



Review Article

Roles of Different Radiations in Treatment of Breast Cancer

Usba Jameel¹, Zubair Janan Orakzai^{2*}, Shamoona Rashid³ and Sumaira Noureen⁴.¹Khyber Teaching Hospital Peshawar, Pakistan²Department of Radiology, Medical Teaching Institution, Mardan Medical Complex, Mardan, Pakistan³Department of Radiology, Aziz Fatima Medical and Dental College, Faisalabad, Pakistan⁴Medical Teaching Institution, Mardan Medical Complex, Mardan, Pakistan

ARTICLE INFO

Key Words:

Radiation Therapy, Breast Cancer Radiotherapy, Radiation Therapy

How to Cite:

Jameel, U. ., Janan Orakzai, Z. ., Rashid, S. ., & Noureen, S. . (2022). Roles of Different Radiations in Treatment of Breast Cancer: Radiations in Treatment of Breast Cancer. Pakistan Journal of Health Sciences, 3(07).

<https://doi.org/10.54393/pjhs.v3i07.416>***Corresponding Author:**Zubair Janan Orakzai
Department of Radiology, Medical Teaching Institution, Mardan Medical Complex, Mardan, Pakistan
zjaurakzai@hotmail.com

Received Date: 7th December, 2022

Acceptance Date: 21st December, 2022

Published Date: 31st December, 2022

ABSTRACT

The review aimed to describe the role of radiations in treatment of breast cancer. The review also describe that which type of radiation is used to treat different stages of breast cancer i.e, metastatic stage, advance stage and early stage of breast cancer. The radiation therapy plays a significant role in the treatment of breast cancer. The treatment delivery methods are considerably changed in the recent decades. The concept of using radiotherapy for the treatment of breast cancer has remained equally important for oncologists throughout the years still research has been going on to make these radiotherapy sessions more and more convenient for the patients. The combination of breast conservation surgery an APBI can result in survival without having any other health related issues for other nearby organs. Recent findings have reported about incorporation of APBI into clinical usage. APBI should be used for patients with low risk of ductal carcinoma or in case of first stage of invasive ductal cancer which has prominent margins for the excision, and where the estrogen receptor positivity is clear. Radiation therapy is effectively used for the treatment and management of loco regionally advanced and distant metastatic disease. There is research going on to find most appropriate technique in which convenient and protected procedure is used for patients to avoid any side effects. New and advanced techniques are used to limit radiation related toxicity.

INTRODUCTION

Breast cancer is the one of the most commonly reported neoplasms. It accounts for almost one-fourth out of all the cancers reported in the female. It has prevalence of 27% in the developed countries. It effect both gender male and female. It is one of the leading cause of mortality among women [1, 2]. But it is most commonly reported in the female. Its incidence is observed 100 times more than the female. The delay diagnosis ultimately leads to the bad prognosis of the cancer. The global burden of this tumor is reported to be rising with the passage of time. It is a major public health concern. The early diagnosis and treatment can prevent the prognosis and further complication.

Mammography is usually used for the screening and detection of the breast cancer. The two famous anti-oncogene for breast cancer are BRCA1 and BRCA2. These are located on the chromosome 17 and 13. These encodes for the anti-suppressor proteins. These proteins repair the double stranded break of the DNA [3-5]. The International cancer registry reported the increasing trends in breast cancer incidence. It was predicted that till 2050 there will be 3.2 million women effected from breast cancer. There is need to adopt the preventive measures. For the management of the distant metastatic, advance and early stage breast cancer the radiation therapy is considered as

well established modality. The novel radiation therapy delivery approaches are considering to reduce the toxicity associated with the radiation therapy. The researchers are also working hard to shorten the duration of the radiation delivery. The patients with distant metastatic disease are usually suggest with the stereotactic radiation delivery. The radiation therapy reduced the need of mastectomy. These also reduced the local recurrence risk. The early prevention can leads to increase the survival rates. In the recent years the survival rate of breast cancer has raised to 80% because of the early diagnosis and prevention [6]. It is difficult to control the breast cancer diagnosed at recurrent locoregional and advanced stage. Approximately the 5% of the breast cancer are associated with the germline mutation. The expression of the BRCA1/2 protein vanish in the breast cancer that effect the DNA repair process. The Double stand breaks are observed in such cases that leads to the genomic instability. These proteins play an essential role in the double-stand break (DSB) and single strand break repair [7-9] The review aimed to describe the role of radiations in treatment of breast cancer. The review also describe that which type of radiation is used to treat different stages of breast cancer i.e, metastatic stage, advance stage and early stage of breast cancer.

The advantage of early breast cancer radiotherapy

The patients suffering from breast cancer are given treatment by either breast conserving surgery or mastectomy, which involves surgery for the removal of breast. Another suggestion given to patients is postoperative radiotherapy. As per previous studies and survey analysis there is increase in survival rate after using these approaches. It is up to patient whether she wants to keep breast or choose mastectomy. Patient can decide whether they want postoperative radiotherapy or not. According to literature most of the time patients prefer to keep breast. Early breast cancer collaborative group have stated that a complete session of radiotherapy after surgery can help decrease the mortality rate up to 5%. In case of breast conservation treatment, the breast cancer tissue is removed along with the lymph node biopsy making axillary clearance leaving the normal breast tissue after brief whole breast radiotherapy [10, 11]. In case of women who are diagnosed with stage 1 breast cancer, the breast conservation approach is effective and curative option. There are few side effects that are reported by patients during radiotherapy that includes erythema and muscle fatigue but the symptoms are gone once radiotherapy sessions are completed. In case of patients that opt for mastectomy had to go for a complicated and laborious breast reconstruction surgery in which breast re-implant is carried out after or during mastectomy. A complete

session of radiotherapy after surgery is recommended and according to statistical analysis it was found that there was an increase in survival rate in patients that had radiotherapy performed after surgery as compared to patients that couldn't get radiotherapy after their surgery [12]. As per studies from 15 trials, that included 9422 patients the results showed that risk of cancer reoccurrence was three times more in patients that skip radiotherapy sessions after surgery. The mortality rate for patients not going for radiotherapy is 8.6 more than the mortality rate of patients receiving radiotherapy [13].

Types of radiations used for the loco regional treatment of breast cancer

The concept of using radiotherapy for the treatment of breast cancer has remained equally important for oncologists throughout the years still research has been going on to make these radiotherapy sessions more and more convenient for the patients as it is important to make the radiation exposure duration as short as possible to avoid any side effects.

Accelerated partial breast irradiation (APBI)

In a traditional approach the concept of targeting whole breast tissue was used previously but now with the advances in science APBI offers the targeted therapy where use of radiotherapy to only the tumor bed area is carried out. The chance of reoccurrence is mostly present around the tumor bed so APBI can save the patient from unnecessary exposure to the normal tissue. Especially in case of elderly patients where the surrounding organs like lungs, heart are already weak, much shorter radiation exposure and targeted exposure can help them get better results [14, 15]. APBI is normally given to patients with stage one breast cancer as they opt for breast conservation therapy, after surgery APBI can be used using a interstitial catheter afterloading procedure. In some cases, intracavitary brachytherapy or 3D external beam radiation therapy (EBRT) can also be used. The combination of breast conservation surgery an APBI can result in survival without having any other health related issues for other nearby organs. Recent findings have reported about incorporation of APBI into clinical usage. APBI should be used for patients with low risk of ductal carcinoma or in case of first stage of invasive ductal cancer which has prominent margins for the excision, and where the estrogen receptor positivity is clear [16].

Hypofractionation

Hypofractionated breast cancer radiation treatment is also under study; it consists of a heavy dose of radiation for a shorter period of time. As per study carried out to find that either 5 week or 3-week radiation schedule is more effective. Women undergoing breast conservation surgery and in patients whose resection margins are prominent,

this type of radiation procedure was used. As per study the risk of reoccurrence was 6.7% as compared to the 6.2% as found in case of hypofractionated regimen. A 10-year study result showed that an original trial consisted of 50.0 Gy of radiation in form of 25 fractions for 5 weeks where a dose of 2.0 Gy was given to patients on daily basis [17]. As per radiology experts a larger dose given to patients on daily basis for a shorter time can prove to be more effective. In this procedure the larger doses of radiations are given to the patients for the very short duration of the time. This procedure can prove to be more effective and convenient for patients and less amount of resources will be used [18].

How to minimize cardiac toxicity after breast cancer radiotherapy?

Radiation therapy is a very popular approach used recently to treat breast cancer. However, the dose of radiations, the type of irradiation is differently used for different physicians. There are novel procedures and techniques used by physicians so that heart and lungs toxicity can be reduced. The key is to adapt the treatment procedure according to the state of the cancer. As per studies techniques like internal mammary chain radiotherapy should be carried out very carefully. The increased risk of heart failure and myocardial infarction are associated with the breast radiotherapy. The irradiation of normal tissue in the breast cancer radiotherapy there are relative residual risk of secondary effects in the patients. These affect the quality of life [19]. The patients can be placed in the prone position to reduce the radiation dose to the heart. Gating and breath hold technique can be used to minimize the cardiac toxicity. Advances in intensity modulated radiotherapies are also significant as these uses the multiple beam angle to ensure that the affected areas get the maximum dose while minimize the dose to the normal structure i.e, heart [20].

IMRT, breathing adapted radiation therapy along with prone-positioning procedure is used to limit toxicity

Techniques like IMRT, breathing adapted radiation therapy are frequently used by physicians to deal with cardiac and skin toxicity after breast cancer radiation treatment. These procedures are effective as heart is close to the breast and in case of pendulous breasts. As the traditional approaches used for radiation therapy had no control over the dose given, intensity modulated radiation therapy (IMRT) proves to be effective technique and it limits the skin related toxicity as well. It uses advanced software programming to change the dose and intensity of the radiation, it leads to a more refined and homogenous distribution of dose. In the prone positioning technique, a customized breast board is made where patient lie prone with the breast in air so that it gets away from the chest wall [21].

Radiation therapy used for treatment of distant metastatic disease

Distant metastatic disease can be defined as breast cancer spread to other parts of the body like lungs, brain and bones. It is highly known as the major cause of cancer-related deaths. The poorest prognosis is observed in case of distant metastatic disease. The mortality rates are reported to be account for the 36%-47% cases out of all tumor specific cases. The metastatic tumor development is highly effected by the distinct tumor features. The most commonly found distant metastatic disease is bone metastasis as 3% cases are reported it is followed by lung and liver cancer [22]. Conditions like spinal cord compression, ocular metastasis and leptomeningeal metastasis are commonly found. As per literature these conditions are effectively treated by radiation therapy. As per studies brain and spine metastasis is effectively treated by SRS (stereotactic radiosurgery) and SBRT (stereotactic body radiation therapy) techniques.

SBRT and SRS for the management of distant metastatic disease

The breast cancer is the genetic disease and it increase with the age. Because of the increase in the elder population it become difficult to treat the patients diagnosed with the cancer. The risk of the breast cancer in the women of age more than 65 years is six times greater than the younger women. The more than the one-third of the cancer are reported in women of age 70 years or more. To treat the older women is even more difficult as they are more vulnerable to the treatment related toxicities. In stereotactic radiation technique the main goal is to maximize the radiation precision by immobilizing the patient, localization of tumor and the targeting of beam to the specific part of the breast. In case of SRS the single heavy dose is given to patient in a single session, however, in SBRT technique low doses are given to the patient. The use of SBRT for oligo metastatic disease is still under debate, however, maximum positive results are obtained in case patients suffering from stage 1 cancer with limited metastasis. The efficacy of the SBRT is dependent on the abscopal effects [23]. The few formal evidences are reported but, still the SBRT is widely using for the treatment. It is majorly use for the oligometastases appear consensual treatment in the elder patients. SBRT is associated with the 13-month improvement. When comparing to the conventional radiotherapies the delayed side effects are associated with the SBRT. No and very few acute complications are associated with the SBRT [24].

Combination of Radiation therapy with neo-adjuvant chemotherapy

For the treatment of the locally advanced breast cancer the neoadjuvant chemotherapy are highly suggested. Triple

negative breast cancer is treated by neoadjuvant chemotherapy. In this type of cancer maximum receptors i.e Human epidermal growth factor receptor 2 and progesterone receptor are negative.

Poly ADP-ribose polymerase Inhibitor with Chemotherapy

The combination of Poly ADP-ribose polymerase Inhibitor with chemotherapy show the potential synergism. However the reason behind the limited use of this combination is the reported PARPi toxicity. The results and outcomes were analyzed and evaluated. This therapy was observed to improve the response rate and quality of the life. The PARPi can be used as an alternative to the platinum based neoadjuvant regimen.

Immune-check point inhibitor with chemotherapy

The immune-check point inhibitor (ICI) have the evident anticancer activity. The patients diagnosed with the breast cancer can derive benefits from this therapy. The chemotherapy and ICI are proved to effective in the treatment of the metastatic breast cancer. Neoadjuvant ICI are associated with the higher outcomes [25].

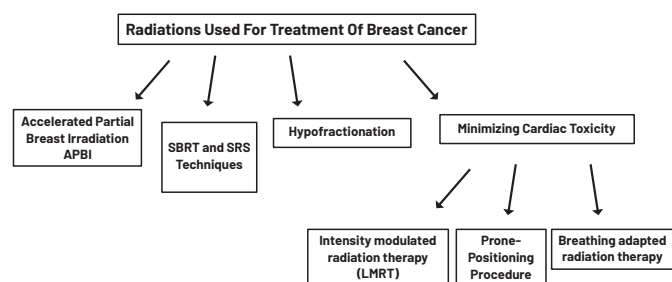


Figure1: Summary

CONCLUSIONS

Breast cancer development is a multi-step process. Multiple cells are involve in the development of breast cancer. Radiation therapy is the mainstay of the breast cancer. Radiation therapy is effectively used for the treatment and management of loco regionally advanced and distant metastatic disease. There is research going on to find most appropriate technique in which convenient and protected procedure is used for patients to avoid any side effects. Neoadjuvant chemotherapies are used to minimize the cytotoxicity. New and advanced techniques are used to limit radiation related toxicity.

Conflicts of Interest

The authors declare no conflict of interest

Source of Funding

The author(s) received no financial support for the research, authorship and/or publication of this article

REFERENCES

- [1] Van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *Journal of the National Cancer Institute*. 2003 Jul; 95(13): 971-80. [doi: 10.1093/jnci/95.13.971](https://doi.org/10.1093/jnci/95.13.971)
- [2] Li F, Zheng X, Liu Y, Li P, Liu X, Ye F, et al. Different roles of CHOP and JNK in mediating radiation-induced autophagy and apoptosis in breast cancer cells. *Radiation Research*. 2016 May; 185(5): 539-48. [doi: 10.1667/RR14344.1](https://doi.org/10.1667/RR14344.1)
- [3] Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clinical Cancer Research*. 2005 Jan; 11(2): 728-34. [doi: 10.1158/1078-0432.728.11.2](https://doi.org/10.1158/1078-0432.728.11.2)
- [4] Eccles SA, Aboagye EO, Ali S, Anderson AS, Armes J, Berditchevski F, et al. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Research*. 2013 Oct; 15(5): 1-37. [doi: 10.1186/bcr3493](https://doi.org/10.1186/bcr3493)
- [5] Majeed W, Aslam B, Javed I, Khaliq T, Muhammad F, Ali A, et al. Breast cancer: major risk factors and recent developments in treatment. *Asian Pacific Journal of Cancer Prevention*. 2014; 15(8): 3353-8. [doi: 10.7314/APJCP.2014.15.8.3353](https://doi.org/10.7314/APJCP.2014.15.8.3353)
- [6] Hillner BE, Ingle JN, Berenson JR, Janjan NA, Albain KS, Lipton A, et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. *Journal of Clinical Oncology*. 2000 Mar; 18(6): 1378-91. [doi: 10.1200/JCO.2000.18.6.1378](https://doi.org/10.1200/JCO.2000.18.6.1378)
- [7] Chinnaiyan AM, Prasad U, Shankar S, Hamstra DA, Shanaiah M, et al. Combined effect of tumor necrosis factor-related apoptosis-inducing ligand and ionizing radiation in breast cancer therapy. *Proceedings of the National Academy of Sciences*. 2000 Feb; 97(4): 1754-9. [doi: 10.1073/pnas.030545097](https://doi.org/10.1073/pnas.030545097)
- [8] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *International Journal of Radiation Oncology* Biology* Physics*. 2011 Jan; 79(1): 10-8. [doi: 10.1016/j.ijrobp.2009.10.058](https://doi.org/10.1016/j.ijrobp.2009.10.058)
- [9] Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American cancer society/American society of clinical oncology breast cancer survivorship care guideline. *CA: a cancer journal for clinicians*. 2016 Jan; 66(1): 43-73. [doi: 10.3322/caac.21319](https://doi.org/10.3322/caac.21319)

- [10] Cui L, Song Z, Liang B, Jia L, Ma S, Liu X. Radiation induces autophagic cell death via the p53/DRAM signaling pathway in breast cancer cells. *Oncology reports*. 2016 Jun; 35(6): 3639-47. doi: [10.3892/or.2016.4752](https://doi.org/10.3892/or.2016.4752)
- [11] Nadine A, Easton DF, Chang-Claude J, Rookus MA, Brohet RM, Cardis E, et al. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. *Journal of Clinical Oncology*. 2006 Jul; 24(21): 3361-6. doi: [10.1200/JCO.2005.03.3126](https://doi.org/10.1200/JCO.2005.03.3126)
- [12] Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al. American Society of Clinical Oncology Clinical Practice Guideline update on the role of bone-modifying agents in metastatic breast cancer. *JCO Oncology Practice*. 2011 Mar; 7(2): 117-21.
- [13] Weichselbaum RR, Ishwaran H, Yoon T, Nuyten DS, Baker SW, Khodarev N, et al. An interferon-related gene signature for DNA damage resistance is a predictive marker for chemotherapy and radiation for breast cancer. *Proceedings of the National Academy of Sciences*. 2008 Nov; 105(47): 18490-5. doi: [10.1073/pnas.0809242105](https://doi.org/10.1073/pnas.0809242105)
- [14] Nandi S, Guzman RC, Yang J. Hormones and mammary carcinogenesis in mice, rats, and humans: a unifying hypothesis. *Proceedings of the National Academy of Sciences*. 1995 Apr; 92(9): 3650-7. doi: [10.1073/pnas.92.9.3650](https://doi.org/10.1073/pnas.92.9.3650)
- [15] Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. *Biological research*. 2017 Dec; 50(1): 1-23. doi: [10.1186/s40659-017-0140-9](https://doi.org/10.1186/s40659-017-0140-9)
- [16] Yu L, Yang Y, Hou J, Zhai C, Song Y, Zhang Z, et al. MicroRNA-144 affects radiotherapy sensitivity by promoting proliferation, migration and invasion of breast cancer cells. *Oncology reports*. 2015 Oct; 34(4): 1845-52. doi: [10.3892/or.2015.4173](https://doi.org/10.3892/or.2015.4173)
- [17] Fan S, Smith ML, Rivert DJ, Duba D, Zhan Q, Kohn KW, et al. Disruption of p53 function sensitizes breast cancer MCF-7 cells to cisplatin and pentoxifylline. *Cancer research*. 1995 Apr 15; 55(8): 1649-54.
- [18] Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & diseases*. 2018 Jun; 5(2): 77-106. doi: [10.1016/j.gendis.2018.05.001](https://doi.org/10.1016/j.gendis.2018.05.001)
- [19] Hussain A, Bourguet-Kondracki ML, Hussain F, Rauf A, Ibrahim M, Khalid M, et al. The potential role of dietary plant ingredients against mammary cancer: a comprehensive review. *Critical Reviews in Food Science and Nutrition*. 2022 Mar; 62(10): 2580-605. doi: [10.1080/10408398.2020.1855413](https://doi.org/10.1080/10408398.2020.1855413)
- [20] Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *European heart journal*. 2016 Jun; 37(21): 1671-80. doi: [10.1093/eurheartj/ehw022](https://doi.org/10.1093/eurheartj/ehw022)
- [21] Horwitz KB, Koseki Y, Mcquire WI. Estrogen control of progesterone receptor in human breast cancer: role of estradiol and antiestrogen. *Endocrinology*. 1978 Nov; 103(5): 1742-51. doi: [10.1210/endo-103-5-1742](https://doi.org/10.1210/endo-103-5-1742)
- [22] Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1999 Feb; 85(3): 640-50. doi: [10.1002/\(SICI\)1097-0142\(199902\)85:3%3C640::AID-CNCR14%3E3.0.CO;2-G](https://doi.org/10.1002/(SICI)1097-0142(199902)85:3%3C640::AID-CNCR14%3E3.0.CO;2-G)
- [23] Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *The lancet oncology*. 2015 Jan; 16(1): 47-56. doi: [10.1016/S1470-2045\(14\)71156-8](https://doi.org/10.1016/S1470-2045(14)71156-8)
- [24] Farnie G, and Clarke RB. Mammary stem cells and breast cancer—role of Notch signalling. *Stem cell reviews*. 2007 Jun; 3(2): 169-75. doi: [10.1007/s12015-007-0023-5](https://doi.org/10.1007/s12015-007-0023-5)
- [25] Ghayad SE, and Cohen PA. Inhibitors of the PI3K/Akt/mTOR pathway: new hope for breast cancer patients. *Recent patents on anti-cancer drug discovery*. 2010 Jan; 5(1): 29-57. doi: [10.2174/157489210789702208](https://doi.org/10.2174/157489210789702208)