2003. Utility of a serum tumour marker panel in the post-operative follow-up of breast cancer patients with equivocal conventional radiological examinations. Tumour. Biol., 24: 275-280.

Nicolini, A., G. Tartarelli, A. Carpi, M.R. Metelli and P. Ferrari *et al*., 2006. Intensive post-operative follow-up of breast cancer patients with tumour markers: CEA, TPA or CA15.3 vs MCA and MCA-CA15.3 vs CEA-TPA-CA15.3 panel in the early detection of distant metastasis. BMC Cancer, 6: 269-269.

Nishimura, R., K. Nagao, H. Miyayama, M. Matsuda, K. Baba, Y. Matsuoka and H. Yamashita, 2003. Elevated serum CA15-3 levels correlate with positive estrogen receptor and initial favorable outcome in patients who died from recurrent breast cancer. Breast. Cancer, 10: 220-227.

O'Brien, D.P., P.G. Horgan, D.B. Gough, R. Skehill, H. Grimes and H.F. Given, 1992. CA15-3: A reliable indicator of metastatic bone disease in breast cancer patients. Ann. R. Coll. Surg. Engl., 74: 9-11.

O'Hanlon, D.M., M.J. Kerin, P.J. Kent, R. Skehill, D. Maher, H. Grimes and H.F. Given, 1995. A prospective evaluation of CA15-3 in stage I carcinoma of the breast. J. Am. Coll. Surg., 180: 210-212.

Petrie, A. and C. Sabin, 2009. Medical Statistics at a Glance. 3rd Edn., John Wiley and Sons, London, ISBN: 140518051X, pp: 20-48.

Ruibal, A., M.G. Pumar and J.I. Arias, 2006. Preoperative serum CA15.3 and CEA levels and clinical-biological parameters in breast tumors. Rev. Esp. Med. Nucl., 25: 180-183.

Tomlinson, I.P., A. Whyman, J.A. Barrett and J.K. Kremer, 1995. Tumour marker CA15-3: Possible uses in the routine management of breast cancer. Eur. J. Cancer, 31: 899-902.

Uehara, M., T. Kinoshita, T. Hojo, S. Akashi-Tanaka, E. Iwamoto and T. Fukutomi, 2008. Long-term prognostic study of carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in breast cancer. Int. J. Clin. Oncol., 13: 447-451.

Velaiutham, S., N.A. Taib, K.L. Ng, B.K. Yoong and C.H. Yip, 2008. Does the pre-operative value of serum CA15-3 correlate with survival in breast cancer? Asian Pac. J. Cancer Prev., 9: 445-448.

Wojtacki, J., W.J. Kruszewski, M. Sliwinska, E. Kruszewska and W. Hajdukiewicz *et al*., 2001. Elevation of serum Ca 15-3 antigen: An early indicator of distant metastasis from breast cancer. Retrospective analysis of 733 cases. Przegl. Lek., 58: 498-503.

Yildiz, M., B. Oral, M. Bozkurt and A. Cobaner, 2004. Relationship between bone scintigraphy and tumor markers in patients with breast cancer. Ann. Nucl. Med., 18: 501-505.

Younsi, N., F. Montravers, C. Philippe, M. Seddiki, S. Uzan, V. Izrael and J.N. Talbot, 1997. CA 15-3 and bone scintigraphy in the follow-up of breast cancer. Int. J. Biol. Markers, 12: 154-157.