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Breast Conserving Therapy vs Mastectomy in Treatment of Early Breast Cancer Patients. Does BRCA1/BRCA2 Status Change Treatment Recommendations?

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Table of Contents

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Abstract

In the United States, breast cancer is the second most common cancer, represents 30% of total cancer cases and 14% of deaths in the United States in 2019. BRCA1 and BRCA2 are genetic mutations that increase the likelihood of developing breast cancer by 57% and 49%, respectfully. Several surgical options are available for those with newly diagnosed early-stage breast cancer. The purpose of this systemic literature review is to evaluation the safety and efficacy of breast conserving therapy versus mastectomy for surgical intervention of early-stage breast cancer patients and evaluate if possessing a BRCA positive mutation changes the recommendation for surgical interventions. In this review, PubMed was searched with a variety of key terms used. 22 sources were selected for literary review that were published after 2001, peer reviewed, and included randomized control trials, systematic reviews, and meta-analyses. The data concludes to breast conserving therapy and mastectomy being effective treatments for those with early-stage breast cancers, although research is conflicted. There were no studies suggesting either treatment was harmful to the patient, although surgical risks are involved. When evaluating for BRCA positive status, both breast conserving therapy and mastectomy appear to be effective treatments. BRCA positive patients who undergo breast conserving therapy carry a significant risk for ipsilateral and contralateral breast cancer years after diagnosis. More research needs to be done to come to a more concise conclusion on whether breast conserving therapy or mastectomy is the preferred surgical treatment and if recommendations change based on BRCA status.

Keywords: BRCA mutations, Breast Cancer, Mastectomy, Breast Conserving Therapy, Surgical management, Early-Stage Breast Cancer.

Introduction

In 2018, breast cancer took more than 600,000 lives. BRCA1 and BRCA 2 genetic mutations are associated with 5-10% of the approximately 2 million new cases of breast cancer in the United States every year. BRCA1 and BRCA2 are genetic mutations that can increase the likelihood of developing breast cancer by 57% and 49%, respectfully. Many breast cancer diagnoses and treatment plans are severely complicated by factors including but not limited to age, overall health of the patient, tumor size, hormone receptors associated with them, staging and the treatment options available for each. Surgical therapies are available for patients in many situations. In some patients, bilateral mastectomy may pose too great a risk to the patient or is not the preferred treatment option. The purpose of this study is to help guide treatment options based on safety and efficacy, while considering patient preference. While there are many other systemic treatment options for breast cancer, the purpose of this review of the literature will look specifically at the safety and efficacy of breast conserving therapy (BCT) compared to mastectomy and then evaluate if these treatment options are different for patients who are positive for the BRCA1/BRCA 2 genetic mutations.

Statement of the Problem

Breast cancer treatments have been around for many years. There are many different options, all with varying degrees of adequacy of treatment and risks depending on the patient's specific diagnosis. Years of research have been published on the safety and effectiveness of mastectomy and BCT. Knowing the BRCA1 or BRCA2 status could impact which treatment option is most appropriate. It is necessary for medical providers to be informed in appropriate treatment options for providing guidance to which is the safest and most effective treatment while considering the patient's personal preference. It is important for provider to be able to

answer a multitude of questions concerning breast cancer and overview of the treatment option that a patient may have before meeting with their oncologist. This may provide some background information on their diagnosis.

Research Question

Is there a statistically significant difference in the safety and efficacy of treatment when using breast conserving therapy verses mastectomy for surgical intervention in patients diagnosed with early breast cancer? Does BRCA1/BRCA2 status have an impact on the recommendations regarding surgical treatment of breast conserving therapy versus mastectomy?

Research Methods

A literature review was performed using electronic search database, PubMed. Both keywords and mesh terms were used to define a set of the literature discussing BRCA mutations and treatment options. The literature was further searched for breast cancer surgical treatments, breast conserving therapy, mastectomy, and breast conserving therapy vs mastectomy in BRCA positive patients all in separate searches. Additional research articles were found via Similar articles in PubMed. Reference list of articles were examined and picked based on applicability. All searches were narrowed to the past 20 years. The searches revealed a total of 55,501 studies for breast cancer surgical treatment, 10, 068 studies for breast conserving therapy, 940 studies for breast conserving therapy vs mastectomy, 571 studies for mastectomy in BRCA. Many studies were excluded as they were focused on other cancers such as endometrial, pancreatic, or ovarian cancer. Multiple studies were excluded because the focus of the study was on prophylactic treatment options exclusively and those with focus on a specific receptor type. All studies not in English were excluded. Multiple studies were excluded as they involved specifically systemic treatment options, holistic options, review analysis, alternative combinations of treatment options, and fertility concerns not included in this literary review.

Studies focusing on hormone status were not included in this study. 7 studies meet the criteria for overall testing and treatment options, 2 studies met the criteria for breast conserving therapy, 1 study met the criteria for mastectomy, 12 studies met the criteria for comparison studies.

Literature review

Breast Cancer Introduction

In 2019 there were approximately 286,670 breast cancer cases and 41,400 breast cancer deaths. This represented 30% of the total cancer cases and 14% of deaths in the United States alone that year. Breast cancer cases are typically in postmenopausal women, however annually about 4%-5% of breast cancer patients are women under the age of 40 (Yu et al., 2020). In 2018 breast cancer was responsible for over 2 million cases and exceeded 600,000 deaths making at the second most common cancer (Schick et al., 2021). 226,870 new breast cancer diagnoses were made in the United States in 2012 (Bayraktar & Gluck, 2012). These numbers represent the second most common cancer in the United States. Within breast cancer diagnosis, there are 21 specific and different types with differing histology. Each type has different presentations, risk factors, treatment options, treatment responses, and outcomes. Breast cancers are classified based on their hormone receptors including estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2). Different hormone receptor status can influence different therapy choices. A person's hormone receptor status can play an integral part in the decision making that goes into systemic treatment plans. This may include selective ER modulators (SERM) such as tamoxifen, chemotherapy such as carboplatin, or aromatase inhibitors (AIs) such as anastrozole and letrozole. The HER2 status can be used to determine if other treatments such as monoclonal antibodies, cyclin-dependent kinase (CDK) 4/6 inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, antibody-drug conjugates or tyrosine kinase hesitators are appropriate treatment options. There are many other experimental drugs that have not been approved by the US Food

and Drug Administration that are currently undergoing clinical trials (Schick et al., 2021). Additionally, lymph node involvement and the size of the tumor are considered when choosing appropriate treatment options. There may be specific sensitivity and resistance to traditional therapy in BRCA positive patients (Bayraktar & Glück, 2012). As of today, it is recommended that BRCA positive breast cancers and BRCA negative breast cancers are treated similarly (Atchley et al., 2008, Bayraktar & Gluck, 2012).

BRCA Introduction

226,870 new breast cancer diagnoses were made in the United States in 2012. Up to 10% may be positive for a genetic mutation known as BRCA1 and BRCA2 (Lambertini et al., 2017). BRCA mutations that affect the breasts are caused by DNA recombination. The BRCA1 is a tumor suppressor gene. Without BRCA1 and BRCA2, a patient's cells are unable to repair double stranded DNA breaks. As the cells continue to divide, the cell with the mutated DNA can become an important cell lineage and progress into a tumor. BRCA1 and BRCA2 tumors may have unique differences and need specific treatments (Bayraktar & Glück, 2012). Having a mutation in the BRCA gene will increase the risk of breast and ovarian cancer in a person's lifetime. The risk of developing breast cancer in a patient with a BRCA mutation by the age of 70 is 57% for BRCA1 mutation and 49% for BRCA2 mutation (Smith & Isaacs, 2011). BRCA mutations are more common during reproductive years for patients with breast cancer (Lambertini et al., 2017).

Contralateral breast cancer 10-year risk for BRCA1 mutation is approximately 27% and for BRCA2 mutation is 19%. There is a 5% risk of contralateral breast cancer for individuals who do not have the BRCA mutation (Park et al., 2018). The younger a patient is when diagnosed, the higher the risk of contralateral breast cancer, especially in BRCA1 positive

patients (Smith & Isaacs, 2011). BRCA1 positive breast cancers can show a higher nuclear grade diagnosis when compared to breast cancer patients with BRCA negative breast cancer and BRCA2 mutation patients ($p< 0.001$). BRCA1 positive patients are more likely to have separate and different pathology when compared to BRCA2 mutation positive patients and BRCA negative patients. Risk factors were noted to be similar between those with and without BRCA1 and BRCA2 mutations. In women with BRCA1 mutations, there were similar characteristics, such as age, use of hormone replacement therapy, number of pregnancies, ethnicity, and BRCA mutation status. BRCA2 mutations tend to be diagnosed at an older age than BRCA1 mutations and in those with negative BRCA mutation (Atchley et al., 2008).

When analyzing the risk of ipsilateral breast cancer recurrence, there was not a statistically significant difference between women who were found to have a BRCA mutation and those who did not have the mutation when treated with breast conserving surgery followed by radiation. There are separate analysis allowing 10 to 15 years to follow up which showed an increased risk of ipsilateral breast cancer recurrence in patients who were BRCA positive compared to those who were BRCA negative. It was noted that if an ipsilateral recurrence was to occur, it would be typically more than five years after the first breast cancer (Ginecologica et al., 2016).

Several factors that were important to understand before making treatment decision for patients with breast cancer. These include BRCA status, tumor pathology, the patient's general health, life expectancy, prognosis of the breast cancer and patient's preference of treatment. There are numerous other treatments that may coincide with surgery including radiation, chemotherapy PARP inhibitors, and tamoxifen (Smith & Isaacs, 2011; t'Kint de Roodenbeke et al., 2020). Additionally, having an oophorectomy to lower the exposure of estrogen in the patient

may be beneficial in breast cancer patients. Oophorectomy showed to lower all causes of mortality by 70%. Many of these treatment options can be used alone or in combinations with each other. Combining different therapies may allow patients the most effective prognosis in their breast cancer while lowering chances of recurrence, drug resistance, and adverse effects (Smith & Isaacs, 2011).

The screening recommendations for BRCA mutation positive patients after oncological treatment depends on the type of treatment the patient underwent. If a patient undergoes a bilateral mastectomy, follow up recommendations include annual breast exams with a medical professional and encouraging self-breast exams. Follow up breast imaging is not needed/required. If a patient has breast conserving surgery, the patient will alternate between having a mammogram or a breast MRI. Only one imaging modality is needed to be done per year (t'Kint de Roodenbeke et al., 2020).

Knowing a BRCA mutation has certain benefits including the possibility of lowering the number of subsequent surgeries, improving survival outcome, assessing for biomarkers (Bayraktar & Gluck, 2012; Park et al., 2018). BRCA genetic testing prior to surgical or other treatments can also be used to determine if the patient is better suited for alternative treatment options as results may change surgical decision making (Smith & Isaacs, 2011).

Breast Conserving Therapy

Breast conserving therapy (BCT) is a surgical technique that includes breast conserving surgery with the addition of adjuvant radiotherapy. In recent time, it has been increasingly popular for the treatment of breast cancer. This surgical technique allows saving healthy breast tissue and can be more aesthetically pleasing while being less invasive. This can result in improved physical and mental health of patients while improving quality of life (Sun et al, 2021).

A study by Botteri et al., (2017) was done to evaluate if BCT prognosis and safety over the years has improved. This study was particularly interested in women younger than 40 years of age due to the likelihood of diagnosis have a poorer prognosis. The study contained 1331 patients who were younger than 40 with early-stage breast cancer and had breast conserving surgery (BCS) with radiation between 1997 and 2010. The patients were followed for an average of 9.3 years and were monitored for local ipsilateral recurrence, additional breast cancer event (any recurrence or death from a breast cancer) and death. Patients were separated into three groups based on date of diagnoses. Group one was from 1997 to 2002 which included 524 patients, group two was from 2003 to 2005 which included 350 patients and group three was from 2006 to 2010 which included 457 patients.

Group one showed a risk of recurrence rate of 1.42 per 100 person-years, breast cancer event 3.01 per 100 person-years, and death risk of 1.59 per 100 person-years. Group two showed a risk of recurrence rate of 0.85 per 100 person-years, breast cancer event 2.52 per 100 person-years, and death risk of 1.22 per 100 person-years. Group three showed a risk of recurrence rate of 0.48 per 100 person-years, breast cancer event 2.07 per 100 person-years, and death risk of 0.64 per 100 person-years. P values for risk of recurrence was 0.028, breast cancer event was 0.004 and death was 0.003.

Results showed that as time passed, patients showed a decreased risk of recurrence, breast cancer event, and death. Large improvements in recurrence of breast cancer, and death were seen after 2005. The hypothesis from Botteri et al., (2017) was that this is due to changes in treatment due to implementation of breast cancer subtyping and trastuzumab as a medical practice treatment. A limitation to this study included using systemic therapy may have decreased patient having initial breast conservative surgery (Botteri et al., 2017).

Breast Cancer Recurrence Risks with Mastectomy

It is very important to consider certain risks before making breast cancer surgical treatment decisions. Risks can include recurrence to the ipsilateral or contralateral breast, survival potential of the patient with prophylactic mastectomy, or other risk factors that could influence any previously mentioned. Patients who opt for BCT endured a statically significant larger risk for ipsilateral breast cancer (IBC) recurrence versus patients who opt for mastectomy. The risk was 23.5% versus 5.5% respectively after 15 years ($p = <0.0001$). Overall survival rate for patients with breast cancer who choose BCT were 91.8% and whose who choose mastectomy was 89.8% ($p = 0.73$). BCT when compared to mastectomy has an increased risk for ipsilateral breast cancer recurrence when comparing tumor stage, age of patient, and chemotherapy use (Hazard ratio (HR) 2.9; 95% CI 1.1-7.8). Use of tamoxifen was not associated with increased ipsilateral breast cancer recurrence risk.

Contralateral breast cancer (CBC) is also a concern with breast cancer patients. Bilateral prophylactic mastectomy is done in hopes of preventing contralateral breast cancer in patients with a BRCA mutation as CBC may not be due to only this genetic mutation. Outside factors such as age of diagnosis, oophorectomy, and use of tamoxifen may influence CBC. This risk may increase with younger age of diagnosis. BRCA1 breast cancer patients older than 50 years of age when diagnosed had a lower risk of CBC. At 15-years follow up, women who were less than 50 years old when diagnosed had a 37.6% risk of CBC versus women greater than 50 years of age having a 16.8% risk of CBC ($p = <0.001$). Patients with positive BRCA mutation carried a higher risk of contralateral breast cancer compared to patients with negative BRCA mutation ($p = <0.001$). After analyzing 11 studies involving 807 patients with positive BRCA mutation and 3163 patients with negative BRCA mutation, the risk of contralateral breast cancer was 23.7%

and 6.83% respectively (p=0.001). When comparing BRCA1 and BRCA2 mutation carriers, contralateral breast cancer rate was 21.1% and 15.1%, respectively. This shows a higher rate for BRCA1 carriers vs BRCA2 carriers(p=0.04). The five-year risk evaluation of CBC for both BRCA1 and BRCA2 mutation carriers was 15% at 9%, respectively. When analyzing only breast cancer specific survival (BCSS), patients with BRCA mutation who underwent contralateral prophylactic mastectomy after 4.3 years show no statistically significant difference in recurrence when compared to those who chose not to have the prophylactic mastectomy after a time of 3.4 years (p= 0.40). A separate study's results done in 2013 showed a statistically significant increased survival rate in patients who chose to undergo prophylactic mastectomy versus patients who chose not to have the mastectomy. The overall survival rate at 10 years was 90% compared to 80% respectively. It was noted that a bias was discovered in the study where patients who underwent mastectomy also received chemotherapy. This called into question the validity of this study's results. A separate study the authors noted concluded that after 20 years the survival rate for patients who received prophylactic contralateral mastectomy had a survival rate of 88% versus 66% for those who did not receive the prophylactic contralateral mastectomy. When factors such as treatment, age of diagnosis, and others were accounted for patients who receive contralateral prophylactic mastectomy had a 48% decreased risk of death from their breast cancer (p=0.03).

This analysis encouraged patient to have a multi-disciplinary team and that treatment options be determined on an individual basis rather than having one decision for all patients. It was specifically discussed that patient who undergo BCT with a BRCA mutation be informed of the higher risk for contralateral breast cancer (Ginecologica et al., 2016).

Breast Conserving Therapy and Mastectomy Comparisons

Those diagnosed with breast cancer at a younger age typically present with tumors that are more aggressive and often have less favorable prognosis. Vila, Gandini, & Gentilini, (2015) conducted a systematic meta-analysis to compare survival rates in women under 40 years of age with early-stage (stage one or two) breast cancer. The analysis was between breast conserving surgery (BCS) with radiotherapy to the whole breast and mastectomy. This study was conducted using MOOSE guidelines for meta-analysis. Six total studies were used: 5 studies with population-based databases and 1 pooled clinical trial. This meta-analysis consisted of 22598 patients who received treatment between 1980 to 2007. In this population of patients, 10898 were treated with BCS and 11700 were treated with mastectomy.

Summarized hazard ratio showed a 10% lower risk favoring BCS over mastectomy (HR=0.90; 95% CI 0.81-1.00). There was not a statistical difference between study heterogeneity ($I2 = 34\%$; Chi-square $p = 0.15$).

Results showed that treatment with BCS with radiation to the whole breast appears to be comparable to mastectomy in breast cancer patients younger than 40 years. This research suggests mastectomy no longer has better overall survival rates and can be used as a safe surgical alternative to mastectomy. These results were found to be more applicable for those with positive lymph nodes (Vila, Gandini, & Gentilini, 2015).

In the past, mastectomy has been the surgery of choice in hopes of decreasing relapse risks, lessen the psychological trauma on the patient, and reduce the disease related deaths. A retrospective study conducted by Yu et al., (2020) analyzed overall survival and breast cancer specific survival rates. Patients were women under the age of 40 who had been diagnosed with

an invasive breast cancer between the years 2010 to 2014. Their information was obtained from the surveillance, epidemiology, and end results database (SEER) database. The study included 8656 patients with 4524 (52.3%) having radical or modified radical mastectomy, 4132 (47.7%) having BSC with 2991 of those patients were also being treated with radiation. Average follow up time was 30 months with a range of 4-59 months. Analysis showed that patients having mastectomy were more likely to have neoadjuvant chemotherapy and those having BCT were more likely to have neoadjuvant radiotherapy ($p=< 0.001$).

BCT treatment group had improved overall survival and breast cancer specific survival when compared to the mastectomy treatment group ($p=0.05$). BCT overall survival was 57.3 months compared with mastectomy overall survival was 55.4 months, on average. Several independent factors for overall survival were identified by the multivariate analysis including surgical methods, lymph node status, histological tumor grade, race, and specific molecular subtype of the tumor. Overall, results found there was a 36.4% decreased mortality for the BCT treatment group vs the mastectomy treatment group ($p=<0.001$). Several limitations were noted in the study. Noted was bias toward surgical treatment since decisions was based on tumor size and patients and/or surgeon preference, not random selection. SEER did not have endocrine therapy use status or patients' comorbidities available for analysis (Yu et al., 2020).

Zhang et.al., (2021) conducted a study comparing early-stage metaplastic breast cancer and analyzed overall survival and breast cancer specific survival in two groups: those treated with BCT and those treated with mastectomy. Metaplastic breast cancer (MBC) is typically a rare and aggressive form of breast cancer linked with poor outcomes. These are most likely due to having patients presenting with bigger tumor sizes, higher cancer staging and grade, along with negative hormone receptors, and are typically older than 50. Typical treatment options such

as chemotherapy and hormone targeted therapy are largely resistant and ineffective in MBC patients. Surgical intervention has been the preferred choice of treatment in MBC. This study was conducted using the SEER database with Chi square tests and Kaplan-Meier to analyze data. 2412 patients diagnosed with early-stage MBC between 2001-2016 were selected for the study. 881 patients were treated with BCT, and 1531 patients were treated with mastectomy. The average follow-up was 73 months. Baseline demographics were taken which included age of diagnosis type of surgery had, radiation, chemotherapy, and tumor characteristics, along with age, gender, and race. Patients who underwent mastectomy has a larger proportion of larger tumor size comparted to BCT treatment patients (83.6% vs 57%, p=< 0.001) (Zhang et al., 2021).

BCT patients showed an improved overall survival rate and improved breast cancer specific survival compared with those who underwent mastectomy. The five-year overall survival rate for BCT was 84.3% versus mastectomy at 62.5%. Ten-year overall survival for BCT was 73% versus mastectomy at 52.1%. (HR =0.43, 95% CI p =0.001). Breast cancer specific survival five-year rate was 89.1% versus mastectomy treatment at 70.8%. Ten-year breast cancer specific survival was 83.9% for BCT versus 67.5% for the mastectomy treatment (HR = 0.83, 95% CI, p< 0.001). These results were adjusted for confounding variables. Limitations noted included tumor specificity such as metastasis and lymph node status. (Zhang et al., 2021).

Previous studies have suggested that in younger women, BCT may not be an appropriate treatment for breast cancer. Sun et al., (2021) investigated survival benefits compared between BCT and mastectomy in women younger than 40 years of age diagnosed with early-stage breast cancer. This retrospective study using SEER database for analyses of 23,810 women diagnosed

and treated between 1988 and 2016. Patients were separated into two groups, 10,681 (44.9%) of patients were treated with BCT and 13,129 (55.1%) were treated with mastectomy. Median follow up was 116 months. Patients in the 18- to 35-year-old category were more likely to be treated with mastectomy ($p=<0.001$). Mastectomy treatment group participants were more likely to have tumors larger in size, positive lymph nodes, and greater histological grade ($p<0.001$). This was likely due to younger patients having more aggressive and advanced tumors. It was noted when younger patients tended to choose mastectomy as treatment it was likely due to increased fears related to relapse, long-term monitoring, anxiety, or concerns of long-term radiotherapy as these treatments could interfere with daily living.

The 10-year breast cancer specific survival in the BCT group was 89.1% and, in the mastectomy group BCSS was 87.7% ($p=0.002$). The 10-year overall survival for BCT was 87.7% and for mastectomy was 85.9%. Breast cancer specific survival and overall survival rates in the 18-35 aged group were similar for BCT and mastectomy. There was no significant difference in the 18-35 aged group. In the 36-40 aged group BCT was favored over mastectomy in both BCSS ($p=0.037$) and overall survival rates ($p=0.041$). Survival benefits was seen in the 36–40-year group with BCT. Several independent factors associated with decreased breast cancer specific survival and decreased overall survival were patients who were younger, greater histological grade, increased T stage, possessing positive lymph nodes status, ER negative status, Her-2 negative status, and surgery. Conclusion stated that BCT, in the 36–40-year group, might have a survival advantage that is not worse when compared to mastectomy. Limitations noted here were a lack of HER-2 receptor status and systemic treatments (targeted therapy, chemotherapy, and endocrine targeted therapy) were not documented for this study and that SEER does not report survival rates related to cancer relapses (Sun et al., 2021).

Maishman et al., (2017) noted that as of 2017, the Association of Breast Surgery guidelines noted target post-surgical local recurrence to be between <3% and at 5 years below >5%. This prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) involving women with breast cancer was conducted between 2000 and 2008 in the United Kingdom. Analysis including influencing factors in recurrence and survival for those with breast cancer diagnosis. 3095 individuals were included in the study with 1464 patients treated with mastectomy and 1395 patients were treated with BCS. All patients had axilla surgery. The removal of only lymph nodes with no breast surgery was done on 23 patients. Patient who underwent mastectomy had an increased chance for larger tumor size, HER2 positive status, and increased extensive intraductal component (p= <0.001). Mastectomy patients had increased incidence of ER+/PR+ receptors verses BCS (ER p=<0.001, PR p= 0.009). Average follow up time was 7.3 years. Local recurrence was noted in 6.8% of BCS patients and 2.7% of mastectomy patients. Local recurrence rate between mastectomy and BCS was not statistically different (p = 0.143) at 18 months; however, there was a statistically significant difference with higher local recurrence rates with BCT patients seen at 5 years (2.63% vs. 5.33%) (p=< 0.001) and 10 years (4.93% vs 11.68%) (p =< 0.001). Overall survival rates showed worse outcomes for mastectomy patients compared with BCS with a univariable analysis (p =<0.001); however, multivariable analysis did not show a statistical difference (p=0.081). Several factors influenced overall survival and distance disease free intervals including margin status, adjuvant radiotherapy, and radiotherapy to the chest wall. Overall conclusions from the authors found that there was no advantage between BCS or mastectomy after correcting for prognostic factors and that evading local recurrence is vital as it is associated with a decrease in overall survival and distance disease free intervals. Local recurrence interval was similar until 18 months, until

recurrence rates were higher in the BCS group. Radiotherapy after mastectomy showed improved local recurrence rates vs without radiotherapy (p=0.015) (Maishman et al., 2017).

A 20-year follow up report was published from the randomized control trial the European Organization for Research and Treatment of Cancer (EORTC) 10801 that ran from 1980 to 1986 involving patients from the United Kingdom, Netherlands, Belgium, and South Africa. Participants were those diagnosed with stage one or two invasive breast cancer under 5 cm, with positive or negative axillary nodal involvement, and menopause status documented. The patients were randomly placed into two groups: BCT included lumpectomy, axillary clearance, radio therapy to the entire breast, and tumor bed boost, or a modified radical mastectomy which was either the Patey or Madden procedure. The trial had 868 eligible patients: 420 were treated with mastectomy and 448 were treated with BCT. Distant metastases were recorded in 175 patients in the mastectomy category and 207 in the BCT category. These statistics for distant metastases were not significantly statistical different between BCT and mastectomy after adjusting for tumor size, lymph node status, and age (p=0.23). After distant metastases were established, 160 of those who underwent mastectomy and 199 BCT patients passed away (Litière et al., 2012).

During this 20-year analysis, statistics estimated overall survival rates to be 44.5% in mastectomy group and 39.1% in BCT group. No statistically significant differences were identified after tumor size, lymph node status in axillae and age were adjusted for (95% CI 0.94-1.33 p=0.23). Overall survival rates were not statistically significant when comparing the BCT and mastectomy. Positive lymph nodes status and increasing age were identified as higher risk factors for death.

Additionally, patients were separated into two age categories: less than 50 years of age and greater than 50 years of age. The incidence of time to distant metastasis and the overall

survival between BCT and mastectomy groups was not statistically significantly different between the two age groups: <50 years 95% CI 0.79-1.51 and >50 years 95% CI 0.90-1.50. This 20-year study concluded that for patients with tumors greater than 5 cm and over the age of 35 treatment with BCT can be adequately and safely done (Litière et al., 2012).

A randomized control trial was conducted between 1976 and 1984 to determine if mastectomy was as efficacious as lumpectomy with and without irradiation. This study contained patients diagnosed with invasive breast cancer less than 4 cm, with either positive or negative axillary lymph nodes and were either stage 1 or 2. Patients were randomly assigned to one of three treatment groups: mastectomy, lumpectomy alone, or lumpectomy with breast radiation, Axillary lymph nodes were removed in all groups. 1851 patients were included in final analysis. Sixty percent of patients were older than 50. Kaplan-Meier analysis and cumulative-incidence were used to analyze disease-free survival, distance disease free survival, and overall survival.

Ipsilateral breast cancer recurrence rates after 20 years were 14.3% for lumpectomy with irradiation and 39.2% for lumpectomy without irradiation (p=<0.001). This value was not dependent on lymph node status as 36.2% without radiation had negative lymph nodes while 44.2% without radiation had positive lymph nodes (p=<0.001). There was a 17% recurrence rate in lumpectomy with irradiation group and negative lymph nodes while 8.8% recurrence in lumpectomy with radiation and positive lymph nodes (p=<0.001). In the lumpectomy alone treatment group, 73.2% of ipsilateral breast cancer recurrence occurred within 5 years of surgery, 18.3% within 5-10 years, and 8.6% greater than 10 years. In the lumpectomy with irradiation group, 39.7% of ipsilateral breast cancer recurrence occurred within 5 years of surgery, 29.5% within 5-10 years, and 30.8% after 10 years.

Disease free survival rates were similar between the treatment groups and showed no statistically significant difference (p=0.26). Rates were 36% +/- 2% for total mastectomy, 35% +/-2% for lumpectomy alone, and 35% +/- 2% for lumpectomy and breast irradiation. Distant free survival rates were similar between the groups and showed no statistically significant difference (p=0.34). Rates were 49% +/- 2% for total mastectomy, 45% +/- 2% for lumpectomy alone, and 46% +/-2% for lumpectomy and breast irradiation. Between lumpectomy alone and lumpectomy and breast irradiation there was no statistically significant difference for distant disease-free survival if the tumor margins were free of tumor (p=0.15). In the 702 instances of first-time recurrences, 69% were found within 5 years of surgery and 11% were found later than 10 years. Local recurrence rate was 9%, regional recurrence was 7%, distant recurrence was 13% and all were found after 10 years. In the 165 instances of contralateral breast cancer, 38% were diagnosed within 5 years and 32% were diagnosed after 10 years of surgery.

At the 20-year mark, there was found to be no difference in overall survival rates between the three treatment groups (p=0.57). Overall survival rates were 47% +/- 2% in total mastectomy, 46% +/- 2% for lumpectomy alone, and 46% +/- 2% for lumpectomy and breast irradiation. Between lumpectomy alone and lumpectomy with breast irradiation there was not a statistically significant difference for overall survival when the tumor margins were negative (p=0.23). There was a slight but significant decrease in deaths caused by breast cancer in lumpectomy with breast radiation when analyzed against lumpectomy alone (p=0.04). The decrease in deaths also had an increase in other cancers causing deaths (p=0.21). Occurrence of death due to any source was 53.5% while 40.4% of those were due to contralateral breast cancer. Those who passed without indication of having breast cancer was 13.2%.

After 20 years of follow up, results have shown that lumpectomy with breast irradiation is an appropriate treatment option for breast cancer affected women if margins are clear of tumor after surgery (Fisher et al., 2002).

Agarwal et al., (2014) set out to analyze different surgical outcomes, specifically BCT and mastectomy for breast cancer patients. Participants consisted of 132,149 patients comparing BCT, mastectomy alone or mastectomy treated with radiation treated between 1998 and 2008. Their patients had new, early stage (defined as tumors smaller than 4 cm with less than 4 lymph nodes that were positive) invasive ductal carcinoma. Data was taken from the SEER database. 70% of patients were treated with BCT, 26.5% treated with mastectomy alone and 3.4% treated with mastectomy with radiation. Kaplan-Meier analysis was used to analyze 5- and 10-year survival rates.

When comparing BCT versus mastectomy alone, there were higher survival rates in the BCT group for patients with tumors smaller than 2 cm, tumors between 2 and 4 cm, and when comparing node-matching patients between groups. The authors hypothesized this could be due to adjuvant chemotherapy, but they were unable to account for it due to inconsistent SEER database records. Several factors may not have been accounted for in the study including that being younger, more aggressive tumors, higher grade tumors, and more nodal positivity for those whose treatment was mastectomy with radiation. Five-year breast cancer specific survival rate for the BCT group was 97%, mastectomy was 94%, and mastectomy with radiation was 90% ($p = <0.001$). Ten-year breast cancer specific survival rate for BCT was 94%, mastectomy was 90% and mastectomy with radiation was 83% ($p = <0.001$). This shows that for 5-year and 10-year survival rates BCT had better outlooks when compared to mastectomy alone and mastectomy with radiation.

Several limitations were noted by the authors including data was limited to SEER database information availability, lack of tumor information which included invasion, metastases, size of metastases, and systemic therapies such as chemotherapy or other endocrine therapies used were not reported. Additionally, this study did not assess tumor recurrences or disease-free survival rates (Agarwal et al., 2014).

BRCA Mutation Comparisons

The risks in treatment of patients with positive BRCA mutation who have breast cancer can be conflicted. A meta-analysis study that had 526 positive BRCA mutation patients and 2320 BRCA negative patients contained 10 studies and showed no significant difference in recurrence rate for ipsilateral breast cancer patient for BRCA positive patients versus the control group of negative BRCA gene patients 17.3% and 11% respectively ($p=0.07$). It was demonstrated that in studies with much longer following, recurrence in patients with BRCA positive mutation increased to 23.7% in relation to BRCA negative patients where recurrence was 15.9% ($p= <0.003$). Overall survival risk differences were not observed between BRCA positive and negative patient who underwent BCT (Ginecologica et al., 2016).

Wan et al., (2021) set out to compare BRCA mutation carriers and noncarriers after their treatment for breast cancer. This was a retrospective cohort study where patients were treated with either BCT, mastectomy with radiation, or mastectomy as monotherapy. Patients were treated between 2003 to 2015 at the Breast Center of Peking University Cancer Hospital in China. Average follow up was 7.5 years with a range of 0.3-16.6 years. This study included 8396 patients with breast cancer ranging from stage one to stage three. 491 had BRCA positive mutation status and 7905 had BRCA negative mutation status. There were 3135 patients who underwent BCT, 1511 patients underwent mastectomy with radiation, and 3750 patients had

mastectomy as monotherapy. This study evaluated for breast cancer specific survival rates, overall survival rates, recurrence free survival rates and distant recurrence free survival rates. Results showed there was statistically no significant difference in breast cancer specific survival rates when comparing BRCA carriers versus non-carriers (p= 0.22). Additionally, BRCA carriers had comparable survival rates between BCT and mastectomy with radiotherapy (BRCA 1 p= 0.44: BRCA2 p=0.52) and mastectomy alone (BRCA1 p=0.63; BRCA2 p=0.37). BRCA1 and BRCA 2 positive patients with stage one or two breast cancer had comparable survival rates in breast cancer specific survival and overall survival rates in the BCT group when compared with both mastectomy with radiotherapy and mastectomy. Results were adjusted for pathologic factors and adjuvant therapies that patients may have received. Multi variable analysis showed that BRCA negative patients had better overall survival outcomes and breast cancer specific survival in BCT versus mastectomy with radiotherapy (p=<0.001), and mastectomy alone (p=<0.001) (Wan et al., 2021).

A separate metanalysis conducted by Davey et al., (2021) used 23 studies which consisted of 3807 patients in 10 countries. Of those patients, 2200 were BRCA1 positive and 1212 were BRCA2 positive. Median follow up was 96 months. 2157 patients were treated with BCT (BCS with clear margins accompanied with radiotherapy) while 1408 were treated with mastectomy. Statistics involving ER status with adjuvant endocrine therapy, adjuvant chemotherapy, adjuvant radiotherapy, prophylactic oophorectomy were noted and outlined.

Their results showed that locoregional recurrence at 5 years was 14.7% for BCT vs. 4.8% for mastectomy. Ten-year LRR was 15.5% for BCT versus 4.7% for mastectomy, 15-year LRR was 27.5% for BCT and 6.2% for mastectomy (all p<0.001). This showed an overall increased risk in the BCT group for locoregional recurrence (HR: 4.54; 95% CI 2.77-7.42; p<0.001). This

risk of locoregional recurrence between BCT and mastectomy was equivalent at the 5-year mark but did increase at the 10-year and 15-year marks (all $p<0.001$). This correlates to 4.5 times increased risk of locoregional recurrence when treated with BCT.

Contralateral breast cancer incidence at 5 years was 11.8%, at 10 years was 29.3%, and at 15 years was 45.6% for the BCT group. This finding was comparable to mastectomy rates ($p=0.510$). Risk for disease recurrence incidences for BCT was 15.5% at five years, 25.4% at ten years, and 23.0% at fifteen years. Risk for disease recurrence incidences for mastectomy was 24.9% at five years, 25.1% at ten years, and 29.9% at fifteen years. These findings were comparable ($p=0.470$). Risk for disease specific recurrence in the BCT group was 14.3% at five years, 18.4% at ten years, and 9.5% at fifteen years. the risk for disease specific recurrence in the mastectomy group was 9.2% at five years, 12.0% at ten years, and 11.0% at fifteen years. These findings were comparable between the BCT and mastectomy group (HR: 1.58; 95% CI 0.79-3.15; $p=0.200$). Mortality occurrence for BCT group was 14.4% at five years, 21.0% at ten years, and 22.2% at fifteen years. Mortality occurrence for mastectomy was 9.2% at five years, 18.4% at ten years, and 23.9% at fifteen years. This risk for comparable between BCT and mastectomy groups (HR: 1.10; 95% CI 0.72-1.69; $p=0.660$). Limitations noted included were evolution of surgical and oncology practices may have limited the results and conclusions due to data taken from nearly 8 decades. Other limitations included inclusion criteria, not evaluating bilateral mastectomy as surgical option, and the difficulty analyzing data from different centers across different countries could have affected conclusions.

In conclusion, there are comparable survival rates for BCT and mastectomy treatment options in patients with BRCA1 and BRCA2 mutations. While there is an increased risk of locoregional recurrence in the BCT treatment group, it does not appear to impact disease free,

disease specific or overall survival rates. BCT should be considered to have a comparable safety margin to mastectomy for BRCA positive patients. There was an emphasis pointed toward understanding personal and familial genetic factors when considering surgical treatment options (Davey et al., 2021).

A separate study focused on the prognosis of breast cancer patients with BRCA mutation carriers in relation to type of surgery treatment. The study conducted by Van den Broek et al., (2019) consisted of 6081 patients included for analysis of overall survival and 3253 patients were included for analysis on local recurrence risk, ipsilateral breast cancer recurrence risk, breast cancer specific survival, metastasis free survival, and breast cancer disease free survival. There were 5820 patients without BRCA mutation, 191 with BRCA1 mutations, and 70 with BRCA2 mutations. All patients were from the Netherlands and treated between 1970 and 2003. Patients were placed into their group determined by the most extensive surgery received. The three groups were: BCT (which included breast conserving surgical therapy with radiotherapy), mastectomy not including radiotherapy and mastectomy including radiotherapy. Subgroups included patients without BRCA mutation, BRCA1 mutations, and BRCA2 mutations. Main analysis outcomes included statistics on local recurrence risk, ipsilateral breast cancer recurrence risk, breast cancer specific survival, metastasis free survival, and breast cancer disease free survival. Of these patients, 44-48% were treated with BCT and the remaining received mastectomy with or without radiotherapy. Those with positive lymph nodes and bigger tumor sizes were more likely to be treated with mastectomy with radiotherapy and receive systemic therapies. Median follow up time was 14.8 years.

Ipsilateral breast cancer occurrence was 4 times higher in BRCA1 and BRCA2 mutation patients and occurred more often in those treated with BCT. Overall survival was comparable

between BCT and mastectomy without radiotherapy in both BRCA negative (HR = 0.96; CI- 0.86-1.08; p=0.52) and BRCA1 mutation positive patients (HR = 0.95; CI- 0.55-1.63; p=0.85). BCT had better overall survival rates compared with mastectomy with radiotherapy in BRCA negative patients (HR = 0.58; CI- 0.53-0.63; p=<0.001) and BRCA1 mutation positive patients (HR = 0.60; CI- 0.37-0.98; p=0.04). For BRCA1 mutation positive patients, lower hazard radio indicating better survival was not significant between BCT (HR = 0.80; CI 0.42-1.51; p=0.50) and mastectomy with radiotherapy or without radiotherapy (HR = 0.83; CI 0.46-1.71; p=0.53). BRCA2 mutation positive patients yielded similar results. Breast cancer specific survival for BRCA1 positive mutation patients had no significant p values when BCT was compared with mastectomy with radiotherapy and without radiotherapy meaning there was no significant difference. Metastasis free survival analysis were comparable to breast cancer specific survival for BRCA negative and BRCA1 mutation patients. Disease free survival rates were comparable. Disease free survival in BCT was worse when analysis compared with other results for BRCA negative patients and BRCA1 mutation patients. The 10-year risk for local recurrence risks, which includes ipsilateral breast cancer occurrence, in BRCA negative patients who received mastectomy with radiotherapy was 1.5 (CI =0.8-2.4) and in BRCA negative patients who received BCT, 10-year risk was 7.9 (CI= 6.5-9.3). In BCT treatment group the BRCA1 positive mutation patients 10-year risk for local recurrence was 7.3 (CI=2.3-16.1) and for BRCA2 positive mutation patients 10-year risk for local recurrence was 19.7 (CI= 6.1-38.9). Risks for local recurrence appears to be similar for those treated with BCT in both BRCA negative groups and BRCA1 positive mutation patients. Risk for ipsilateral breast cancer is nearly zero post mastectomy. No difference in prognosis was found between BRCA negative and positive patients between the treatment groups. Several limitations were noted in the study to include

missing data from analysis which include specific tumor characteristics as well as adjuvant treatment that may have been received. Another limitation noted was a small patient size in the BRCA1 and 2 groups. It was noted due to the especially small sample size of BRCA2 mutation the analysis can be "interpreted with caution." There were patients included in the study from a time when BCS was not a viable treatment option and any treatments introduced after 2003 were not analyzed (Van den Broek et al., 2019).

A meta-analysis conducted by Valachis et al, (2014) analyzed for CBC and IBC using 23 studies to look at safety in BCT and mastectomy in BRCA positive and negative patients. When looking at IBC following BCT in patients, 526 patients with BRCA positive mutation and 2320 patients with BRCA negative mutation showed 17.3% IBC (95% CI 11.4-24.2%) and 11% IBC in BRCA negative patients (95% CI 6.5-15.4%) which was not statistically significant ($p=0.07$). Additionally, there was not a statistically significantly higher rate of true recurrences ($p=0.59$); however, there was a higher rate of new cancers and BRCA positive patients ($p=0.05$). There was no statistically significant difference between BRCA1 and BRCA2 positive patients in terms of risk of recurrent IBC ($p=0.20$).

Patients who had BCT posed an increased risk for IBC when compared with patients who underwent mastectomy. The 15-year estimated risk was 23.5% versus 5.5%, respectively. Overall survival in both groups was shown to be similar after 15 years. When analyzing overall survival there was no difference found between patients with or without BRCA mutation in several studies. One study that found an increased risk for CBC risk with BRCA mutation positive patients. Several factors could have influenced these results including oophorectomy, older age at diagnosis, and tamoxifen use. CBC rates were higher in patients with BRCA positive vs BRCA negative patients ($p= <0.001$). A separate study noted no significant difference in

survival rates for those who did not have a prophylactic mastectomy versus those who did, when adjusted for prophylactic oophorectomy (p=0.14). Several limitations were noted by the authors to include selection bias for women who consented for genetic testing, not having the DNA tested, patients who are still living and able to consent, misclassifying BRCA status (Valachis et al., 2014).

Another study was done to directly compare ipsilateral breast cancer recurrence and contralateral breast cancer in BRCA positive and negative women. The study contained 54 women with having BRCA positive mutation and 162 BRCA negative patients with no family history of breast cancer. All the patients had breast cancer. All patients were treated with BCT and whole breast radiation. Both groups were followed up for an average of four years and monitored for ipsilateral breast cancer recurrence and contralateral breast cancer.

Results were able to show that when observing for ipsilateral breast cancer recurrence there were 6 BRCA positive women and 4 women BRCA negative, 11% and 2% respectively. The 5 and 10-year ipsilateral breast cancer recurrence was 15% and 27% in BRCA positive patients. The 5 and 10-year contralateral breast cancer was 4% for both groups (p= 0.03).

The incidence of contralateral breast cancer was 5 BRCA positive women and 1 BRCA negative women, 9% and 0.6%, respectively. The 5-year and 10-year ipsilateral breast cancer recurrence rates were 0% and 25% in BRCA positive patients (p= 0.03). The 5-year and 10-year contralateral breast cancer rates in BRCA negative patients were 1% in both groups (p=0.03). Overall results showed an increased risk in BRCA positive women of ipsilateral breast cancer recurrence and contralateral breast cancer at both the 5-year and 10-year time when compared to BRCA negative women. The most notable limitation was that BRCA positive patients who developed IBC recurrence or CBC were all referred for genetic testing after having these

cancers. By using these subjects after learning their outcomes may have influenced the BRCA positive group toward having an IBC recurrence or CBC, overestimate risks, and have a sample bias toward increased germline mutation with increased penetrance (Garcia-Etienne et al., 2009).

Discussion

Is there a statistically significant difference in the safety and efficacy of treatment when using breast conserving therapy verses mastectomy for surgical intervention in patients diagnosed with early breast cancer?

BCT is a common surgical practice for the treatment of early-stage breast cancer patients. Many patients might wonder what the safety of this procedure. Botteri et al., (2017) concluded that when analyzing BCT there were large improvements to recurrence of breast cancers, breast cancer events, and deaths when comparing records of patients from 1997 to 2010. A substantial improvement was seen after 2005 which was hypothesized to be due to breast cancer subtyping information and the use of trastuzamuab. Overall, this improvement is great for the oncology community as it offers a safe and effective treatment for early-stage breast cancer, especially for those who do not wish to have a mastectomy.

As mentioned, BCT is a common surgical option and many patients may wonder how it compares to mastectomy, another common surgical option for early-stage breast cancer. Many studies have conclusions that were consistent with BCT and mastectomy being of equal surgical efficacy. Vila, Gandini, & Gentilini (2015) were able to conclude that there were comparable outcomes for mastectomy and BCS with radiation. Both were found to be appropriate surgical approaches for those with early-stage breast cancer. Maishman et al (2017) had similar findings in that after correcting for their prognostic factors in a multivariable analysis there was no

advantage between BCT or mastectomy outcomes. Their report did find higher rates of local recurrence 18 months post-surgery with the BCT treatment group. Litiere et al., (2012) concluded that at their 20-year analysis overall survival rates between BCT and mastectomy were not statistically different (p=0.23). Additionally, their analysis showed that when comparing age the time to distant metastasis and overall survival in the BCT and mastectomy groups was not statistically different (<50 years 95% CI 0.79-1.51 and >50 years 95% CI 0.90-1.50). A separate 20-year analysis conducted by Fisher et al., (2002) concluded similar data. Their analysis showed no difference in overall survival rates, disease free survival rates, and distant free survival rates between mastectomy, lumpectomy alone and lumpectomy with breast irradiation (p=0.57). Lumpectomy with breast irradiation did show slight decrease in death when compared against lumpectomy alone (p-0.04). Their conclusions showed that BCT was an appropriate treatment option if the tumor margins were clear.

Not all studies had the same conclusions as those listed above. In fact, several other studies have found that their data were more consistent with favoring BCT over mastectomy. Yu et al., (2020) found that BCT had improved and favored overall survival rates and breast cancer specific survival rates when comparing to mastectomy (p=0.05). The authors did include there were multiple independent factors influencing overall survival. Overall, they found that there was a 36.4 percent decrease in mortality favoring BCT over mastectomy. Additionally, Zhang et al., (2021) found that even with a more aggressive type of early-stage breast cancer, called metaplastic breast cancer, BCT showed improvements in overall survival rates and breast cancer specific survival rates when analyzed against mastectomy (p<0.001). When broken down by age, Sun et al., (2021) was able to conclude that while there was no difference in the 18-35 age group in BCT vs mastectomy, in the 36-40 age group there was a slight improved outcome in both

BCSS (p=0.037) and overall survival rates (0.041) favoring BCT over mastectomy. Again, many independent factors were noted by the authors to have influence over the outcomes. Agarwal et al, (2014) had data concluding that after 5-year and 10-year survival rates were analyzed, BCT had better outcomes when compared to mastectomy alone and mastectomy with radiation (p=<0.001). Multi variable analysis conducted by Wan et al., (2021) showed that BRCA negative patients had better overall survival outcomes and breast cancer specific survival in BCT versus mastectomy with radiotherapy (p=<0.001), and mastectomy alone (p=<0.001).

While there is conflicting data, it seems to point to both treatments being effective treatments for those diagnosed with early-stage breast cancers. There were not studies suggesting either treatment was going to be harmful to the patient, although surgical risks are always involved and should be thoroughly discussed. There were many independent factors to consider when making this decision. Other systemic therapies not noted in this literary review are to be considered but were outside the scope of this paper. Using an intra-disciplinary team and evidence based medical decision making that is unique to each patient seems to be a favorite approach among some of the authors. Understanding patient's wants, needs, and quality of life goals were also pointed out by several authors. More research will need to be done in the future to come to a more concise conclusion on whether BCT or mastectomy is the surgical treatment of choice.

Does BRCA1/BRCA2 status have an impact on the recommendations regarding surgical treatment of breast conserving therapy versus mastectomy?

Based on research that is highlighted above, data has shown that both BCT and mastectomy are both effective and safe. For patients who have a positive BRCA mutation, patients could wonder what impact this has on surgical decision making. Wan et al., (2021)

showed that there was no significant difference in breast cancer specific survival rates when comparing BRCA carriers versus non-carriers (p=0.22) in those treated with BCT, mastectomy with radiation and mastectomy as monotherapy. BRCA1 and BRCA2 positive patients had comparable survival rates in breast cancer specific survival and overall survival rates in the BCT group when compared with both mastectomy with radiotherapy and mastectomy alone. Results were adjusted for pathologic factors and adjuvant therapies that patients may have received.

Recurrence risk is always a concern when discussing breast cancer and BRCA status. The metanalysis conducted by Davey et al., (2021) concluded that there is a 4.5x increased risk of locoregional recurrence when treated with BCT versus mastectomy. This risk of local recurrence between BCT and mastectomy was equivalent at the 5-year mark but did increase at the 10-year and 15-year marks (all $p<0.001$). When analyzing contralateral breast cancer incidence, the findings for 5-year, 10-year, and 15-year risks were comparable between the BCT and mastectomy group (p=0.200). Similar findings were documented for overall mortality and found equal rates among BCT and mastectomy treatment groups. Van den Broek, et al., (2019) found similar results with ipsilateral breast cancer occurrence being 4 times higher in BRCA1 and BRCA2 mutation patients and occurred more in those treated with BCT. Overall survival was comparable between BCT and mastectomy without radiotherapy in both BRCA negative (p=0.52) and BRCA1 mutation positive patients (p =0.85). BCT had better overall survival rates compared with mastectomy with radiotherapy in BRCA negative patients (p=<0.001) and BRCA1 mutation positive patients (p= 0.04). Breast cancer specific survival, metastasis free survival, disease-free survival rates were all found to have similar results among BRCA positive and negative patients. Risk for IBC is nearly zero post mastectomy. A meta-analysis conducted by Valachis et al, (2014) using 23 studies concluded that patients who had BCT posed an

increased risk for IBC when compared with patients who underwent mastectomy. overall survival rates showed there was no difference found between patients with or without BRCA mutation. CBC rates were higher in patients with BRCA positive versus BRCA negative patients ($p = <0.001$). Garcia-Etienne et al., (2009) had similar data showing increased rates of ipsilateral breast cancer recurrence and contralateral breast cancer after BCT in BRCA positive patients.

Overall, both BCT and mastectomy appear to be effective treatments for BRCA1 and BRCA2 positive patients. The data from multiple authors seems to show that BRCA positive patients who undergo BCT carry a significant risk for ipsilateral breast cancer and contralateral breast cancer in the years after diagnosis. This is a very important factor for patients to understand when making their surgical decision and going forward with their cancer treatment.

Clinical Application

This literature review will be able to give medical providers information to guide their newly diagnosed patients with early-stage breast cancer. This can be an extremely emotional and uncertain time for patients and information coming from someone they trust can be crucial. This literary review can help make informed decisions about treatment options for those who opt for BCS with radiation and those who opt for a mastectomy.

Overall, it seems that there can be some confounding findings. Several studies found that is an increased risk for breast cancer recurrence with BCT when compared to mastectomy, the overall survival rate for patients is not affected (Maishman et al., (2017); Valachis et al., 2014; Van den Broek et al., 2019). Others suggested BCT was favored versus mastectomy (Agarwal et al., 2014; Sun et al., 2017). This literary review also will be able to highly how their BRCA status may provide valuable information to assist in determining an appropriate treatment plan.

For those with BRCA1 and BRCA2 positive mutations, CBC, and IBC rates trend toward having higher rates vs those without the BRCA mutation (Garcia-Etienne et al., 2009; Valachis et al., 2014); however, that factor may not affect overall survival rates (Davey et al., 2021). Both surgical interventions have been proven to be efficacious in the surgical treatment of early-stage breast cancer (Fisher et al., 2002; Vila, Gandini, & Gentilini, 2015).

Many years of research has been put into breast cancer research. As from this research analysis, the treatment of breast cancer is not so black and white and takes more than just the primary surgical operation to overcome. The literature review can help to highlight the safest and most efficacious options based on evidence-based medicine. It can be a starting point for patient to have the information to weigh the benefits and risks each procedure comes with. There are many other factors needing to be considered including tumor size, age, overall health, lymph node status, metastasis status, and hormone receptor status among others. An additional important factor to consider is the patient's treatment preference and their goals in life. Having this information for a patient to make their own decision can be a powerful and impowering first step into the realm of cancer treatment. An individualized decision-making process with each patient, oncologist, and surgical team will be best for treatment and survival outcomes. Further research will still be needed as new and improved surgical techniques, radiation, hormonal therapies, and chemotherapy agents are developed.

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