Scholars LITERATURE

Journal of Clinical Oncology and Therapeutics

Research Article

DOI: https://doi.org/10.47275/2690-5663-138
Volume 7 Issue 1

Alkaline Phosphatase as a Biomarker for Metastatic Breast Cancer

Hiba Jumaa Abdul-Khaliq[1], Mohammed Ali Khudair[1*], Khudair Jassim Al-Rawaq[2] and Ahmed Salih Alshewered[3]

[1]Oncology and Nuclear Medicine Center, Al-Imam Al-Sadiq Teaching Hospital, Babylon Health Directorate, Ministry of Health, Babylon, Iraq
[2]Department of Surgery, College of Medicine, University of Baghdad, Baghdad, Iraq
[3]Misan Radiation Oncology Center, Misan Health Directorate, Ministry of Health, Misan, Iraq

Abstract

Breast cancer is the most common malignancy in women worldwide and the leading type of cancer among Iraqi women with a rapidly rising incidence. Different breast cancers have different prognoses and treatment requirements, therefore, staging allowed reliable distinction between those differences. Early detection is essential for its cure. However, most cancers produce symptoms after the tumor is too large for surgical removal or after metastasis. This necessitates the need for non-invasive and sensitive methods for early detection. Changes in serum alkaline phosphatase (ALP) level may be useful in the diagnosis and follow up of breast cancer. The aim of the study is to assess the relationship between increased serum ALP level and the occurrence of metastasis in breast cancer patients, and to assess the possibility to use this enzyme as a biomarker for the detection of metastasis in breast cancer. This study is a case-control study conducted from December 2017 through April 2018 and included 140 patients with breast cancer. 70 of them had metastasis (cases) and 70 had no metastasis (controls). Blood samples were collected to determine serum ALP level. Statistical analysis has shown that there is statistically significant difference in the ALP level for cases with metastasis ($M = 320.5$, $SD = 254.9$) and controls ($M = 85.1$, $SD = 34.9$) who have no metastasis; $t(138) = 7.65$, and $p < 0.001$. Serum ALP level is an important diagnostic tool for monitoring of progression of breast cancer, and it could be used as a biomarker for detection of metastasis in breast cancer patients.

Keywords: Alkaline phosphatase, Breast cancer, Metastasis

[*]***Correspondence to:*** Mohammed Ali Khudair, Oncology and Nuclear Medicine Center, Al-Imam Al-Sadiq Teaching Hospital, Babylon Health Directorate, Ministry of Health, Babylon, Iraq.

Citation: Abdul-Khaliq HJ, Khudair MA, Al-Rawaq KJ, Alshewered AS (2025) Alkaline Phosphatase as a Biomarker for Metastatic Breast Cancer. J Clin Oncol Ther, Volume 7:1. 138. DOI: https://doi.org/10.47275/2690-5663-138

Received: November 13, 2024; **Accepted:** January 08, 2025; **Published:** January 10, 2025

Introduction

ABreast cancer is the most common malignant disease in women worldwide [1]. It is considered the most common type of cancer in both developing and developed countries, and is the fifth cause of cancer mortality in the world [2]. In Iraq it is the leading type of cancer among Iraqi women, accounting for one-third of the total registered female cancer patients in Iraq [3], with a rapidly rising incidence among Iraqi population [4].

Breast cancer patients who are presented with locally advanced disease require management by a multidisciplinary team that utilizes diagnostic imaging, chemotherapy, surgical intervention, and pathological assessment. The outcome of treatment for each patient could depend on the level of integration of this multidisciplinary approach in addition to the experience of the team members. Coordination between those members is of particular importance in the management of those patients with locally advanced breast cancer, because those patients have a high risk of recurrence of the disease if no optimal treatment was provided. However, the outcome of patients with locally advanced disease has improved recently with the routine use of chemotherapy. Before the routine use of chemotherapy there was a high rate of distant metastases and death among patients treated with mastectomy or radiation [5].

Early detection of breast cancer is essential for its cure. Cancers that are detected early when the tumor is still small in size can potentially be cured by complete surgical removal [6]. However, most cancers produce symptoms only after the tumor is too large for surgical removal or after the spread of cancerous cells to other tissues by metastasis [7].

These facts necessitate the need for non-invasive and sensitive methods for early detection of malignant diseases. This can be achieved by measuring certain products and metabolites that are associated with the malignant tumor [7, 8]. These products are called tumor markers, and are useful for screening of populations, diagnosing, staging and prognosis. Tumor markers are also useful for detecting the presence of occult metastatic disease and to monitor the response to treatment [8].

Breast cancer has different types that exhibit variable histopathological and biological features, with difference in clinical response and outcome. The histopathological classification is adopted worldwide and is based on the diversity of the morphological features of the disease. It classifies the disease into either invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), or not otherwise specified [9]. Different breast cancers have different prognoses and different treatment requirements; therefore, certain characteristics have been defined that allow reliable distinction between those that require aggressive treatment and follow-up from those that don't [10].

To investigate for the disease, a complete history is essential, followed by triple assessment which include physical examination, radiological investigation, and needle biopsy. It is preferred to use core biopsy rather than fine-needle aspiration since the core biopsy

provides a histological diagnosis and can be used for differentiation between invasive and in situ carcinoma. Also, it is possible to test for estrogen receptor, progesterone receptor and human epidermal growth factor status using biopsy specimen. Other investigations include full blood count, liver function tests, and calcium level in serum [11]. Routine staging of asymptomatic patients with T1 or T2 primary breast cancer is not indicated. However, staging investigations are performed in patients with advanced disease since it may affect management, and these investigations include chest X-ray, liver ultrasonography, bone scan, computed tomography (CT) scan of thorax or abdomen, and magnetic resonance imaging (MRI) scanning [12]. Also, there is growing interest in the use of 18F-fluirodeoxyglucose positron emission tomography (PET)/CT in the staging of disease in patients with locally invasive breast cancer, especially in inflammatory disease. In a study conducted on 41 females with inflammatory breast cancer, it was found that PET/CT could detect distant metastases that could not be detected by other studies in 17% of the study participants [13].

Therefore, changes in serum ALP level may be useful in the diagnosis and follow up of breast cancer [14]. The level of ALP in serum normally varies with age, generally as a result of bone growth and development. It is found to be higher in childhood and puberty, followed by a decline after the age of 15, then rise again after the age of 50. It is also slightly higher in males than in females. As a serum protein, ALP has a half-life of 7 days, but the site of its degradation is not known [15].

Various methods exist for determining the level of serum ALP. The difference among those methods is generally in the used substrate, alkaline buffer pH value, and the resulting normal values. The main principle for these tests is based on the ability of ALP to hydrolyze phosphate esters. The most commonly used method worldwide uses p-nitrophenyl phosphate as a substrate, with amino-alcohol as the buffer. The activity of ALP is detected by measuring the rate of release of either phosphate or p- nitrophenol from the substrate, and the result is given in IU/L. Those various methods seem to have similar effectiveness in measuring abnormalities in ALP level [15].

When ALP is elevated alone or elevated out of proportion with other liver enzymes; evaluation of the patient should be directed towards the identification of the cause of this elevation and the source of abnormality. Highest elevations (up to 4-fold increase of the upper normal value) are usually seen in cases with cholestasis, whether intrahepatic or extrahepatic. Such high increases are also seen in other conditions including biliary obstruction resulting from malignancy. Certain infections such as cytomegalovirus or cryptosporidiosis especially in AIDS patients are also associated with high levels of ALP. Moderate elevations are usually considered non-specific and may be associated with various conditions including liver cirrhosis, viral hepatitis, congestive heart failure, and certain malignancies [15]. Malignancy may raise ALP level by several mechanisms: it may locally obstruct the bile duct, increasing the leakage of liver isoenzyme. It may produce its own ALP such as Hodgkin lymphoma. Or it may have certain paraneoplastic effect that causes the hepatic isoenzyme to leak into the circulation [15].

Management of early breast cancer in primary disease is done with surgery, specifically modified radical mastectomy, which involves the surgical removal of the entire breast, areola and nipple. It is commonly accompanied by axillary dissection of lymph nodes. While breast conservation therapy comprises wide local excision and postoperative radiotherapy. Similar outcomes were found for either approach [16, 17].

Patients with invasive breast cancer usually undergo axillary dissection, which was the preferred technique until recently, and required at least 10 lymph nodes for the pathologic evaluation in order to stage the axilla accurately [18]. Clearance of axillary node comprise clearing the contents of axilla contained within the following boundaries: anteriorly pectoralis muscles, posteriorly teres major, latissimus dorsi and subscapularis, medially chest wall, laterally the axillary skin, and superiorly the lower border of axillary vein. Certain complications are associated with axillary node clearance including pain and numbness in axilla, chronic lymphoedema, and limitation in the movement of the arm [11].

Bisphosphonates are given for patients with bone metastasis to relieve the pain and reduce the skeletal-related events frequency. Other localized problem may arise in patients with metastatic breast cancer, requiring certain treatment modalities including radiotherapy, surgery, or regional chemotherapy [11].

The aim of this study is to assess the relationship between increased serum ALP level and the occurrence of metastasis in breast cancer patients, and to assess the possibility to use this enzyme as a biomarker for the detection of metastasis in breast cancer.

Methods

This study is an analytical case-control study conducted from November 2017 through April 2018. It included a total of 140 patients from Oncology Teaching Hospital in Medical City, Baghdad, who were already diagnosed with breast cancer. 70 of these patients had metastasis cases and 70 had no metastasis at time of data collection (controls).

Blood samples from study participants were collected to determine serum ALP level, 5 ml of blood were drawn from participants into a plain tube or gel tube, then the blood sample was centrifuged within 5 min in order to obtain blood serum. About 200 µl of the resulting supernatant (serum) is transferred to the integrated chemistry system Siemens® Dimension® RxL Max®, which gives the result of ALP level in serum within 10 min. Normal value of serum ALP in the laboratory used in the study is 46 - 110 IU/L.

The inclusion criteria for the study were female patients with breast cancer who are older than 18 years. Exclusion criteria were patients with hepatitis, liver cirrhosis, liver malignancy, gallstones, or pregnancy.

Patient information was collected using specially constructed interview questionnaire, comprised of the basic demographic information of the patients, clinical history of the participants, disease presentation, diagnosis, and staging.

Statistical analysis

SPSS Software version 23.0 has been used to perform statistical analysis for this study. Qualitative data are presented as number and percentage, while continuous numerical data are presented as mean SD. Comparison of study groups was carried out using chi-square test for categorical data, and using student's t-test for continuous data. P value of < 0.05 was considered statistically significant.

Results

This study included a total of 140 patients with breast cancer: 70 with metastatic disease (cases) and 70 without metastasis (controls). All of the participants were females. The mean age for the study participants was (50.8 ± 13.3) years. Table 1 compares the two study groups (cases and controls) regarding age.

Distribution of study participants according to their stage of disease is summarized in figure 1. 47% of cases with metastasis were presented at early stage of the disease and had no metastasis at time of

Table 1: Comparison of two study groups (cases and controls).

Study	Cases (n = 70)	Controls (n = 70)	P value
Range	25 - 73	29 - 71	0.409
Mean	51.7	49.9	
SD	13.7	12.8	

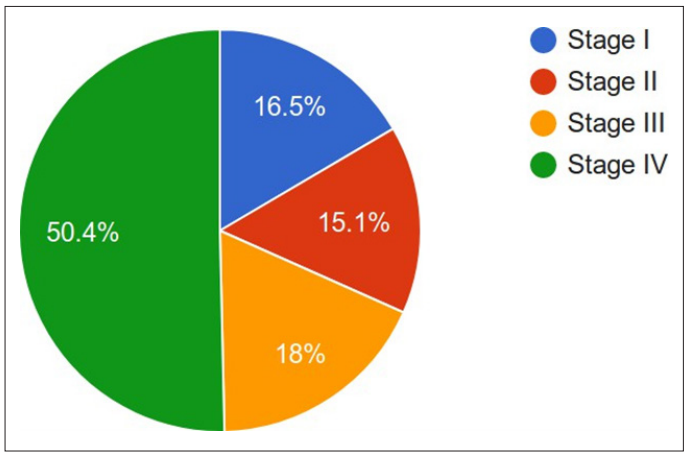

Figure 1: Distribution of study participants according to their disease stage.

diagnosis, while the remaining 53% were already having metastasis at time of diagnosis.

Sites of metastasis included bone metastasis, liver metastasis, lung metastasis or brain metastasis. Table 2 summarizes the sites of metastasis for the metastatic cases group of the study. Total number of cases with bone metastasis was 51, the majority of them (60.8%) had no other site of metastasis, while 23.5% of them had metastasis at liver as well, the remainder had metastasis to either lung, brain or skin.

Among cases with bone metastasis, 70.6% had symptomatic bone metastasis, while the remainder 29.4% had no symptoms of bone metastasis. Other characteristics of study groups are described in table 3. Distribution of ALP level among study population according to disease stage is described in table 4.

Comparison between study groups regarding ALP level was done using chi-square test (Table 5). There is a statistically significant relationship between elevated level of ALP and the incidence of metastasis among breast cancer patients ($\chi 2 = 68.61$, d.f = 1, and $p < 0.001$). Odds ratio was 32.18 (95% confidence interval: 12.71 - 81.46).

Table 2: Sites of metastasis in metastatic cases group.

Site of metastasis	Frequency (n = 70)	Percentage (n = 70)
Bone	31	22.10%
Liver	12	8.60%
Brain	4	2.90%
Lung	3	2.10%
Bone + liver	12	8.60%
Bone + lung	3	2.10%
Bone + brain	3	2.10%
Bone + skin	2	1.40%

Table 3: Other characteristics of the study groups.

Characteristic	Cases (n = 70)	Controls (n = 70)
Pre-menopause	32 (45.7%)	38 (54.3%)
Post-menopause	38 (54.3%)	32 (45.7%)
Invasive ductal	60 (85.7%)	66 (94.3%)
Invasive lobular	10 (14.3%)	4 (5.7%)

Table 4: Mean ALP level according to disease stage.

Disease stage	Mean ALP level (IU/L)
Stage I	65.0 ± 18.6
Stage II	86.9 ± 40.0
Stage III	102.0 ± 33.2
Stage IV	320.5 ± 254.9

Table 5: Distribution of serum ALP levels in study groups.

Cases		Serum ALP level (n = 70)	Controls (n = 70)	Total (n = 140)
Normal (46 - 110 IU/L)	Frequency	11 (15.7%)	60 (85.7%)	71 (50.7%)
	Mean ± SD	87.6 ± 13.3	73.3 ± 18.8	75.5 ± 18.7
Elevated (>110 IU/L)	Frequency	59 (84.3%)	10 (14.3%)	69 (49.3%)
	Mean ± SD	363.9 ± 255.0	155.8 ± 23.4	333.7 ± 247.0
Total	Frequency	70 (100%)	70 (100%)	140 (100%)
	Mean ± SD	320.5 ± 254.9	85.1 ± 34.9	202.8 ± 216.4
$\chi^2 = 68.61$, d.f. = 1, and $p < 0.001$.				

An independent-samples t-test was conducted to compare mean ALP level in patients with metastasis and patients with no metastasis. There was a statistically significant difference in the ALP level for cases with metastasis (M = 320.5, SD = 254.9) and controls (M = 85.1, SD = 34.9) who have no metastasis; t (138) = 7.65, and $p < 0.001$. Chi-square test was also employed to assess the association between ALP level and certain characteristics including histopathology of disease and menopause (Tables 6 and table 7, respectively). No statistically significant relationship was found between ALP and any of those characteristics ($p > 0.05$).

Independent samples t-test was utilized to compare ALP level for patient's symptomatic bone metastasis and patients with non-symptomatic bone metastasis. There was a statistically significant difference in ALP levels for patients with symptomatic bone metastasis as compared to patients with non-symptomatic bone metastasis (Table 8). These results suggest that there is a strong statistical association between ALP level and the presence of symptoms in bone metastasis.

The relationship between ALP level and site of metastasis was assessed for each site using t-test (Table 9). There was positive value oft-test for bone and liver metastases, indicating positive direction of effect, while there was negative value of t-test for lung, brain and skin metastases, indicating negative directions of effect in these sites of metastasis. However, those results had no statistical significance ($p > 0.05$) which could be attributed to the relatively small sample size.

Table 6: Comparison between ALP level and histopathology.

ALP level	IDC	ILC	Total
Normal (46 - 110 IU/L)	64 (50.8%)	7 (50.0%)	71 (50.7%)
Elevated (>110 IU/L)	62 (49.21%)	7 (50.0%)	69 (49.3%)
Total	126 (100%)	14 (100%)	140 (100%)
$\chi 2 < 0.01$, d.f. = 1, and $p = 0.955$.			

Table 7: Comparison between ALP level and menopause.

ALP level	Pre-menopause	Post-menopause	Total
Normal (46 - 110 IU/L)	38 (54.3%)	33 (47.1%)	71 (50.7%)
Elevated (>110 IU/L)	32 (45.7%)	37 (52.9%)	69 (49.3%)
Total	70 (100%)	70 (100%)	140 (100%)
$\chi^2 = 0.71$, d.f. = 1, and $p = 0.398$.			

Table 8: Comparison between ALP level and symptomatic bone metastasis in cases with bone metastasis.

ALP level	Symptomatic bone metastasis present (n = 36)	Not present (n = 15)
Mean	407	201
SD	309	104
t = 3.54, d.f. = 48, and p = 0.001.		

Table 9: Relationship between ALP level and site of metastasis.

Mean	ALP level metastasis		t-test	P value
	Present	Not present		
Bone	346 ± 280	250 ± 151	1.4	0.165
Liver	363 ± 281	298 ± 240	1.01	0.317
Lung	280 ± 171	324 ± 262	-0.41	0.686
Brain	189 ± 57	335 ± 264	-1.45	0.153
Skin	258 ± 112	22 ± 258	-0.35	0.726

Discussion

This study investigated the possibility to using the enzyme ALP as a biomarker for the detection of metastasis in breast cancer. It comprised a total of 140 patients diagnosed with breast cancer, 70 of them had metastatic disease and were considered as cases, whereas the remaining 70 patients had no metastasis at the time of data collection for the study and were considered as controls. Age of participants was between 25 years and 73 years, and patients with hepatitis, liver cirrhosis, liver malignancies, gallstones or pregnant patients were excluded from the study, since these conditions are typically associated with elevation in serum ALP level [14], and could affect the findings in this study by giving high serum ALP levels not related to metastasis.

Assessment for the relationship between each site of metastasis and the serum ALP level was performed using Student's t-test, none of the sites have shown statistically significant relationship ($p > 0.05$). However, this non-significant finding could be explained partly because of the relatively small size of the sample, and also because of the determination of non-tissue-specific ALP enzyme during this study rather than tissue-specific ALP enzymes. The positive value of t-test value for bone metastasis and liver metastasis indicates a positive direction of effect, meaning that bone and liver metastases would be associated with increased ALP if the result was found to be statistically significant. On the other hand, the negative value of t-test in lung, brain, and skin metastases would mean a negative direction of effect, linking those sites of metastasis with decreased ALP level if the results were found to be significant in statistical terms. In a study by Mayne et al. [19] conducted in 1987 there was an increase in total ALP level in only 20% of patients with bone metastasis, while tissue-specific bone ALP was increased in 42% of those patients [19].

Blood samples were collected from study participants in order to determine their serum ALP level, and statistical analysis was performed to assess the relationship between the level of serum ALP that is acquired from those blood sample and the various clinical details regarding the disease including the presence of metastasis, its site, and related symptoms. The utilization of the same laboratory facilities is important to achieve comparable and reliable values and avoid unnecessary bias that might result from minor differences among values obtained from different laboratories using different equipment.

In this study, statistical analysis has shown that there is increasing mean ALP level with increased disease stage (Table 6). This finding is consistent with current scientific knowledge of increasing ALP level in relation to advancement of the disease [7, 14].

The most common histopathological type in the study population was IDC (90%) while the remainder were having ILC, this finding is consistent with the data from the Iraqi Cancer Registry for cancers diagnosed between 2000 and 2009 in Iraq, which have shown that 73% of the Iraqi patients diagnosed with breast cancer had IDC [4].

Comparing the serum ALP level between the study groups have shown a statistically significant association between elevated level of ALP and metastasis in patients with breast cancer. The association was highly significant with a p value of less than 0.001. Odds ratio was found to be 32.18 (95% confidence interval = 12.71 - 81.46), this means that patients with breast cancer who have elevated ALP are 32 times more likely to have metastatic disease as compared to other patients with no elevation in ALP level. A similar study conducted in India on 2012 and involved 388 breast cancer patients have shown a similar result with a p value of less than 0.001, and suggested the presence of higher serum ALP levels in patients with advanced stage of breast cancer [14].

Another study conducted on 2004 and involved 102 clinically established and histopathologically confirmed breast cancer patients have also shown a significant rise in ALP in metastatic cases up to 6 times as compared to cases with no metastasis [6].

The relationship between serum ALP level and symptomatic bone metastasis was assessed using student's t-test between patients with bone metastasis who showed symptoms of bone involvement and patients with bone metastasis who showed no symptoms of bone involvement. There was a statistically significant association between the appearance of bone involvement symptoms and the level of serum ALP with a p value of 0.001, indicating a strong statistical association. This finding is consistent with a study conducted in England by Mayne et al. which shows that patients with symptomatic bone metastasis had significantly higher bone plasma ALP level as compared to patients with asymptomatic bone metastasis [19].

However, the median ALP level in our study for symptomatic bone metastasis patients was 344 IU/L compared to 100 IU/L in the British study, and for patients with asymptomatic bone metastasis our study shown a median of 180 IU/L while the British study shown a median of 38 IU/L). This difference could be explained by the fact that our study determined total ALP level while the British study used affinity electrophoretic procedure to separate bone ALP, giving the level of tissue- specific ALP in particular [19].

Conclusion

Serum ALP level increases with the progression of breast cancer disease, and could be considered an important diagnostic tool in the monitoring of the progression of the disease. A highly increased ALP level is suggestive for the presence of metastasis in patients with breast cancer, and may be considered as a biomarker for the detection of metastasis in breast cancer. The most common site for metastasis in patients with metastatic breast cancer was bone metastasis, followed by liver as the second most common site for metastasis. The most common histopathological type in the study population was IDC followed by ILC. Elevated serum ALP level is strongly associated with the presence of symptoms of bone metastasis in patients with breast cancer disease who develop bone metastasis. No significant relationship was found between ALP level and site of metastasis. ALP level had no significant relationship with menopausal state of participants.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Stieber P, Nagel D, Ritzke C, Rössker N, Kirsch C, et al. (1992) Significance of bone alkaline phosphatase, CA 15-3, and CEA in the detection of bone metastases during the follow-up of patients suffering from breast carcinoma. Eur J Clin Chem Clin Biochem 30: 809-814. https://doi.org/10.1515/cclm.1992.30.12.809
2. Ferlay J, Shin H, Bray F, Forman D, Mathers C, et al. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893-2917. https://doi.org/10.1002/ijc.25516
3. Iraqi Cancer Board (2010) Results of the Iraqi Cancer Registry 2010. Baghdad: Iraqi Cancer Registry Center, Ministry of Health.
4. Al-Hashimi M, Wang X (2014) Breast cancer in Iraq: incidence trends from 2000-2009. Asian Pac J Cancer Prev 15: 281-286. https://doi.org/10.7314/APJCP.2014.15.1.281
5. Haagensen CD, Cooley E (1969) Radical mastectomy for mammary carcinoma. Ann Surg 170: 884-888. https://doi.org/10.1097/00000658-196912000-00005
6. Mishra S, Sharma D, Sharma P (2004) Studies of biochemical parameters in breast cancer with and without metastasis. Indian J Clin Biochem 19: 71-75. https://doi.org/10.1007/BF02872394
7. Chandrakanth K, Kpyati A, Murthy J (2016) Significance of serum total alkaline phosphatase levels in breast cancer. Int J Clin Biomed Res 2: 13-15.
8. Lindblom A, Liljegren A (2000) Tumour markers in malignancies. BMJ 320: 424-427. https://doi.org/10.1136/bmj.320.7232.424
9. Viale G (2012) The current state of breast cancer classification. Ann Oncol 23: x207-x210. https://doi.org/10.1093/annonc/mds326
10. Singletary SE, Connolly JL (2006) Breast cancer staging: working with the sixth edition of the AJCC cancer staging manual. CA Cancer J Clin 56: 37-47. https://doi.org/10.3322/canjclin.56.1.37
11. Hanna L, Crosby T, Macbeth F (2008) Practical clinical oncology.
12. Barter S, Britton P (2014) Breast cancer. In Nicholson T (ed) Recommendations for Cross-Sectional Imaging in Cancer Management, Second Edition. London: The Royal College of Radiologists.
13. Brady LW, Halperin EC, Pérez CA (2008) Principles and practice of radiation oncology. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.
14. Singh A, Pandey A, Tewari M, Kumar R, Sharma A, et al. (2013) Advanced stage of breast cancer hoists alkaline phosphatase activity: risk factor for females in India. 3 Biotech 3: 517-520. https://doi.org/10.1007/s13205-012-0113-1
15. Lowe D, Sanvictores T, Zubair M, John S (2023) Alkaline phosphatase. In StatPearls. Treasure Island (FL): StatPearls Publishing.
16. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, et al. (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347: 1233-1241. https://doi.org/10.1056/nejmoa022152
17. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, et al. (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347: 1227-1232. https://doi.org/10.1056/nejmoa020989
18. NIH consensus conference. Treatment of early-stage breast cancer.
19. Mayne PD, Thakrar S, Rosalki SB, Foo AY, Parbhoo SP (1987) Identification of bone and liver metastases from breast cancer by measurement of plasma alkaline phosphatase isoenzyme activity. J Clin Pathol 40: 398-403. https://doi.org/10.1136/jcp.40.4.398