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# Most Efficient Methods to Treat Breast Cancer

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# Most Efficient Methods to Treat Breast Cancer

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### Abstract
Breast cancer is rampant in today's world. Because there are many different cases and so many different ways to classify breast cancer, a multidisciplinary approach must be taken. Many patients undergo breast conserving surgery which creates a need for the eradication of any remaining tumor residue through radiation. Fifty Gy of radiation should be applied to the breast with an additional 16 Gy as a boost. If a mastectomy is performed to remove a large tumor and 4 or more positive lymph nodes were present, radiation should be applied as well. If the tumor expresses HER2 protein, Trastuzumab should be given to "turn off" the protein. If a patient's cancer is hormone receptor positive, Tamoxifen should be given. If, however, the patient is premenopausal, the Tamoxifen must be given together with ovarian suppressors.

### Introduction
Breast cancer can almost be considered an epidemic in today's world. It is the most frequently occurring cancer in women worldwide. (Li, 2016) It has become evident that breast cancer diagnoses have increased because screening methods have become more efficient and because overall life expectancy has been lengthened in recent years. In most cases, breast cancer is treated by removal of the tumor and surrounding areas. Sometimes neo-adjuvant (prior to surgery) therapy is given. Alternatively, treatment only begins after surgery. Afterwards radiation is applied to the tumor site and surrounding areas. In addition, if the tumor is hormone receptor (estrogen or progesterone or both) positive, patients will undergo hormone therapy as well as chemotherapy. This paper will discuss radiation therapy and hormone therapy as a systemic treatment but will not cover chemotherapy.

### Methods
This article was written through the analysis of various original research and peer reviewed journal articles. Access was obtained through PubMed and the Touro College Library.

### Results and Discussion
### Breast Conserving Treatment and Mastectomy
Breast cancer treatment has shifted from total mastectomy toward breast conserving therapy. From the 1970's, studies have shown that breast conserving surgery with radiation have the same effects as the Halsted (radical) Mastectomy for tumors up to 5 cm. (Veronesi, et.al 2013) When a patient with breast cancer undergoes breast conserving therapy, radiation of the breast and some surrounding areas is usually applied (Aebi, et.al 2011). Even after mastectomy, radiation is required if there are four or more lymph nodes found that ae positive for cancer.. There was no observed benefit from radiation in women with node negative disease. (EBCTCG, McGale, et.al. 2014) Post-mastectomy radiation is recommended if the tumor is 5 cm or larger, there are at least 4 positive nodes, a positive margin of resection, or skin involvement. However, because of the psychological effects of mastectomy, breast conserving surgery is now considered an acceptable form of treatment even when the tumor is large, as long as the breast can be reshaped. Now, about 25% of women diagnosed with breast cancer undergo mastectomy, usually because of large tumor size, location of the tumor, or local recurrence following a previous breast conserving surgery. (Orecchia, 2015)

In order to reduce the psychological effects and cosmetic drawbacks of mastectomy, the skin sparing method has been introduced. One recent development in the skin sparing method is nipple-sparing mastectomy which allows for the preservation of the nipple areola complex. However, there has been increased recurrence behind the areola following nipple sparing mastectomy. Therefore, radiation is performed on patients that are at greater risk of recurrence. There is no standard practice in patients who have an intermediate or low risk and radiation's role in this case is unclear. (Orecchia, 2015) Although further research is needed, this new method can open up new opportunities for better methods of breast reconstruction.

### Comparison of Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation
A study was performed to see whether mastectomy, lumpectomy, and lumpectomy plus irradiation had different effects on survival. Follow up after 20 years showed no significant difference in survival between the group that underwent mastectomy as opposed to the groups that underwent lumpectomy with or without radiation. This study did not show any risk of radiation causing cancer in the contralateral breast which is a common concern. The findings at 20 years of follow up did indicate that lumpectomy with irradiation significantly decreases recurrence when compared to lumpectomy without irradiation. However, perhaps, if wider margins were removed at the time of breast conserving surgery, the need for radiation afterwards would be eliminated. (Fisher, et.al. 2002)

### Effects of Radiation following Breast Conserving Surgery
Breast conserving surgery can be performed on women with a less advanced stage of breast cancer by removing any microscopic residual of the cancer. However, macroscopic bits of the tumor can remain in the breast or nearby area; therefore radiation is commonly used to prevent local recurrence and distant metastases. In one study, 10,801 women were included to see how radiation can reduce the risk of recurrence and death

including different variables, such as age, tumor size, and nodal status. This study differs from previous studies in three ways. Firstly, it assumes that all recurrence whether it is locoregional or distant is related to the tumor that preceded it. Therefore all recurrence is considered as first recurrence. Secondly, previous studies obtained follow up results for 10 years, and this one goes up to 15 years. Lastly, previous studies considered death of unknown causes within the first 10 years to be attributed to breast cancer, but this study attributes it to other causes. (EBCTCG, Darby, et.al. 2011).

When radiation was applied after breast conserving surgery, the 10-year risk of recurrence dropped to 19.3% as opposed to 35.0% in women that did not undergo radiotherapy. The risk reduction in this case is 15.7% for women who had radiotherapy following breast conserving surgery. Three quarters of the recurrence in those that had no radiation therapy was of a local nature while fewer than half of those in the radiation group had a locoregional recurrence. In addition, radiation reduced the risk of cancer related mortality to 3.8% in 15 years, which suggests that for every 4 recurrences avoided due to radiation, one death was prevented.

Radiation halved the risk of annual first recurrence and it reduced cancer related death by a sixth. However, mortality without recurrence (death from other causes) was slightly higher during the first 10 years in the radiation following breast conserving surgery group than those who did not have radiation. The higher death rate in the radiation group can be attributed to the toxicity of the radiation. However, this is not considered significant because it is such a minuscule percentage. On average, including all the women of all the different groups (node status, age, endocrine receptor responsiveness, etc.), during a 15-year period, one death was avoided for every four recurrences avoided by year 10.

This study considers any instance of recurrence, no matter where it occurs, as a first event rather than only considering locoregional recurrence as a first event as other studies have done. This gives more accurate results than previous studies. Different kinds of recurrences cannot be ignored because radiation is assumed to reduce all recurrences. Because this study gathered data from patients with a wide range of risks and overall, radiation halved the risk of recurrence, it can be assumed that it will reduce the risk in future patients as well by a half. (EBCTCG, Darby, et.al. 2011).

### Boost

After 50 Gy radiation on the breast, a 16 Gy boost is recommended except for in patients with a low risk for local recurrence. (Aebi, et.al 2011) As stated previously, radiation prevented one death in a 15-year follow up for every four instances of local recurrence prevented in a 10-year follow up. However, because of the intensity of the radiation, fibrosis frequently occurred which caused a poor cosmetic result. (Bartelink, et.al. 2007) In one trial, the boost dose was lowered from the previously accepted 25 Gy to 16 Gy because of the high percentage of patient fibrosis which resulted from the intensity of the boost. There were 5,569 breast cancer patients who were included in the boost vs. no boost study. The patients were no different from each other with respect to surgery or whole breast irradiation. Local recurrence in the no boost group after 10 years was 4% higher than in the boost group. Incidence of fibrosis at 10 years was 4.4% in the boost group as opposed to 1.6% in the no boost group. Although a boost of 16 Gy was shown to decrease the rate of local recurrence in this study, no improvement has been discovered in disease-specific survival or overall survival. However, this could be because of the success of salvage mastectomy which was performed on the no boost group when they began to exhibit signs of local failure. The risk of fibrosis for those in the boost group is not of a significant level. (Bartelink, et.al 2015).

The above study was done over a period of 10 years. A different study was performed which included 20-year follow up for all patients. This trial was performed to see if a boost dosage of 16 Gy decreased the rate of recurrence. A 5-year follow up study showed that it does decrease recurrence. A 10-year follow up showed that when a boost is delivered, the rate of salvage mastectomies decreases. In the 20-year follow up, local recurrence was 13% in the no boost group as opposed to 9% in the boost group. Incidence of fibrosis was a little bit higher (about 4%) in the boost group. The cumulative percentage for salvage mastectomies performed on the boost group was 6.4 vs. 10.3 for the no boost group. The fact that there was no improvement in overall survival in the boost group seems to show that the boost is not needed. However, this must be the result of the high rate of successful salvage mastectomies performed. The boost the number of salvage mastectomies by a third. (Bartelink, et.al 2015)

### Effects of Radiation following Mastectomy

Post mastectomy radiation is used to treat women with four or more positive lymph nodes to ensure complete removal of any residual tumor foci. However, the role of radiation in treating women post mastectomy with one to three positive lymph nodes still remains uncertain. As of now, post mastectomy radiation is not given to women who have node-negative disease. The following study included 8,135 women who had 1 to 3 positive lymph nodes. About 20% of the women had node-negative disease, 72% had node positive disease, and the nodal status for the remaining ones was unknown.

Radiation therapy was shown to significantly decrease the rate of recurrence and breast cancer death in the group that had 1 to 3 positive lymph nodes. Radiation was not seen to have any added positive benefit in women who had node negative disease. Radiation reduced the 10 year risk of recurrence in women with 1 to 3 positive lymph nodes from 45.7% to 34.2% which is an overall absolute benefit of 11.5%. Today, radiation treatments cover more of the high risk areas, such as the chest wall. In addition, the doses are lower than they used to be so the risks of radiation have decreased. Therefore, the proportional gains of radiation today are probably greater than the results of this study. However, within the 20 years in which this study has been performed, methods of detection and treatment have improved; therefore the absolute benefits of radiation are lower than those reported in this study. (EBCTCG, McGale, et.al 2014).

### Intraoperative Radiotherapy

There is new research in the field of intraoperative radiotherapy to treat many different kinds of cancers including breast cancer. Instead of a few weeks or months of radiation post breast conserving surgery, patients can be treated with a dose of radiation at the surgery itself. Although the average time of radiation has decreased over the last couple of years, it is still a strain and inconvenience on the women who must travel to the hospital every day for about 30 days to receive treatment. Another advantage of intraoperative therapy over mastectomy is that if recurrence occurs after breast conserving surgery and a mastectomy is needed, it is easier to perform it with the now popular method of skin and or nipple sparing procedures if no radiation was applied to the skin because radiation can cause necrosis. (Veronesi, et.al. 2013) In addition, intraoperative radiation therapy can target the cancerous tissue while protecting the normal tissue around the tumor. (Najafipour, et.al, 2015).

In one trial, the effects of intraoperative radiation on a number of different cancers was tested. Intraoperative radiation was found to increase survival in patients with pancreatic cancer. When used on patients with early breast cancer, it was found to decrease life expectancy by less than a day. Although it may increase operating room load, it is generally a cost effective and considered a safe method to treat breast cancer. (Najafipour, et.al, 2015) However, more research must be done to see if this new method has any real advantage.

In another study, 1305 patients were randomized, 654 belonging to the external radiotherapy group and 651 to the intraoperative group. Only 11% had more than 4 positive nodes. In this study, ipsilateral breast tumor recurrence was defined as "the sum of local recurrence plus 2nd ipsilateral tumors." Local recurrence was considered the recurrence of the carcinoma at the previous location. Within five years of follow up, there was a significantly greater instance of recurrence in the intraoperative radiation therapy group than in the external radiotherapy group. Overall survival, however, did not differ significantly between the two groups. Predictions are that in the future, better methods will be used to differentiate between patients who are at higher risk of recurrence and therefore need external whole breast irradiation or intraoperative radiation plus external radiation. (Veronesi, et.al 2013) It must be noted that this study only measured 5 years which considered short term follow up in a study of this sort.

### Testing for Endocrine and HER-2 Receptivity

*Trastuzumab*

Overexpression of HER2 protein occurs in 20-25% of breast cancers, causing high-grade tumors, increased growth rates, early systemic metastasis, and reduced rates of overall and disease free survival. (Slamon, et.al 2011) Trastuzumab (Herceptin) is given many times in conjunction with chemotherapy, but it can also be given alone. Trastuzumab does not cause the negative side effects that other chemotherapy medications are known for, such as alopecia, myelosuppression, and severe nausea. However, Trastuzumab has been known to cause cardiotoxicity in 1.4% of those to whom it was administered to. (Piccart-Gebhart, et.al 2005) Various studies were performed to find out how much Trastuzumab actually improved disease free survival and whether the increase in cardiotoxicity was a cause for concern.

One study included 4,482 women. Both groups received Trastuzumab after undergoing primary treatment (surgery, chemotherapy, radiation, ect.). One group received it for one year, the other for two. Patients with a history of cardiac trouble were excluded from this study. The study shows that Trastuzumab given after primary treatment reduces the rate of recurrence by 50%. It does not seem to make a difference what type of chemotherapy is received. The risk of cardiotoxicity is low; however, it is possible that this is because there is a short follow up in this study. In addition, there is a concern that longer term follow up will show that Trastuzumab does not reduce disease recurrence in the central nervous system. The results of this study indicate that one year of Trastuzumab should be used following primary treatment of breast cancer. (Piccart-Gebhart, et.al 2005).

A study was performed to see whether an anthracycline-based regimen increased Trastuzumab's toxicity. There were 3,222 women who were divided into three groups. One group underwent an anthracycline regimen. In the second group, the patients received anthracycline with Trastuzumab. In the third group, the patients only received Trastuzumab. All three groups

underwent an intense cardiac monitoring schedule. A significant benefit was seen in patients who received Trastuzumab as opposed to patients who did not. There were no apparent differences between the two Trastuzumab goups; however the trial was not set up to discern a difference between them. Congestive heart failure occurred more often in the group that received anthracycline in addition to Trastuzumab. In addition, treatment time is decreased when anthracycline is not given. (Slamon, et.al. 2007).

### Hormones and their effect on Breast Cancer and breast cancer treatment

In the Million Women Study conducted in the UK, over 1 million women between the ages of 50-64 were recruited to have a breast screening every three years. The women were given a survey to complete shortly before their screening. (The questionnaire can be viewed at http://www.millionwomenstudy.org). The purpose of the study was to see if and how hormone replacement therapy affects breast cancer. In total, 50% of the population had used hormone replacement therapy at some time. The results of the study proved that recent or current users of hormone replacement therapy are at increased risk of breast cancer. Those using estrogen-progestogen combinations have a four times greater risk than those using estrogen-only preparations. However, past users of hormone replacement therapy have almost no increased risk. In all, hormone replacement therapy results in 5 to 6 more cancers per 1,000 women with 5 years use and 15-19 extra cancers per 1,000 women with 10 years use. (Million Women Study Collaborators, 2003).

The Million Women Study, because of its large number of participants and span of time, has been the source of much controversy. It has been pointed out the women who participated in the study are not a good sampling of the general population because women that use hormone replacement therapy are more likely to be concerned about their risk of cancer and go for a mammogram. (Eden, 2010) However, the Million Women Study represented 53% of the population, so although this may be 53% of the population that is more likely to be affected by hormone replacement therapy, over half a population is a good indication of the rest of the population.

### Hormone Therapy

Soon after a patient is diagnosed with breast cancer, she is tested to see whether her tumor is hormone receptor positive of negative, defined by estrogen and/or progesterone receptivity. Accurate assessment is critical in deciding whether to treat with hormone therapy; however, accurate results are difficult to obtain.

In the past, tumors that showed less than 10% positivity were not given hormone therapy because they seemed similar to patients who tested negative for hormone receptivity. Recently, however, The ASCO/CAP guidelines were revised to treat women in the 1%-9% positivity group with hormone therapy. Now 3% more women are being treated with hormone therapy. The problem is that although for a small minority of cases, hormone therapy has a good positive result on those in the 1-9% group, physicians must consider the benefits of endocrine therapy versus its cost and side effects. (Yi M, et.al 2014) The goal of this study, as noted above, was to show that perhaps the benefits of treating the 1-9% group with endocrine therapy do not outweigh the costs. However, this study has limitations. They retroactively collected the data and because of that, the Estrogen receptor status is not known for certain because the patients obtained their diagnosis outside the facility where this study was performed. In addition, the study's limited sample size makes it very difficult to analyze the data based on results from adjuvant chemotherapy and endocrine therapy.

A later study shows that even with a very small percentage of Estrogen receptor positivity, adjuvant hormone therapy cut breast cancer mortality by a third for fifteen years. Those who had hormone receptor treatment were found, initially, to have lower rates of recurrence than those without; however, they do risk relapse for up to fifteen years despite usage of Tamoxifen for five years. (EBCTCG, Davies, et.al. 2011).

The suppression of hormones and the target of HER2 receptors is a not a new development in medicine. Two cohorts, comprised of 7,178 patients, were studied to see whether current hormone treatment is more effective than that of the past. One cohort was diagnosed recently, and the other was diagnosed from 1986-1992. Relapse event was any disease recurrence. In all, 1,700 patients had relapsed in 9 years of follow up. The result showed that the current treatments are more effective because they are used for longer and they are more efficient. However, patients with ER+ tumors do seem to have a late relapse and ER- tumors have an early relapse in patients that were recently diagnosed. (Cossetti, et.al 2014).

Another study was performed in 1996 to see whether there is a difference and how significant of a difference 2 years of Tamoxifen makes compared to 5 years of treatment . The results showed that 5 years was more effective. They did not test past 5 years; therefore, they do not know if more than 5 years would be more effective. (Swedish Breast Cancer Cooperative Group, 1996).

Premenopausal hormone receptor positive breast cancer is treated by ovarian ablation or suppression. The ovaries still

function in premenopausal women and they are the main site for hormone production. The aromatization of androgens in the adrenal glands produces hormones in postmenopausal hormone-receptor positive breast cancer. Aromatase Inhibitors (AI's) inhibit the production of those hormones. AI's fall into two categories: non-steroidal and steroidal AI's. Across the board, AIs are superior to Tamoxifen. The ovaries are only temporarily suppressed when women are premenopausal for preservation of fertility. (Li, et.al. 2016).

### The Premenopause/Post-menopause treatment methods

Tamoxifen is the standard drug to treat hormone receptor positive breast cancer. Premenopausal patients, however, are often resistant to Tamoxifen. Therefore ovarian function suppression medications are combined with Tamoxifen in order to reduce disease recurrence in pre-menopausal women. Ovarian function suppression medications increase toxicity, complicating overall treatment regimens. (Kim et. al, 2016).

Two trials were performed, the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT), to determine whether the aromatase inhibitor Exemestane improved survival in premenopausal women when used in conjunction with Tamoxifen as opposed to women treated with ovarian suppressors with Tamoxifen. The combined data from the two studies shows that Exemestane plus ovarian suppression as opposed to Tamoxifen plus ovarian suppression significantly improved survival and decreased risk of recurrence. (Pagani et. al, 2014) However, in the SOFT study, the women who remained premenopausal and had an increased risk of recurrence and therefore needed adjuvant chemotherapy, the addition of ovarian suppression treatments improved survival rates (Kim et. al, 2016) Because these women received additional chemotherapy, it is not clear whether it is the chemotherapy or the ovarian suppression that increased survival.

A Korean Study was performed to compare ovarian function suppression with Tamoxifen versus just Tamoxifen in young, premenopausal women who had undergone chemotherapy. The main purpose of this study was to compare the 5-year disease-free survival rates between the two groups. The Korean Breast Cancer Society focused on this age range because although South Korea has an overall smaller number of breast cancer diagnoses compared to the world at large, 48.7% of breast cancer diagnoses are in premenopausal women under the age of 50 which is a much higher percentage of young women than in other countries.

The advantage of this study over other studies is that there is repeated evaluation of ovarian function, which allows for better selection of patients that should be receiving ovarian function suppression treatments, avoiding unnecessary side effects. Ovarian suppression causes menopausal symptoms which significantly alter the the quality of life. These symptoms can lead to a lack of patient compliance and can also destroy physician-patient relationship (Kim et. al, 2016). This study shows the benefit of Tamoxifen plus ovarian suppression therapy in premenopausal patients with Estrogen receptor positive breast cancer treated with chemotherapy. This trial helps determine the optimal endocrine therapy needed based on ovarian function status of premenopausal patients.

### Conclusion

The patient must undergo a mastectomy if reconstruction of the breast post breast conserving surgery is impossible or not feasible. However, mastectomy is not as radical as it once was. Moreover, now there are new skin sparing methods, such as the nipple areolar sparing method which allows for a more natural reconstruction after surgery. Post mastectomy radiation is given in women with 4 or more positive lymph nodes, but in women with 1-3, the question still remains. Studies show that in women with 1-3 positive lymph nodes, recurrence is reduced by over 10%.

In about 75% of cases, patients undergo breast conserving surgery. Except in cases of very low risk of recurrence, patients must have radiation afterwards. However, perhaps better tumor residue removal will be employed which can eliminate the need for radiation therapy. After breast conserving surgery, radiation reduces risk of recurrence within 10 years from 35% to 19%, a significant difference. Radiation prevents one death for every four recurrences prevented (a 3.8% decrease). Radiation does increase toxicity; however, the percentage is so low, that they give radiation anyways. However they do try to keep dosages low. A radiation boost after the radiation treatment regimen decreases recurrence by 4% over a period of 10 years and after 20 years. There is no difference in overall survival between the group which received a boost and the one that didn't because of salvage mastectomies and other retroactive treatments performed. The risk of fibrosis does increase by the same percentage as survival in the boost group.

Trastuzumab is given to those that test positive for HER2 expression. Although it does increase cardiotoxicity in 1.4% of cases, it has less side effect than other chemotherapy medications. However, the risk of toxicity may be low in this study because of a short (5 year) follow up. A longer follow up may show a larger percentage of toxicity.

Hormone replacement therapy increases one's risk of getting breast cancer. Those who take an estrogen-progesterone

combinations have a four times greater risk of developing cancer than those who take estrogen only. Each woman together with her doctor must decide whether the benefits outweigh the risks in taking hormone replacement treatment. This treatment increases the quality of life for post-menopausal women; however if someone has an increased risk of developing breast cancer, they should not take this treatment. The Million Women Study does represent most of the population. However, sometimes large studies cannot take certain factors into because although they do divide their sample by different characteristics, there are too many people to be very exact and specific.

New guidelines have been set up, so now women with 1-9% hormone positive lymph nodes get hormone therapy. However the study that proved that this change is necessary (from the previous about 10%) has limitiations. Firstly, they collected the data retroactively, so they could not be certain that all of it was correct, and they had a limited sample size. Those that are hormone receptor positive and take hormone therapy for five years do initially have decreased recurrence, but they do risk relapse for up to 15 years.

In the study where a group received hormone therapy from 1986-1992 was compared to a more recent group, it was proven that hormone therapy is more effective now because the therapies are more efficient and they are used for longer than they once were. Although those with hormone receptor positivity have a better prognosis, they are at risk for a relapse albeit much later than those with hormone receptor negative cancer. Hopefully new research and discoveries will lead to a more permanent and better prognosis.

Premenopausal women are resistant to Tamoxifen, so it is usually applied together with ovarian suppressors. These suppressors can increase toxicity, but they do improve. As the Korean study noted, repeated evaluation of ovarian function can allow for better selection of patients which can avoid unnecessary side effects which lower quality of life.

All the above research shows that there is no one best method to treat breast cancer. Treatment must have a multidisciplinary approach. Each patient must be treated as an individual with all symptoms and disease specifics taken into account.

There are various limitations that studies have. One limitation is that studies, by their very nature, must be performed under certain assumptions, like assuming that death of an unknown cause within 10 years is disease mortality which may or may not be the case. In addition, a large sample size can cause a "one size fits all" attitude. Trials involving breast cancer patients have an advantage because there are many people who have breast cancer. However because of the large study size, at times there is not enough specification of treatment. One woman may seem to have the same diagnoses as another, but some important differences may not be accounted for. For example, a woman who tests positive for HER2 receptor and has 8.5% hormone receptor positivity will be given Trastuzumab and hormone therapy, but perhaps she has a risk of heart disease in her family and the increased cardiotoxicity will be more harmful for her than the average patient. It is not enough for doctors to be up to date on different treatment advances, they must create a treatment plan that takes each individual patient's needs, background, and overall health into account.

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