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# The Role of BNCT in Breast Cancer Treatment

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**ABSTRACT**

Boron neutron capture therapy (BNCT) is a promising future technique of breast cancer therapy. BNCT is a cell-targetting therapy. In BNCT, the use of boron-10 combined with curcumin analog will provide selective radiation therapy only to breast cancer cells, whereas healthy cells will not be affected. This is because the alpha radiation from the boron-10 nuclei that fission due to thermal neutron irradiation only has a short range of between 4 and 9 μm, whereas the cell diameter is between 10 and 20 μm, so the reaction is limited only to the cancer cells. If the development of BNCT succeeds, then in the future the malignancy of the breast cancer will be effectively treated by cancer-cell targeted therapy, thereby avoiding the side effects of conventional therapy.



## INTRODUCTION

Presently, many people fear cancer because this disease is regarded as a drumbeat of death. In fact, cancer is a very serious disease, but with the advancement of medical science and medicine, make the number of deaths due to cancer which continues to decline from year to year. There are actually several effective treatments for cancer. A new generation of cancer therapies can selectively kill cancer cells without damaging healthy cells around them and these therapies are being developed. The therapies and the drugs used are also called targeted therapies and targeted drugs, respectively. According to the definition, targeted therapy or molecularly targeted therapy is one of the major modalities of medical treatment for cancer, the others being hormonal therapy and cytotoxic chemotherapy. As a form of molecular medicine, targeted therapy blocks the growth of cancer cells by interfering with specific targeted moleculs needed for carcinogenesis and tumor growth [1-4]. Targeted cancer therapies are expected to be more effective than older forms of treatment and less harmful to normal cells. In the common solid tumors, by contrast, there are many potential targets but no obvious crtitical molecular driver, making the development of targeted therapy much more challenging [2,4,5]. There are targeted therapies for colorectal cancer, head and neck cancer, breast cancer, multiple myeloma, lymphomas, prostatic cancer, melanoma, and other cancers [2-5].

There are various types of therapeutic drugs for various targets, one of which is a monoclonal antibody that will stimulate the natural immune system that specifically attacks cancer cells. The growth of blood cells that supply oxygen and nutrients to cancer cells will also be inhibited by these drugs so that the cancer cells shrink or contract and then die [6]. These drugs are still quite expensive. For example, for a series of cancer treatments combined with chemoradiation therapy, it costs 40-50 million IDR (≈ 2,700-3,400 USD). Appropriate target therapy is generally given to solid tumors such as lung, breast, colorectal, and kidney cancers. These medications usually cause severe side effects, including nausea, vomiting, and hair loss [3].

Signal transduction research has shown the importance of members of the human epidermal growth factor receptor (HER) family of transmembrane tyrosine kinases in a number of solid tumors. The gene for this receptor (HER2) is amplified up to 30 percent of breast cancers, leading

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to aggressive behavior and an unfavorable prognosis. However, the overexpressed HER2 receptor protein also serves as a target for anti-HER2 antibody (trastuzumab) therapy. The absence of amplification can be used to differentiate patients who may have a response to the antibody from those who wll not have a response. The likelihood of tumor regression with trastuzumab therapy may be as high as 35 percent among patients with tumors that strongly overexpress HER2 [7,10].

Boron neutron capture therapy (BNCT) is a technique of internal radiation in which boron-10 (B-10) in a curcumin analog compound is irradiated with neutrons and then fissions into He-4 and Li-7. The He-4 nuclei, or alpha particle radiation, can kill both cancer cells that are actively dividing and that are not dividing. The alpha particle radiation is only limited to cancer cells into which B-10 is filled and not reach healthy cells that do not contain B-10. The B-10 compound-curcumin analogs have only high affinity for breast cancer cells with positive HER2 tumor markers. This therapeutic application with the BNCT method can be used for local regional therapies for advanced breast cancer with positive HER2 tumor markers [8-11]. Bevarnegin conducted a study on neutron beam which was implemented as a BNCT reactor to medically treat tumors so that this method could be used routinely for cancer therapy and therefore needed a neutron source in the hospital [8]. Technical improvement in BNCT application has led to consideration of this technique in soft tissue tumors such as breast cancer. Recently, BNCT comes to the fore as an alternative approach to therapy [9].

This paper describes BNCT therapy for treating breast cancer. It is hoped that BNCT technique can reduce the morbidity and mortality rate of breast cancer. Therapy with BNCT is still in the early stage of research and still in the first year of implementation. It is expected that in the first year, the development of neutron generator can be completed, then in the second year, research on B-10 and curcumin analog compounds can performed well, subsequently in the third year will be completed with clinical trial.

## THEORY

When does breast cancer develop from the breast tissue? Signs of breast cancer may include a lump in the breast, a change in shape, wrinkled skin, skin resembling orange peel, the discharge of fluid from the nipple, or the color of reddish patches on the breast skin [5,7]. In the presence of distance metastasis may prove to be in bone, swelling of lymph nodes, shortness of breath or the presence of yellow skin [6,7]. There are many risk factors for the occurrence of breast cancer. Some of those risk factors are the presence of obesity that is often undetected during physical examination, alcohol consumption, hormonal replacement therapy during menopause, ionizing radiation, early menstruation, and slow early childhood development [6,12].

In Indonesia, the SADARI examination is the breast self-examination to find out whether there is a lump in the breast that may indicate cancer. It can be done alone by palpating the breast thoroughly to feel if there is a lump and, if so, whether the lump moves relative to the surrounding tissues, as shown in Fig. 1. If a lump is palpable, then a doctor should be consulted. The doctor will conduct further examinations such as a mammographic examination. Through mammography, it can be seen whether the lump is malignant. Signs of malignancy on mammography include a mass picture with microcalcifications, star formation. This examination will be strengthened if there is retraction from the mammary papilla in the breast [12,13], as shown in Fig. 2.

**Fig. 1.** Performing breast self-check (SADARI). If a lump is found, a doctor is to be contacted immediately [10,12].

**Fig. 2.** A normal mammogram (left) and mammogram exposed to cancer shown a mass with the surrounding star formation (right) [12,13].

Approximately 5-10 % of cases involve genetic inheritance from parents, including BRCA1 and BRCA2 in addition to others [14]. Breast cancer develops in many cells of the milk ducts and lobules

that supply the milk ducts. Breast cancers that develop from the ducts are known as ductal carcinoma, while the ones that develop from lobules are known as lobular carcinoma [15]. In addition, there are more than 18 other subtypes of breast cancer. Some cancers develop from pre-invasive lesions such as ductal carcinoma *in situ* [16]. The diagnosis of breast cancer is confirmed by biopsy on the lump. The advantages and disadvantages of breast cancer screening are still controversial [16-19]. The 2013 Cochrane review emphasizes that it remains unclear if mammography screening is more beneficial or detrimental. According to the US Preventive Services Task Force in 2009, the review found evidence of benefits at age 40-70 years, and the organization recommends screening every two years in women aged 50-74 [19]. Tamoxifen or raloxifene may be used in an attempt to prevent breast cancer in those at high risk for breast cancer. Surgery by removing both breasts is a prevention effort in some women with high potential for breast cancer [18,19]. In those already diagnosed with cancer, a number of treatment modes may be used, including surgery, radiotherapy, chemotherapy and target [16-18]. Surgical therapy varies from breast-conserving surgery to mastectomy. Breast reconstruction may be possible at the time of surgery or later. In those who already have metastasis to other organs, treatment is aimed at improving the quality of life and happiness of life [18,19].

The outcome of breast cancer is relatively dependent on the type of cancer, the extent of the disease, and the age of the patient [18]. The average survival rate in developed countries is high, in the range of 80-90 % in England, and in the US the patients last an average of 5 years [19]. In developing countries the average survival rate is very low [19]. Breast cancer worldwide is the most common case of cancer in women, around 25 % of all cases. In 2018, there were 2.08 million new cases with 626,679 deaths in the world. This type of cancer is common in developing countries and more than 100 times more common in women than in men [17,19]. The incidence of breast cancer varies greatly in the world. It is lower in less-developed countries and higher in more highly-developed countries. In twelve regions of the world, the annual incidence rates by the age of the average standard per 100,000 women are as follows: East Asia 18; South Central Asia 22; Sub-Saharan Africa 22; South-East Asia 26; North Africa and West Asia 28; South and Central America 42; Eastern Europa 49; South Europa 56; North Eurpa 73; Oceania 74; Western Europa 78; and North America 90 [17,19].

The presence of a lump in the axillary area may also indicate the possibility of breast cancer. Other symptoms may include breast thickening, unequally-sized breasts, mammary papillae that change position or shape or become inverted, wrinkled breast skin, reddish patches around the mammary papillar, fluids from mammary papillae, pain in the breast or axilla, and swelling around axilla and collarbone [12,18]. The symptoms and signs of breast cancer can be seen in Fig. 3.

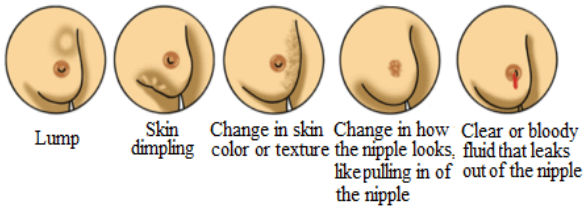


**Fig. 3.** Early signs of a possible breast cancer [12,18].

**Fig. 4.** Breast cancer, swelling, nipple pulled in, wrinkled skin [12,18]

Inflammatory breast cancer is a frequent type of breast cancer and can be positioned as a substantial challenge of diagnosis. Symptoms may include inflammation of breast tissue, itching, pain, swelling, inversion of the nipple, warmth and redness around the breasts, the presence of peau d'orange as breast cancer with inflammation that does not appear to have swelling or lumps, may sometimes result in a diagnosis which is late (Fig. 4) [18]. In radiation treatment used multiple beam angles to reduce exposure to the skin and to ensure a good dose rate exceeds the targeted volume of treatment. However a placement of light beam begins, this being that the location of the tumor volume and the relative location in the patient's body, is limited to the number of views that will result in a defined T/S ratio in this case [6,11]

The choice of direct, perpendicular beam to skin surface has been chosen as a representative therapy for this study. This placement results in an effective tumor depth, approximately 1 cm in length. Another possible angle of light has an effective tumor depth of 2-4 cm. This results in other

complications that will be explained below, but it is assumed that the results are above the representative of a potential therapeutic plan, so that other angles of light can be considered [5,6,11].

## Risk factors

### *Gender and age*

Cancer can attack people of all ages. The highest cancer prevalence is at the age of more than 75 years at 5.0 % and the lowest is at 1-14 years at 0.1 % [17]. The main risk factors of breast cancer are gender and age [13,17,18]. Lung cancer is not only the type of cancer with the highest new cases and the leading cause of death in the male population, but it also has a high percentage of new cases in the female population, which is 13.6 % and lung cancer deaths of 11.1 %. Breast cancer is the cancer with the highest percentage of new cases (after being controlled by age) at 43.3 %, and the percentage of deaths (after being controlled by age) due to breast cancer is 12.9 % [17,19]. Other risk factors include genetic factors, infertility, non-breastfeeding women, diet with high hormone levels, and obesity [18-20]. Another factor is pollution [21].

### *Lifestyle*

Smoking tobacco raises the risk of breast cancer; the more smoke inhaled and the earlier the age smoking habit begins, the higher the risk. In older smokers, the risk increased 35 %-50 % [17,19]. Lack of physical activity involved close to 10 % of cases [18,19]. Indicated also the use of oral contraceptives will increase the risk of premenopausal breast cancer, although this is still in debate [19]. There is a link between diet and breast cancer, high fat diet increases risk, alcohol intake, and obesity, association with high cholesterol [14,16,18]. Another risk factor is radiation [18], polycyclic aromatic hydrocarbons, organic solvents and some pesticides [17,18,22]. Radiation risk due to mammography exists despite small doses; it is estimated that a year at the age of 40-80 years can cause 225 cases of fatal breast cancer per million women who have been screened [19].

### *Genetic*

Genetic factors are one of the risk factors that assume cancer can be passed on to the next generation. In this situation if the parents suffer from cancer then the child will likely be able to suffer from the same cancer. History of families suffering from cancer can increase the risk of exposure to cancer. In 5-6 % cases, familial breast cancer is closely related to the presence of genetic mutations in the BRCA1, BRCA2, P53, ATM, and PTEN genes [15,23]. Genetic risk factors are believed to be the primary cause of 5-10 % of all cases [22,23]. There were zero, one, and two cases of breast cancer before the age of 80 with an incidence rate of were 7.8 %, 13.3 % and 21.1 %, and with mortalities of 2.3 %, 4.2 %, and 7.6 %, respectively [19,23].

### *Medical condition*

Breast tissue changes as atypical ductal hyperplasia and lobular carcinoma *in situ*, found in benign breast conditions such as fibrocystic breast changes, are associated with increased risk of breast cancer. Diabetes mellitus may also increase the risk of breast cancer [18-20]. More than 30 % of cancers can be prevented by changing the risk factors for behavioral and dietary causes of cancer. A cancer case that is discovered early has the possibility to get better treatment. Preventive efforts are needed to increase public awareness in recognizing the symptoms and risks of cancer so that they can determine appropriate preventive measures and early detection. If cancer is diagnosed and treated early, the chances of recovery is higher [20,22,24,25].

### *Pathophysiology*

Breast cancer, like other cancers, occur because of the interaction between external environmental factors and heredity. Normal cells divide themself as many times as needed and then stop dividing. They stick to other cells and stay together on a tissue. Cells will become cancerous when they lose their abilities to stop dividing, attach to other cells, stay where they are, and then die at a certain time. Normal cells will experience apoptosis when they are no longer needed. Until then, they are protected from the incidence of apoptosis by some protein caster in some way. The presence of cell mutations can be followed by breast cancer in experiments with estrogen exposure [21,22]. Signal growth factor abnormalities in the presence of interactions between stromal cells and epithelial cells may facilitate the growth of malignant cells [22,26]. In breast fat tissue the excessive expression of the lectin may be followed by increased cell proliferation and cancer [14,22,27]. Mutation in BRCA genes occurs in 2 % to 3 % of all breast cancers [10,23]. Levin *et al.*, stated that the cancer could not be avoided for mutations in BRCA1 and

BRCA2 gene carriers [15,23]. Approximately half of the declining ovarian-breast cancer syndrome involves an unknown gene [28].

### *Diagnosis*

Most types of breast cancer are relatively easy to diagnose microscopically from biopsy preparations of the affected breast area. Sometimes, rare breast cancers require special laboratory tests. The preparation can be taken by FNAB (fine needle aspiration biopsy) or FNAC (fine needle aspiration and cytology). Performed together, physical examination of the breast, mammography, and FNAC will be better and more accurate. Other biopsy methods include core biopsy or vacuum-assisted biopsy, ultrasound guiding biopsy, a procedure for partial breast lump surgery, or excisional biopsy when all lumps are removed. Often additional examinations with ultrasound and MRI images are assured on excisional biopsies for diagnosis and primary treatment methods. There are several staging systems for breast cancer. The stage of a breast cancer case determines its prognosis and affects the therapy response. Three of such staging systems are histopathologic staging, grading, and TNM system. Histopathologic staging is based on such features as ductal or lobular carcinoma (carcinoma *in-situ*, Invasive carcinoma). Grading divides breast cancer into (low grade, intermediate grade, and high grade. The TNM system stages cancer based on tumor (T), lymphonodi (N) and metastasis (M). It divided into stage 0, which is precancerous (*in situ* carcinoma), stages 1 to 3, where cancer is still in breast or regional lymph nodes, and stage 4 in which there are distant metastases [18,25].

### *Management of Breast Cancer*

Treatment of breast cancer is usually by surgical removal of the tumor, which may have to be continued with chemotherapy or by radiotherapy or both that is a multidisciplinary approach [13,24,25,29,30]. Positive hormone receptor cancer is often treated by blocking hormones for several years. Monoclonal antibodies or treatments with other immune modulations may be given to certain breast cancer cases with metastases and other cancers at an advanced stage. Surgery can be done by mastectomy method by removing the whole breast, quadrantectomy by removing a quarter of the breast, or lumpectomy by removing a small portion of the breast. Furthermore, a breast recontruction surgery or plastic surgery can be performed to improve appearance or aesthetics, or breast prostheses can be used for simulation of breast that is not present or nipple/areola prostheses can be used after mastectomy. Another treatment method that can be followed, although rare due to its newness, is boron neutron capture therapy (BNCT). BNCT has been widely used to treat head and neck cancer and has been shown to be effective [8,9]. BNCT is a biologically-targeted treatment based on radiation production in tumors using B-10 and thermal neutrons. B-10 is inserted in cancer cells with the aid of a special phenylalanine carrier and subsequently the tumor is radiated with low-energy neutrons. The neutrons' reaction with B-10 results in high-LET radiation that damages cancer cells. One or two BNCT sessions may be able to damage the tumor with no radiation effect on surrounding healthy cells or only minimal effects [8,9,11,31]. According to Barth *et al.* when B-10 is irradiated with low energy thermal neutrons, recoiling alpha helium-4 and lithium-7 nuclei with high LET are produced [32,33] (Fig. 5).

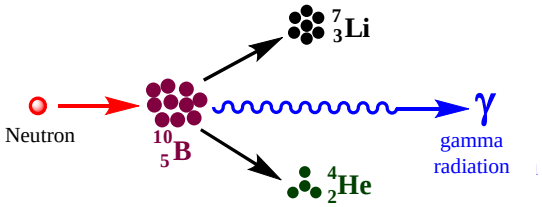


**Fig. 5.** Generation of high-energy alpha particles of $^{4}$He and $^{7}$Li atoms.

BNCT clinical interventions are a focus on the treatment of high grade gliomas and cutaneous melanoma tumors or melanomas that metastasize to the brain, neck, and head and liver cancers. This research with randomized controlled trial (RCT) design states that BNCT is an efficacious therapy and in the future is an adequate therapy modality. In Indonesia is being developed treatment with BNCT method is to treat breast cancer. This is because breast cancer has a high incidence and prevalence. In developing countries including Indonesia most cancers are occupied by lung, stomach, and liver cancer in men, as well as breast, cervical and lung cancers in women [3,19]. In Indonesia, cancer is most prevalent among highly educated people with the highest index of ownership, where Yogyakarta Special Region ranks first (4.1 %), followed by Central Java (2.1 %) and Bali (2.0 %) [17,26].

## METHODS

This article used a literature research from many references that related with the potency BNCT as breast cancer therapy.

## DISCUSSION

BNCT is a therapy performed based on nuclear reactions that occur when boron-10 contained in pharmaceutical compounds is irradiated with low-energy neutrons to produce high-energy alpha particles ($^{4}$He nuclei) and $^{7}$Li atoms. Irradiation of neutron beam to the boron compound causes the boron-10 atoms to split to Li nuclei and alpha radiation (He nuclei) which only give intracell effects within cancer cells [8,9,11,31-34] as shown in Fig. 6 [35,36].

At the Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, analog derivatives of curcumin are modified into pentagamaboronon-0 (PGB-0) as boron atomic carrier compounds into cancer cells in BNCT applications for breast cancer treatment. The modification of curcumin analog compounds with the addition of boron-10 atom to PGB-0 compounds is an attempt to obtain boron-10 binding compounds with specific targets for breast cancer with positive HER2. However, PGB-0 is poorly soluble in water. Formulations of PGB-0 with monosaccharide, fructose, or sorbitol were synthesized to improve its solubility; those formulations are PGB-0-F and PGB-0-So. These formulations are accumulated and distributed within the cytoplasm and cell nuclei. PGB-0 also has an antimetastatic activity toward breast cancer cells by exerting antimigratory substances, namely boronocaptate sodium (BSH) and boronophenylalanine (BPA) [37], that prevent the metastasis of cancer cell.

Boron neutron capture therapy has been developed and used in several countries, such as Japan, Finland, and Taiwan. This new procedure has been used as an alternative cancer therapy for several cases, especially malignancy in head and neck area, such as glioblastoma multiforme. BNCT shows a good result in glioblastoma multiforme, where most of BNCT patients show improvements of health status and survival rate. BNCT is also proven to have better efficacy for treating cancer compared to surgical or radiation procedures [31,33].

BNCT was primarily intended to be utilized for the treatment of neck and head cancers, but some technical improvements in BNCT application and usage of new boron carier, PGB-0, has led to the possibillity of applying this technique in soft tissue tumors, such as breast cancer. A suitable thermal/epithermal neutron flux is needed to maximize BNCT's therapeutic potential, so that B-10 can selectively enter the target tissue. With neutron sources and PGB-0, as new boron carrier, BNCT can fill an important niche for soft tissue malignancies, especially breast cancer [37,38].

Breast cancer may recur after primary resection both locally or in distant sites. The higher risk of recurrence is associated with developed micrometastatic in healthy cells. BNCT plays a major role for large local recurrences after radiotheraphy and mastectomy. The benefit of the application of BNCT to recurrent and advanced breast cancer is that this therapy works selectively within the cell level, the boron atom will accumulate in the cancer cell and invade the malignant neighboring tissue in cell unit. BNCT is not performed yet in patients with breast cancer, so it still has low evidence. However, BNCT is considered as an ideal therapy for the future for locally-recurrent breast cancers that are unresponsive to conventional therapies [39].

The implementation of BNCT for breast cancer bring a major advancement to promote a higher life expectancy for breast cancer patients. BNCT is a selective method to kill cancerous cell by using the high LET energy from irradiated boron-10, Fig. 6(a). Breast cancer that is in a relatively early stage and has no injury or ulceration can be examined by mammography that gives either a normal mammogram or a cancer one as presented in Fig. 6(b). Breast cancer that is already in an advanced stage with injuries or ulcerations, as in Fig. 6(c), can no longer be examined with mammography because it is not possible to do breast compression that must be done during mammography. In this advanced stage of breast cancer, it is expected that the BNCT method can be used for the treatment of breast cancer. Neutron irradiation only kills cancer cells that capture B-10 compounds, while healthy cells do not capture B-10 compounds and are not influenced. Thus the side effects are expected to be relatively milder, and may be none, compared to conventional breast cancer treatment with chemo- and radiation therapies (Fig. 6).

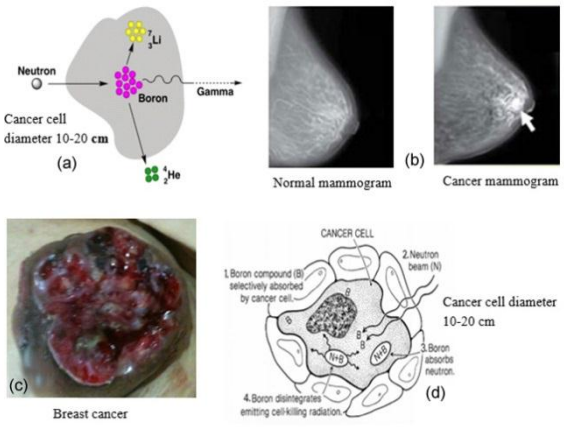


**Fig. 6.** Boron neutron capture therapy. (a) theory of boron neutron reaction in cancer cell. (b) normal and cancer mammogram, (c) advanced breast cancer, (d) boron neutron therapy mechanism in kiling cancer cell [9,11,32,33].

Determination of the stage of cancer is based on the size, location of the tumor and the extent or spread, the lymph nodes involved, and whether there is a distant metastasis. If the stage is already high when diagnosed, then the prognosis will be worse. The stage increases with the number of lymph nodes involved, chest wall and skin or organ under it, and the presence of distant metastases to other organs. In addition to hormone receptors, HER2 status directly leads to existing therapies. Patients with positive HER2 have more aggressive disease and can be treated with targeted therapy, trastuzumab (herceptin), or monoclonal antibodies that have targeted proteins and can significantly improve prognosis. Young women have a poorer prognosis than postmenopausal women, caused by several factors: breast cycling, breastfeeding, and possible lack of awareness of changes in the breasts. Thus, young women are generally diagnosed at an advanced stage. It is also likely due that there is a contribution of biological factors to the high risk of breast cancer recurrence in young women [6,10,25,27,29,30]. Breast cancer in men is generally detectable at an advanced stage, and output is generally very poor [13].

Cancer therapy was performed while continually evaluated with randomized controlled trials (RCTs). The evaluation is meant to determine the efficacy of drug administration and comparison of individual drugs, as well as comparison of combinations of drugs, surgery, and radiation techniques. Investigations include a new type of targeted therapy as well as a cancer vaccine. Clinically good metabolic markers used for breast cancer are estrogen and progesterone receptors in use to predict a response to hormone therapy. Potential new markers for breast cancer include BRCA1 and BRCA2 to identify patients at high risk for breast cancer, HER-2 and SCD1 to predict the presence of response to plasminogen activator regimen and urocinase activator, and PAI-1 and SCD1 for assessing prognosis [10,15,22,24,29,30]. BNCT research using B-10 in combination with curcumin analog was performed at Universitas Gadjah Mada, Yogyakarta.

## CONCLUSION

Treatment of breast cancer is done in a multidisciplinary manner, not only with single therapy but in many ways the combination of which has been commonly performed is surgery, systemic chemotherapy and local regional intraarterial, and radiotherapy. At present BNCT therapy has been developed by using Boron-10 which is labeled with curcumin analog compound given intravenously into the body which is then captured selectively in breast cancer cells which then shot with thermal neutron radiation will selectively kill only cancer cells, and healthy cells are not detrimentally affected. This preliminary research now is being done in Indonesia.

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