

European Journal of Breast Health

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Aims and Scope

European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. It is the official publication of the Turkish Federation of Breast Diseases Societies, and Senologic International Society is the official supporter of the journal.

European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

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The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media
BI-RADS: Breast imaging, report and data systems					

titled as Background, Present Study, and Implications. Authors are expected to describe the background of the subject/study briefly, critically discuss the present research, and provide insights for future studies.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Conference Proceedings: Bengissson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. *MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics*; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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Sars-CoV-2 (COVID-19) Outbreak and Breast Cancer Surgery in Turkey

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The initial COVID-19 outbreak in Wuhan, China, in December 2019 had devastating global effects in a short period of time. The disease rapidly spread globally and was announced as a pandemic on March 11th by World Health Organization when the first case was officially declared in Turkey. Turkish Ministry of Health has established COVID-19 Scientific Committee, and this took precautions on time and emphasized to accelerate public awareness in terms of social distancing, route of transmission, the period of infectivity and basic protective measures by means of social and mass media. Before the first official case the leaderships of all hospitals around the country, irrelevant of governmental or private origin, established COVID-19 committees and began to get prepared for the worst possible scenario about infection. All the medical staff and health care providers obliged to enter courses about personal protective measures. The shifts of all working groups re-organized in case of overloading.

Ministry of Health published a circular informing all physicians to discontinue every intervention, but only emergency and cancer surgeries where long-term outcomes are dependent on timely interventions. During this pandemic, one of the major issues is to protect health care providers from getting infected. To conserve or restore critical resources, including an intensive care unit, in-patient, and out-patient hospital beds, mechanical ventilators, transfusion products, and protective equipment, is vital for protecting uninfected patients and staff from extra viral exposure and intra-hospital transmission. The overwhelming number of infected patients with rapidly generated tragic health emergencies due to COVID-19 led to take strict precautions in the management of resources in terms of health care providers and protective equipment. Since COVID-19 pandemic became one of the greatest threatens against all humanity, causing thousands of deaths, the surgical algorithms have been impacted worldwide. As health care providers, we are currently facing a great challenge to provide assistance to all infected patients and, at the same time, treat non-deferrable oncologic and emergency cases. Not all cancer patients can be outlined, accordingly, we should be aware of the facts of our institute and focus on managing cancer with the maximum diligence during the pandemic. In this regard, to cancel the performance of elective surgical procedures is a must at this point. The estimation of expert projections about the full impact of COVID-19 varies and depends on multiple factors, one of the most important one is the optimal practice of social distancing which is a dynamic process and despite the vital importance in the disease course, this rule is not strictly obeyed in certain places. The pandemic is threatening our nation and all nations in all continents, and we should all be prepared to a potential increase in COVID-19 cases. Accordingly, various international surgical societies reported recommendations about possible strategies for the reorganization and rescheduling of surgical routine practice during this unpredictable period of time.

This editorial highlights the national and international approach to surgery under exceptional circumstances and challenges of breast surgery during COVID-19 pandemic. The importance of national governmental approach, the institutional organization, structure of triage of elective surgical interventions, physical and psychological preparations, infrastructure requirement analysis, the agility of mind, rational medical judgment and adjudication is also emphasized. This document could be a valid material to be used in routine clinical practice and potentially may serve as a cornerstone for advanced discussion on international similarities or differences about surgical approach algorithms under the shadow of COVID-19 pandemic which may provide beneficial recommendations for particularly breast surgeons in the state of emergency. Globally, we all share the same vision and mission for continuing to serve human well-being in the face of ambiguity and unpredictability. To establish our common goal we must accurately delineate priorities. With the key goals to reduce morbidity and mortality, minimize disease transmission, protect healthcare personnel and preserve healthcare system functioning, Cen-

ters for Disease Control (CDC) and Prevention in the US suggests that “elective surgeries” at in-patient facilities be re-scheduled if possible and elective urgent inpatient diagnostic and surgical procedures are shifted to outpatient settings, when feasible (1). Similarly, The American College of Surgeons (ACS) has published guidance advising hospitals to discontinue elective surgery with guidance on the triage of non-emergent surgical procedures during the pandemic (2, 3). ACS also encourages to create a surgical review committee for COVID-19-related surgical triage decision-making and recommends those decisions on surgery cases be made on a daily basis, no later than the day before surgery, by a leadership team representing surgery, anesthesiology, and nursing (4). Moreover, in conjunction with the surgical specialty societies ACS has launched triage criteria to serve as a resource for decision making and announced additional advice about triage of patients for cancer surgery (5, 6). The guiding principles for cancer care triage include resource considerations, cancer care coordination and general comments regarding cancer care triage *by pandemic phases and institutional resources*. These comments stresses to organize decision-making into three phases of the pandemic that describe the acuity of the local COVID-19 situation. Phase I; the semi-urgent setting, in which there are few COVID 19 patients, hospital resources are not exhausted, the institution still has intensive care unit ventilator capacity, and COVID trajectory not in rapid escalation phase. Phase II is defined as an urgent setting and there are many COVID 19 patients, intensive care unit and ventilator capacity limited, operation room supplies limited or COVID trajectory within the hospital in the rapidly escalating phase. Phase III is the phase when all hospital resources are routed to COVID 19 patients, no ventilator or intensive care unit capacity and operation room supplies exhausted. In regard to this phasing ACS’s recommendations for each cancer type in terms of surgical management differs. ACS’s COVID-19 Guideline for Triage of Breast Cancer Patients recommends surgery restricted to patients likely to have survivorship compromised if surgery not performed within the next 3 months during phase I. These cases that need to be done are as follows; patients completing neoadjuvant treatment, clinical stage T2 or N1 ER+/PR+/HER2 negative tumors, triple-negative or HER2 positive patients, discordant biopsies likely to be malignant and excision of malignant recurrence. Depending on the institutional resources, decisions may be made to proceed with surgery versus subjecting a patient to an immunocompromised state with neoadjuvant chemotherapy. ACS encourages breast conserving surgery whenever possible but defers definitive mastectomy and/or reconstruction (autologous and implant) until after the COVID 19 pandemic resolves. During phase II (urgent setting) and phase III, due to large numbers of COVID-19 patients and limited hospital *resources surgery restricted to patients likely to have survivorship compromised if surgery not performed within the next few days or hours including*; incision and drainage of breast abscess, evacuation of a hematoma, revision of an ischemic mastectomy flap and revascularization/revision of an autologous tissue flap. Under these circumstances, all other cases advised to be deferred (7). Recommendations for Prioritization, Treatment, and Triage of Breast Cancer Patients During the COVID-19 Pandemic developed by the COVID 19 Pandemic Breast Cancer The consortium which is made up of representatives from the National Accreditation Program for Breast Centers (NAPBC), Commission on Cancer (CoC) American Society for Breast Surgeons, ASBrS, and National Comprehensive Cancer Network (NCCN) (8, 9). The consortium comprises recommendations in regard to priority categories based on patient condition. Priority A defines a patient’s condition as immediately life-threatening and clinically unstable, Priority B defines a patient’s situation as noncritical but delay

beyond 6-8 weeks could potentially impact the overall outcome and Priority C defines patient’s condition as stable enough that services can be delayed for the duration of the COVID-19 pandemic. Recommendations to defer or perform surgery are similar to ACS’s COVID-19 Guidelines for Triage of Breast Cancer Patients that phases I,II,III in ACS’s guideline comprises priority categories of A,B,C in Consortium guideline (8). Society of Surgical Oncology (SSO) publicized a resource for management options of breast cancer during COVID-19 on 23rd of March supporting the need for treatment decisions to be made on a case-by-case basis pending hospital resources and restrictions. SSO’s recommends deferring prophylactic and risk-reducing surgery-reconstruction and surgery for atypia and benign breast disease at least 3 months. For ER+ DCIS, SSO’s recommendation is to defer surgery for 3-5 months and treat with endocrine therapy and monitor monthly for progression. Untreated DCIS has high priority for surgery as soon as safe operation rooms are available. SSO encourages endocrine or chemotherapy in neoadjuvant fashion per multidisciplinary tumor board for ER+ Stage I-III invasive breast cancer. Patients with triple-negative/HER2+, T2N0-3M0 or T0-4N1-3M0 invasive breast cancer should begin neoadjuvant chemotherapy. Patients with T1N0M0 disease should be considered a high priority for surgery. For post-neoadjuvant chemotherapy setting patients with ER+ invasive breast cancer with a partial/complete clinical response, converting to endocrine therapy could be considered in order to delay surgery versus surgery within 4-8 weeks. If the patient is also HER2+, converting to endocrine therapy could be considered in addition to anti-HER2 therapy in order to delay surgery. After neoadjuvant chemotherapy for triple-negative/HER2+ invasive breast cancer patients, surgery should only be delayed within a 4-8 week post-chemotherapy window, depending on the response as long as possible. These patients should be high priority for operation when deemed safe by the individual health system/hospital (10). Additionally, SSO strongly discourages not delaying patients with progressive disease on systemic therapy, angiosarcoma, and malignant phyllodes tumors and these cases should be considered for urgent surgery (10). The European Society of Surgical Oncology (ESSO) statement on COVID-19 advises no surgery for benign disease or risk-reduction should be performed (11). ESSO encourages maintaining weekly multidisciplinary team or tumor board meetings, preferably done remotely via video conferencing or telephone. The Surgical Royal Colleges of the United Kingdom and Ireland published guidance for surgeons working during the COVID-19 pandemic informing that the surgical workforce will need to adapt during the COVID-19 pandemic and listed the priorities in terms of the importance which are to maintain emergency surgery capabilities, to protect and preserve the surgical workforce, to fulfill alternate surgical roles and to fulfill alternate non-surgical roles (12). The overarching principles are to triage and deliver healthcare to patients for maximal benefit as in a mass casualty scenario and to protect and preserve the surgical workforce. This guideline defines acute patients as surgeons’ priority and recommends any patient currently prioritized to undergo urgent planned surgery must be assessed for COVID-19 and the current greater risks of adverse outcomes factored into planning and consent (13). American Society of Clinical Oncology (ASCO) commented on CDC’s guidance for health care facilities and ASC guidelines to answer the question Can/should surgery be canceled or delayed? If surgery is delayed, should patients be started earlier on neoadjuvant therapy if that is an available option? ASCO advice for clinicians and patients is to make individual determinations based on the potential harms of delaying needed cancer-related surgery; in many cases, these surgeries cannot be considered “elective” (14). ASCO also

encourages to consider neoadjuvant therapy in some situations including early-stage breast cancer when available, but not in routine fashion. To consider neoadjuvant therapy may be reasonable to simply delay surgery in selected cases. ASCO advises to consider the risks of tumor progression with delay in definitive surgery should be weighed against the potential added burden on hospital resources, case complexity and patient risk of exposure to COVID-19 and emphasizes the issues of neoadjuvant therapy itself that should be also considered. These are the requirement of clinic visits and clinician-patient contact and immunosuppression caused by neoadjuvant treatment that is associated with risks to the patient.

Nationally, Turkey announced very strict regulations officially in terms of resource management on time. Elective procedures postponed immediately aiming to reduce hospital admissions and decrease transmission of disease between symptomatic and asymptomatic patients and health care staff. Moreover, this strategy serves to save resources including hospital beds, personal protective equipment, and preserve the surgical staff from getting infected. In Turkey, surgeons are all very well aware of the fact that our major mission is to preserve human resources and be prepared for the worst scenario ever. On March 29th, the total number of test performed in Turkey is 65.446, the official number of COVID-19 cases is 9217 and we lost 131 patients since the first diagnosis. Fortunately, Turkey has more than 20.000 adult intensive care beds all around the country most of which are ready to serve COVID patients, if required.

Our tumor boards declared that the management of new and old breast cancer patients during the COVID-19 period should be personalized according to hospital resources and restrictions. In all patients with DCIS, surgery may be deferred for 3-6 months together with monthly physical examination and ultrasound, ER+ patients will receive endocrine therapy in this period. Patients with triple-negative/HER2+, T2N0-3M0 or T0-4N1-3M0 invasive breast cancer should begin neoadjuvant chemotherapy. We also recommend endocrine or chemotherapy in neo-adjuvant fashion for ER+ Stage I-III invasive breast cancer. After neoadjuvant chemotherapy for triple-negative/HER2+ invasive breast cancer patients, surgery should be one of our priorities whenever the health system allows. Surgery will be delayed for 4-8 weeks if there is a good response to neoadjuvant chemotherapy. Hormonal therapy should be the first choice in old patients with ER+ breast cancer. And, patients with progressive disease on chemotherapy, malignant phyllodes, and aggressive sarcomas should have priority for surgery.

In regard to breast cancer surgery today in Turkey, high volume centers in which routine monthly volume is between 20 to 50 breast cancer cases, decreased the surgical interventions to the least possible rates, with great attention to patient and tumor biology and a shared decision making due to multidisciplinary tumor boards designed in a web-based fashion. In specific, only 17 patients (17/48, 35%) in the Breast Unit in the Istanbul Breast Center and 12 (12/32, 37.5%) patients in the Breast Unit in Zonguldak Bulent Ecevit University School of

Medicine, who had decisions for surgery at diagnosis or completed neoadjuvant chemotherapy and within the last period of window period underwent surgery in the last month. The decision-making process is organized by means of periodic web-based multidisciplinary tumor boards and the patients are informed via phone calls. We encourage endocrine or chemotherapy in neoadjuvant fashion according to the decision in multidisciplinary tumor board for ER+ Stage I-III invasive breast cancer. Neoadjuvant chemotherapy is the preferred treatment of choice for patients with triple-negative/HER2+ or locally advanced disease, as well. However, in cases where surgery needs to be prioritized, to inform patients about the risks and benefits surgery under the circumstances of the pandemic is of paramount importance.

COVID-19 creates overwhelming challenges not only in the era of surgery but in all aspects of our healthcare systems. This is a dynamic process and evolving rapidly. Strategic planning during the COVID-19 pandemic will keep all health care providers safe and resistant which in turn allows us to provide the best quality of care to the nations we serve. This is a global war against an invisible enemy, we had to be tougher, stronger and together more than ever. Change has come to healthcare systems and change is coming to surgery at all. Nothing will be the same again; we have to adapt the provision of surgery. We, as scientists and physicians should act in a way to share experiences and recommendations in order to establish the best practices and save lives.

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Breast Cancer Diagnosis, Treatment and Follow-Up During COVID-19 Pandemic

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The COVID-19 Pandemic has not only changed our daily routines but also forced us to re-think the approach to cancer patients in these unprecedented times. Breast cancer is the most common cancer in women globally. It is unfortunate that there are subsets of those affected by COVID-19 who will experience more severe symptoms and are considered a vulnerable population: cancer patients fall into this category. Fortunately, developments in breast cancer diagnosis and treatment provide us with options such as neoadjuvant systemic therapy in the form of hormonal therapy, anti-HER2 or systemic chemotherapy and a variety of modifiable breast reconstruction strategies.

Based on the “CMS Adult Elective Surgery and Procedures Recommendations (1)” breast cancer is a Tier 2a, low risk cancer and *similar to The U.S. Centers for Disease Control and Prevention, and The American College of Surgeons*, the recommendation is to postpone surgery if possible or consider performing the procedure at an ambulatory surgery center.

It is obvious that we should minimize utilization of medical resources and supplies for non-urgent procedures; this approach helps us to maintain reserves that may be needed to care for COVID-19 affected patients, including personal protective equipment, ICU beds, cleaning supplies, and ventilators. We should also keep in mind that every hospital visit exposes patients and health care providers to the risk of contracting COVID-19. The American College of Surgeons (ACS) (2) has issued a statement and distributed to their members that “each hospital, health system, and surgeon should thoughtfully review all scheduled elective procedures with a plan to minimize, postpone, or cancel electively scheduled operations, endoscopies, or other invasive procedures until we have passed the predicted inflection point in the exposure graph and can be confident that our health care infrastructure can support a potentially rapid and overwhelming uptick in critical patient care needs.”

Although medical centers must continue to offer care that cannot be post-poned for months for some non-COVID-19 related conditions (e.g. cancer), the benefits of this care should be balanced against the risk of COVID-19 exposure for patients and staff during this pandemic. For each breast cancer patient, the risk/benefit ratio should be considered; if the risk of postponing breast surgery (breast imaging as well) confers minimal to no harm (defined as a negative impact on survival), then the option of postponing the surgery until the COVID-19 pandemic is under better control should be discussed with patient.

Herein, we present the current approach to COVID-19 pandemic of the Magee-Breast Cancer Program, one of the busiest breast care centers in the US. The Magee Breast Cancer Program leaders (Surgery, Medical Oncology, Radiation Oncology, Plastic Surgery, Pathology and Genetics) came to a consensus and prepared a statement (updated every week) that may guide breast care professionals.

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Table 1. Magee Breast Cancer Program Response to COVID-19 Pandemic

Breast Imaging	1. Screening and routine, non-urgent diagnostic imaging: all patients will be contacted and given the option to defer to a later date 2. Urgent diagnostic imaging and biopsies will proceed as usual 3. Seed placement (or wire) will be scheduled on same day as surgery to minimize hospital trips for patients
Pathology	1. Will work to keep reporting timeline for biopsies as usual 2. Receptor status for DCIS will be on a per-request basis 3. Surgical pathology reporting timelines may be delayed by 1 or 2 more days longer than usual 4. Intraoperative frozen sections to be reported via phone call into OR instead of in-person pathology report to minimize use of PPEs
Surgery	Surgical Consultations/Appointments 1. New patients scheduled for breast cancer consultations will be seen with an in-person visit to establish plan of care 2. New patients scheduled for non-cancer consultations will be contacted by scheduled provider or to offer a virtual visit or deferred in-person appointment 3. Mid chemotherapy visits should be contacted for a virtual visit 4. End chemotherapy visits can be done at the discretion of the provider with a preference for a video visit when possible 5. Post-operative visits will be seen as a virtual visit unless there is need for an in-person appointment (i.e., drain pull, incision and drainage) 6. Breast Cancer Surveillance/follow-up appointments will be contacted for the option to have virtual visit or postponement of appointment to later date 7. New patients for lymphedema will be contacted for the option to have a virtual visit or postponement of appointment to later date 8. Surveillance for lymphedema will be contacted for option to have a virtual visit or postponement of appointment to later date
Surgical Procedures	1. Patients who cannot afford a delay in surgical intervention will be offered a procedure immediately a. Those who have completed chemotherapy and have no other alternative medical therapies b. Those who have T1a-bN0 (premenopausal) T1a-cN0 (postmenopausal) triple negative or ER negative, HER2 positive breast cancer c. Those for whom systemic chemotherapy is not an option (elderly/frail triple negative or HER2 positive breast cancer) 2. Patients who can reasonably postpone their operation without compromising outcomes will be offered medical intervention while awaiting surgery a. Hormone receptor positive breast cancers (including ER positive DCIS): i. Tamoxifen 20mg PO Q day if premenopausal, with reassessment of situation every 2 weeks (for feasibility of surgical intervention) ii. Anastrozole 1mg PO Q day if postmenopausal, with reassessment of situation every 2 weeks (for feasibility of surgical intervention) b. Premenopausal women with T1cN0 or greater triple negative breast cancers or ER negative, HER2 positive breast cancers: i. Neoadjuvant systemic chemotherapy c. Postmenopausal women with T2N0 triple negative breast cancers, discuss with medical oncology regarding merits of neoadjuvant systemic therapy or primary surgical intervention d. Hormone receptor positive breast cancers who have completed chemotherapy and demonstrate an imaging response should be continued on systemic therapy with tamoxifen or anastrozole e. High risk and benign surgeries f. Risk-reducing surgeries
Medical Oncology	1. Surveillance and routine follow-up visits to be done via telemedicine, e-mail or phone (provider preference). 2. Infusions and monthly injections to proceed as usual.

Table 1. Magee Breast Cancer Program Response to COVID-19 Pandemic

Plastic Surgery	3. Metastatic breast cancer patient protocols to proceed as usual.
	1. In general, much of breast plastic surgery is not time dependent. Outcomes are identical or similar if performed several months after originally scheduled surgical date. These types of procedures include delayed breast recon, second stage breast recon, cosmetic surgery, breast reductions, and other non-cancer related issues.
	2. Breast reconstruction as a part of breast cancer treatment has more nuanced issues that can impact how timing of surgery affects results. For the most part, performing delayed reconstruction several months after mastectomy results in similar results as performing it in the immediate setting, with some exceptions. We are favoring delayed reconstruction after the Covid-19 crisis has abated unless there are extenuating circumstances that suggest clear benefit of immediate reconstruction over delayed. These will be assessed on a case-by-case basis. We are asking our referring physicians to use their best judgement in determining whether a patient has an extenuating circumstance necessitating immediate reconstruction. If they do, we will conduct a virtual appointment with these patients. If not, we request that they hold for a physical plastic surgery appointment until after the pandemic.
	3. As much as possible, clinic appointments will be converted to virtual appointments. There will still be a need for physical appointments for recent surgical patients requiring TE inflations, drain removal, and assessment for potential complications.
Radiation Oncology	1. New consultations will be seen via telemedicine if needed.
	2. Timelines for treatment of most patients to remain the same.
	3. Timelines for low risk, luminal patients may be delayed without compromise. Additionally, patients will be offered abbreviated, 1-week course instead of usual 3 weeks.
Genetics	1. Urgent consultations still seen in person (blood draw done same day)
	2. Non-urgent consultations already on schedule offered telemedicine appointment or option to reschedule to later date (blood draw done at later date)
	3. The service is currently only scheduling urgent patients
Research	1. Biospecimen lab. is closed.
	2. Clinical trial accrual still open
Multidisciplinary Meetings and Teaching Conferences	Proceed as scheduled using video conference

Lung Changes on Chest CT During 2019 Novel Coronavirus (COVID-19) Pneumonia

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The novel Coronavirus, currently named as SARS-COV-2, was first identified in Wuhan, in December 2019. Within a few months, the virus has spread from China to worldwide. On March 11, 2020, the World Health Organization (WHO) declared this global outbreak as a pandemic (1). In Turkey, the first case was reported on March 11. The number of COVID-19 positive cases increased meanwhile and by March 30, 10827 cases have been reported (2).

The clinical diagnosis of COVID-19 is confirmed by the real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) assay through combined oropharyngeal and nasopharyngeal swab samples. RT-PCR assay is referred to as the reference standard for diagnosis. The total positive rate of RT-PCR assay was reported to be 30-60% at the period of initial presentation (3). This high false-negative rate and limited availability of RT-PCR tests during the outbreak are the major drawbacks of this test. Ai et al. (4), has mentioned about the complementary role of noncontrast Chest Computed Tomography (CT) in patients with false-negative RT-PCR test results. Regarding RT-PCR as the reference, they reported the sensitivity of Chest CT imaging as 97%. Similarly, Fang et al. (5) reported the greater sensitivity of Chest CT (98%) compared with RT-PCR (71%). In a meta-analysis, the pooled positive rate of thin-slice CT imaging was 90.35% (6). These findings support that CT examination may help diagnosis especially in cases with high clinical suspicion and negative RT-PCR test results at initial presentation. This point of view seems reasonable considering the importance of early recognition of the disease can facilitate patient isolation and treatment.

While emphasizing the importance of CT findings, it must be mentioned that chest radiography is typically the first-line imaging modality. However, the most common infiltration pattern is ground-glass opacity (GGO) and it may be overlooked on chest x-rays. Correspondingly, there are studies showing the lower sensitivity of chest x-ray compared with that of CT (7).

To date, several studies characterizing the CT imaging findings have been published. Ye et al. (8), in their review article, revealed the diversity of the imaging findings seen on chest CT. Some of these CT findings such as infiltration and distribution patterns are more prominent and provide insight regarding the diagnosis. For instance, the distribution pattern of the lesions is of great importance at the characterization of COVID-19 pneumonia. Most of the patients have bilateral, peripheral and subpleural lung involvement (9-11). Lower lobes are the most frequently affected areas and additionally, some studies showed that lesions tend to be placed in the dorsal part of the lungs (8, 12). GGO is the most common and early detected infiltration pattern (9-11, 13, 14). GGOs may be patchy or rounded. Pure GGO, GGO with reticular and/or interlobular septal thickening (crazy-paving pattern), and GGO with consolidation are the different forms of infiltration. Song et al. investigated CT findings of 51 patients and reported that GGO with reticular and/or interlobular septal thickening was the second most common (75%) form of infiltration following pure GGO (77%). GGO with consolidation (59%) and complete consolidation were relatively less common (55%) findings in the same study and these two patterns were considered as an indication of disease progression (9). Another combination of GGO and consolidation known as "reverse halo sign", defined as central GGO surrounded by ring-like consolidation, were reported in some studies (7). Air bronchograms, discrete GGO nodules and solid nodules (with or without halo sign), and subpleural lines are other featured parenchymal CT findings (7, 8, 12, 15, 16). Airway involvement (dilatation, wall thickening), vascular enlargement, pleural thickening are relatively rare, but possible imaging findings of the disease (8). Although lymph node enlargement, cavitation, pericardial and pleural effusion are uncommon

findings, they may be seen with disease progression (17). Li et al. (18) investigated CT features of 25 patients in severe condition and revealed higher incidences of lymph node enlargement, pericardial effusion and pleural effusion than the ordinary patients.

CT imaging not only helps in the diagnosis of the disease but also gives information about comorbid situations such as the presence of emphysema, fibrosis. Regarding the clinical findings, disease progression and treatment response can be monitored with serial CT examinations. Lung abnormalities that are detected in patients with COVID-19, peak around 6-11 days after the onset of the symptoms (19). The improvement of CT findings appear around 14 days, the absorption stage may extend beyond 26 days (20).

Radiologists must be aware of complications, particularly, acute respiratory distress syndrome (ARDS). In their cohort study, Wu et al. (21) reported that 84 of 201 patients (41.8%) have developed ARDS and of those 44 patients (52.4%) have died. Given the role of imaging in the diagnosis and follow-up of ARDS, the knowledge of the imaging findings is crucial.

Within this period, our hospital serves as a quarantine hospital. All of the departments including emergency, microbiology, radiology, chest and infectious diseases work together in diagnosis and follow-up. The most common symptoms of patients are fever and cough. Most of the patients undergo both RT-PCR test sampling and chest CT examination. At the early stages of the disease (1-4 days), on chest CT images, we commonly see GGOs distributed mostly bilateral and peripheral with lower lobe predilection. Later on, GGO with consolidation or septal thickening (crazy paving pattern), pure consolidation, and subpleural lines are seen as additional imaging findings. We rarely observe unilateral, central distribution, and isolated upper lobe infiltration as an initial finding. Pleural and pericardial effusion, mediastinal and hilar lymphadenopathies are uncommon imaging findings.

Conclusion

Diagnosis, treatment, and follow-up of COVID-19 pneumonia is a teamwork. Radiologists have an important role, since imaging plays a critical role in initial diagnosis as well as in assessment of disease severity and progression.

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360 Health Analysis (H360) – A Proposal for an Integrated Vision of Breast Cancer in Portugal

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ABSTRACT

H360 aims to provide a comprehensive picture of breast cancer management in Portugal by retrieving real-world data from 10 Portuguese hospitals and deriving a snapshot from the medical interpretation of evidence-based data to patient perspective on the quality and effectiveness of medical care provided. This article reviews evidence on breast cancer clinical practice and quality of care and disease management in Portugal. A review of evidence on breast cancer clinical practice and quality of care over the last 10 years was performed in PubMed using the query “Organization and Administration”[Mesh] AND “breast cancer”[All Fields] NOT “Review” [ptyp]. National cancer initiatives relevant for quality of care and national and international guidelines and consensus were analyzed. Retrieved results showed that breast cancer incidence is still increasing, including in Portugal. Studies investigating disease outcomes seek to derive improvements to clinical practice and better financial resource allocation. Setting performance measures (KPIs) in institutions treating cancer is not a reality in Portugal yet, but has potential to leverage the quality of clinical performance. A multidisciplinary approach within one health structure is also desirable. More investment in clinical (including academic) research is key to optimize the quality of care. Implementation of clinical practice guidelines (largely based on ESMO guidelines in Portugal) is crucial to improve patient outcomes. Not less importantly, quality of life is a treatment goal on its own in breast cancer care. Breast cancer remains a health challenge and a multidimensional, 360-degree appraisal, beyond the exclusively clinical perspective, may provide new insights towards an optimal patient-centered approach.

Keywords: Breast cancer, Portugal, multidimensional, real-world, review

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Introduction

Breast cancer is a highly prevalent disease associated with clinical, financial, and social burden worldwide. H360 Health Analysis is a multicentric pioneer project conducted in Portugal that aims to provide a comprehensive analysis of breast cancer management in Portugal. Collection of real-world data from 10 Portuguese hospitals and analysis of patients', health professionals', and hospital administrators' perspectives on the quality and effectiveness of breast cancer care provided is currently ongoing.

The present manuscript represents the first phase of this project and aims to provide a comprehensive review (a “360-degree” appraisal) of the state of the art regarding disease epidemiology, research, and management of breast cancer in Portugal, providing a framework for ‘H360 Health Analysis’ project.

Methodology

An electronic search on PubMed database was performed comprising the last 10 years using the query “Organization and Administration”[Mesh] AND “breast cancer”[All Fields] NOT “Review” [ptyp]. Search results were narrowed by selecting studies in humans, written in Portuguese or English, with open access, and comprising the following article types: clinical study, congress, consensus development conference, or guide-

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Table 1. Standardized mortality rates for breast cancer in Portugal, by region (2010–2015) (7)

	North	Center	LTV	Alentejo	Algarve	Azores Islands	Madeira Islands
All ages (deaths)	461	359	525	149	74	37	55
All ages (SMR)	15.5	15.6	20.9	21.1	20.2	20.6	25.9
<65 years (deaths)	178	96	164	49	90	11	18
<65 years (SMR)	9.3	8.3	11.6	13.7	13.7	9.7	13.2

SMR: Standardized Mortality Rates; LTV: Lisbon and Tagus Valley

line. Relevant articles within the study's scope were selected. National cancer initiatives relevant for the quality of care, as well as national and international guidelines and consensus acknowledged in Europe and Portugal were further included.

Epidemiological overview of breast cancer

Breast cancer is the second most common cancer worldwide after lung cancer, and the leading cancer in women (1). With an incidence of 1.67 million in 2012, estimates indicate a rise to 1.97 in 2020 (1). Such incidence is unevenly distributed, higher in Western Europe, Australia, New Zealand, and North America, and lower in Africa and Asia. Half of new cases are reported in less developed regions (2, 3).

Breast cancer ranks as the fifth cause of death from cancer worldwide and the leading cause of cancer-related deaths in Europe (1). In 2012, 131,347 people died of breast cancer-related causes in Europe, with projections estimating 141,053 deaths in 2020 (1). In 2010, the national registry – North Regional Oncology Registry (RORENO) – reported 1,659 deaths (out of 6,541 diagnosis) from breast cancer in Portugal (3).

An increase in breast cancer incidence has been reported over the last years due to aging of the population and to introduction of screening programs (4). This led to an increase in disease prevalence, also partly accountable to better treatment outcomes (1, 4).

Approximately 5–10% of new cases are diagnosed in advanced (locally advanced and metastatic) stages of the disease, responsible for the majority of breast cancer-related deaths (5). Metastatic breast cancer remains an incurable disease, with a median overall survival (OS) of 2–3 years (6).

In Portugal, breast cancer incidence was 6.608 per 100,000 inhabitants in 2010, according to RORENO, and 6.088 per 100,000 inhabitants in 2012 with a projection of 6.479 per 100,000 in 2020, accord-

ing to GLOBOCAN (1, 3). The 2017 Portuguese Health Authority (Direção-Geral da Saúde, DGS) analysis of incidence and mortality of the most common cancers in Portugal between 2011 and 2015 reported more than 1,600 deaths every year attributable to female breast cancer, with a maximum of 1,752 deaths in 2012 (7). However, there is a regional and age asymmetry in these figures (Table 1) (7).

Although breast cancer incidence is steadily increasing worldwide, a drop or stabilization on incidence rates, particularly in white postmenopausal women, has been reported in developed countries at the beginning of the 21st century (4). However, the number of new diagnoses in women under the age of 45 is still increasing (1, 4). In Europe, up to a quarter of breast cancer cases occur before the age of 50, and less than 5% before the age of 35 (4).

A similar trend is observed in Portugal, with a global breast cancer incidence of 62.5 per 100,000 cancer cases and an incidence peak between the ages of 65–69 (3). The disease incidence markedly increases until the age of 45, steadily increases until the age of 69, and slightly decreases afterwards (3).

Breast cancer outcomes within the Portuguese healthcare structure

Several studies have sought to investigate the costs of breast cancer care and established guidelines for quality assurance in breast cancer screening and diagnosis (8).

Studies are disparate regarding cancer outcomes and health care expenditure, with some showing that a higher healthcare expenditure may not always translate into improved outcomes and others showing otherwise (9, 10).

Analysis of the correlation between variables associated with the healthcare system and cancer outcomes might be relevant. Studies have been published comparing differences in cancer outcomes in developed countries with comparable healthcare systems (9, 11, 12). Factors that have been identified as potentially negatively impacting cancer outcomes include the centralization of services, patient lists per general practitioner, patients having unrestrained access to different primary care physicians, and access time to secondary care (9, 11). However, a causal correlation could not be established for any of these factors.

In Portugal, multicenter studies have investigated breast cancer outcomes, including effectiveness of adjuvant ovarian function suppression in premenopausal women with early breast cancer, use of different types of adjuvant chemotherapy in patients with stage I breast cancer, and treatment adoption and relative effectiveness of aromatase inhibitors (AIs) compared to tamoxifen in early breast cancer (13, 14). Analysis of results from these multi-institutional studies – made possible by data assembled in the Regional Oncology Registries (RORs) – allow to

Key Points

- H360 intends to provide a comprehensive, overall picture of breast cancer management in Portugal.
- Setting key performance measures (KPIs) in cancer-treating institutions can leverage the quality of clinical performance.
- A multidisciplinary approach within one health structure is desirable.
- More investment in clinical (including academic) research is crucial.
- Quality of life is a treatment goal on its own.

Table 2. Treatment and access and patients flow performance indicators for breast cancer [adapted from Khare SR et al. 2016] (16)

Indicator	Description
Treatment	
1	Percentage of patients with early stage breast cancer (stage I or II) and clinically negative axillary nodes who receive sentinel node biopsy
2	Complete synoptic pathology report according to the Canadian Association of Pathologists or Rossy Cancer Network guidelines
3	Percentage of patients with involvement of axillary lymph nodes (1-3 nodes or more) who received adjuvant radiation
4	Percentage of patients with estrogen receptor-negative invasive carcinoma (tumor > 1cm or node-positive) who received adjuvant chemotherapy within 8 weeks of surgical resection
5	Percentage of patients with inflammatory breast cancer or locally advanced nonresectable estrogen receptor-negative carcinoma who received neoadjuvant chemotherapy
6	Percentage of patients with stage III breast cancer who underwent baseline staging, including bone scan, liver ultrasonography, and chest radiography
7	Percentage of patients who received systemic-relapse post-adjuvant therapy within 5 years of diagnosis
8	Percentage of patients with primary operable breast cancer who developed first recurrence to ipsilateral breast or skin or chest wall (or both) within 5 years after mastectomy or breast-conserving surgery
9	Percentage of biopsies performed at first site of metastasis (stage IV patients)
10	Percentage of patients receiving chemotherapy with grade 4 toxicity
Access and patient flow	
11	Time from abnormal mammogram to diagnostic biopsy
12	Time from diagnostic biopsy to initial breast cancer surgery
13	Percentage of breast cancer patients treated on a clinical trial
14	Percentage of breast cancer patients offered referral to genetics for evaluation and counselling
15	Percentage of breast cancer patients presented to the multidisciplinary tumor conference (tumor board) at any time after diagnosis
16	Wait time for adjuvant radiation therapy from the final pathology report
17	Wait time for systemic therapy from the final pathology report
18	Wait time for first line chemotherapy for metastatic disease, from medical oncology visit that decides on chemotherapy
19	Wait time for computed tomography or magnetic resonance imaging from doctor's requisition

derive clinical and financial implications, as modifications to clinical practice and financial resource allocation.

The fourth edition of the European guidelines for quality assurance in breast cancer screening and diagnosis stresses the importance of breast cancer screening, but also of providing highly effective diagnostic services and developing specialized breast units (8). Nevertheless, it has been shown that early breast cancer detection and diagnosis do not always significantly impact disease-associated mortality (8).

Additionally, it is acknowledged that implementation of clinical practice guidelines in cancer care improves patient outcomes. The European Society of Breast Cancer Specialists (EUSOMA) provided a voluntary certification process for breast centers that ensure multidisciplinary care and minimum standards of care (15).

Setting performance measures – known as Key Performance Indicators (KPIs) – in cancer is a mechanism of quality monitoring and mea-

surement with improvement purposes (Table 2) (16). KPIs allow a meaningful comparison between cancer centers and the identification of areas for improvement, including in the patient care pathway. It should be noted that differences in disease stage at the time of presentation may reflect different patterns of access to diagnosis and that a KPI-based assessment will provide insights into significant disparities between different hospitals, always taking into account the demographic differences in breast cancer incidence and mortality that exist in Portugal. KPIs are increasingly becoming a formal requirement in healthcare delivery in most institutions around the world.

Engaging national clinicians and their institutions to set KPIs as a key element in cancer care has the potential to leverage the quality of clinical performance.

Additionally, integration of different disciplines - General Practice, Imaging, Pathology, Surgery, Radiotherapy, Medical Oncology, spe-

cialized Nursing, Public Health, Pharmacy, Economy, Patient Advocacy, and Hospital Administration - within one structure is desirable as the foundation for a true patient-centered approach.

A systematic analysis using KPIs as a tool for assessing quality of care remains an unmet need in Portugal.

Clinical research

Investment in clinical research in Portugal is lower compared with most other European countries that are part of the European Union (EU). This is true both for academic and industry-sponsored trials (17). Overall, a low number of clinical, mostly Phase III trials are taking place in Portuguese Centers, along with an even lower number of registry and academic studies. In the academic setting, investigation of the BRCA gene in the Portuguese breast cancer population is an example of research developed in the country over the last years. More recently, multicenter studies have investigated breast cancer outcomes in the Portuguese patient population (11, 13, 14).

Clinical practice guidelines

The most widely used guidelines in breast cancer management are the European Society for Medical Oncology (ESMO) Breast Cancer Guidelines and the National Comprehensive Cancer Network (NCCN) Guidelines in Breast Cancer, with remarkable differences in levels of evidence and grades of recommendation (4, 18).

In Portugal, breast cancer guidelines issued by the Portuguese Health Authority DGS and by the Portuguese Society of Breast Cancer (Sociedade Portuguesa de Senologia, SPS) are available to guide clinical decisions (4, 19). DGS guidelines are largely based on ESMO guidelines but lack comprehensive information on several aspects of breast cancer management. The SPS guidelines are more detailed and regularly updated (every two years).

Breast cancer risk factors

Recognized risk factors for breast cancer are those intrinsic to the subject - female gender, older age, early menarche, late menopause, age at first pregnancy, and family history of breast cancer at young age - and those associated with previous treatments - including hormonal therapy substitution and radiotherapy (RT) of the thoracic wall (4). Other acknowledged risk factors are presence or history of benign disease of the breast, high-density breast, and genetic factors, particularly BRCA1/2 gene mutations (20, 21). Lifestyle and dietary factors also play a role, with obesity and inactivity associated with a higher risk in postmenopausal women and dose-dependent alcohol consumption (and possibly also tobacco) associated with a higher risk in both pre- and post-menopausal women (4).

Breast cancer screening

Breast cancer screening is performed in women without signs or symptoms of the disease, for an earlier-as-possible detection.

Many European countries established national or regional population-based mammography screening programs to detect breast cancer at a preclinical stage. The European guidelines for quality assurance in breast cancer screening and diagnosis recommend implementation and monitoring of performance parameters and indicators in every screening program (4).

According to ESMO guidelines, mammography screening every two years has the greatest mortality reduction benefit in the 50-69 age group, and Portugal complies to this recommendation (4, 7, 22). Following the same guidelines, annual magnetic resonance imaging (MRI) concomitantly or alternating with mammography every six months is recommended in the country for patients in high risk for breast cancer (22).

Breast cancer diagnosis

At least 60% of breast cancer patients present with a breast lump which may or may not be painful, fixed or demarcated from the surrounding tissue (4). Unlike screening imaging, which is used to detect cancer in asymptomatic women, diagnostic evaluation is used to characterize a clinical finding or a possible abnormality during screening.

Breast cancer diagnosis is based on clinical examination combined with imaging and confirmed with pathologic assessment. Clinical examination includes assessment of general health status and of the primary tumor, regional lymph nodes, and possible distant metastases. Imaging includes bilateral mammography and ultrasound of the breast and regional lymph nodes. In accordance with ESMO guidelines, breast MRI should be considered only in cases of familial breast cancer associated with BRCA mutations, breast implants, lobular cancers, suspicion of multifocality/multicentricity, large discrepancies between conventional imaging and clinical examination, or in the context of neoadjuvant therapy (22).

Pathological diagnosis should be based on a core needle biopsy. Analysis of tissue sample should allow detection of invasive tumor growth and identification of histological type, tumor hormone (estrogen [ER] and progesterone [PR]) receptor (HR) status, human growth factor receptor 2 (HER2) status, and ki-67 expression.

Breast cancer staging

Every patient with breast cancer should be assigned a clinical and a pathological stage of disease, according to the TNM (primary tumor [T], regional lymph nodes [N], distant metastasis[M]) system of the American Joint Committee for Cancer (AJCC) (23). The most recent (eight) edition highlights that ensuing advances in clinical and laboratory science and translational research seriously challenge the relevance of the previously used purely anatomic TNM staging for breast cancer. Therefore, while anatomic TNM classification remained the basis for the eighth edition staging groups, tumor grade, hormone receptor status, and HER2 status have been considered important additional determinants of outcome, and have now been incorporated into parallel prognostic stage groups that recognize the intrinsic tumor biology (23).

Breast cancer treatment

Breast cancer treatment should be guided by several factors, including tumor burden, location, and biology, patient's general health status and comorbidities and, very importantly, patient preferences.

The treatment strategy must always comprise a multidisciplinary approach incorporating specific therapies (surgery, radiation therapy, medical therapy, and others) with imaging and pathology assessment (including molecular profile, if needed). In the era of personalized medicine, integration of these therapeutic tools is mandatory for an optimal medical practice.

Early breast cancer

Curative resection of the tumor and involved lymph nodes remains the cornerstone of breast cancer treatment. In Western Europe, 60–80% of newly diagnosed cancers are submitted to breast conserving surgery (BCS) followed by RT.

Guidelines agree that all patients should be considered for postoperative whole breast RT following BCS.

Adjuvant systemic treatment should be considered after surgery according to relapse risk and tumor characteristics. It is recommended for most triple negative (TN), HER2-positive, and high-risk luminal HER2-negative tumors.

Assessing tumor biology features - like tumor intrinsic subtype - rather than relying solely on standard criteria has the potential to improve response to systemic therapies. Low-risk luminal A tumors can often be treated with endocrine therapies (ETs) alone. Luminal B tumors usually require both chemotherapy (CT) and ET and HER2-positive tumors rely on adjuvant CT plus anti-HER2 therapy (22). Moreover, gene expression profiles may be used for additional prognostication and predictive information regarding the potential utility of adjuvant CT (22).

For HR- and HER2-positive disease, ESMO guidelines recommend CT plus anti-HER2 therapy for all patients (except in selected cases with very low risk, such as T1aN0 tumors). ESMO and NCCN guidelines currently recommend adjuvant ado-trastuzumab emtansine instead of trastuzumab for HER2-positive cases with residual disease after neoadjuvant therapy and surgery (24). In the adjuvant setting, the same guidelines consider dual HER2 blockade with trastuzumab and pertuzumab for 1 year (for high-risk patients with N-positive or ER-negative disease) or neratinib (for selected high-risk patients not previously treated with dual HER2 blockade) (22, 25, 26).

ET is indicated for all patients with detectable HR expression (defined as $\geq 1\%$ of invasive cells). Agent choice is primarily determined by patient menopausal status. CT is generally selected for high-risk or luminal A tumors with extensive local disease, also considering patient's genetic profile (22).

TN tumors benefit from adjuvant CT, with the eventual exception of low-risk histological subtypes, such as secretory juvenile, apocrine, or adenoid cystic carcinomas.

Protocols for this tumor stage are well described at ESMO, NCCN, American Society of Clinical Oncology (ASCO), and Saint Gallen guidelines (18, 22, 27, 28). In Portugal, treatment decisions are evidence-based, according to what is stated in the referred guidelines. Recently, Arlindo et al. reported variations in the type of adjuvant chemotherapy received by stage I breast cancer patients in a multi-institutional Portuguese cohort (29). This study showed that most patients receive non-intensive regimens (such as doxorubicin plus cyclophosphamide) and that taxane-based non-intensive regimens (such as docetaxel plus cyclophosphamide) were infrequently used. It also reported striking institutional variations in chemotherapy use (ranging from 0 to 43.4%) (29).

Advanced breast cancer

Advanced breast cancer (ABC) includes both locally advanced breast cancer (LABC) and metastatic breast cancer (MBC) and the disease management encompasses both treatment and supportive care.

Locally advanced breast cancer (inoperable and non-metastatic)

Systemic treatment should be the initial choice for LABC, with a combined treatment modality (systemic therapy, RT, and surgery) indicated in most cases. CT is the recommended option for most patients, with anthracycline- and taxane-based CT as standard regimens.

For HER2-positive breast cancer, concurrent anti-HER2 therapy plus CT is recommended after evidence showing an increase in the rate of pathologic complete response (pCR) (30, 31).

Surgery is an option for some patients following primary CT. Mastectomy with axillary dissection can be considered in most cases. For patients with axillary low burden of disease at presentation with complete response after systemic treatment, sentinel lymph node biopsy can be an option (6). As there is a significant risk of recurrence, adjuvant RT is indicated after surgery for most patients.

Adjuvant ET and up to one year of trastuzumab should be completed following surgery in HR- and HER2-positive patients, respectively. In both cases, concurrent administration of adjuvant RT is possible.

Metastatic breast cancer

In this setting, although treatable the disease is virtually incurable and treatment intent is palliative. Median OS for MBC is 3 years and 5-year survival is approximately 25% (32, 33).

Systemic therapy is the most frequent option and decisions are taken according to HR and HER2 expression status, tumor burden, response to previous therapies and associated toxicities, disease-free interval (DFI, in case of breast cancer recurrence), need for rapid disease control (e.g. visceral crisis), and patient characteristics, as comorbidities, performance status, age, menopausal status, psychological factors, and socio-economic situation.

In this setting, the main clinical endpoints are improvement of OS and progression-free survival (PFS), symptomatic control, metastatic remission and quality of life (QoL).

Both NCCN and the 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC4) are widely adopted for MBC treatment and used in Portugal (6, 18).

Radiological assessment plays an important role in treatment of bone and brain metastases. Metastases-directed surgery is also performed in some patients, including those with bone lesions with impending fracture risk or spinal cord compression and in selected patients with operable lung or liver metastases.

Quality of life and social integration - Where do we stand?

Breast cancer is the most prevalent tumor type in women globally (34). The number of women living with the disease increases every year, including those with metastatic and recurrent disease (35). Since breast cancer has a considerable impact on women's QoL from the moment of diagnosis, this is an increasingly relevant issue for breast cancer survivors (36).

QoL is increasingly recognized by health care professionals as a treatment goal on its own and has been incorporated in clinical guidelines issued by the main organisations involved in cancer care worldwide.

ESMO and NCCN guidelines provide recommendations on the subject, with NCCN yielding important indications, although predominantly focused on supportive and palliative care (6). ESMO also recently issued the ESMO Magnitude of Clinical Benefit Scale, providing a validated tool to assess the magnitude of clinical benefit from new cancer therapies taking into account multiple variables, including QoL (37). ABC4 specifically focuses QoL as a critical parameter for an optimal disease management (6).

The ability to perform daily activities, as well as functioning levels and patient satisfaction are key issues when addressing QoL in breast cancer survivors (36).

Validated instruments for measuring QoL are in place, which allow for comparisons between different population and country outcomes and provide valuable tools for research, clinical practice, and policy making (38). Most used cancer-specific (including breast cancer-specific) instruments include the European Organization for Research and Treatment of Cancer-Breast Module (EORTC QLQ-BR23) and the Functional Assessment of Cancer Therapy-Breast (FACT-B) (39).

The population of breast cancer survivors has disparate health requirements due to heterogeneity of sociodemographic characteristics, pre-existing comorbidities, tumor stage at diagnosis, tumor biology characteristics, and experienced treatment modalities.

According to patients' perceptions, healthcare professionals do not provide sufficient information regarding disease progression, coping skills, and patient education resources, making them seek information and support from various organizations (40). Furthermore, when discussing treatment options with their patients, physicians should inform them on QoL differences associated with different options (41).

Because MBC has a median survival of 2–3 years after diagnosis, treatment is focused on disease control and QoL (42). However, and despite efforts, QoL for these patients has not improved over the last decade (5, 32).

Challenges for men with MBC are even bigger, since they are a generally neglected subpopulation (43).

The Global MBC Vision 2025 Call-to-Action program has been developed and is currently in progress to address the unmet needs faced by MBC patients and help define optimal care practices for this vulnerable group (44).

Supportive care should be an integral part of the treatment plan offered to MBC patients. ABC4 strongly recommends access to palliative care early after MBC diagnosis, emphasizing that patient preferences at the end of life should not be neglected but instead discussed in a timely manner (6). Also NCCN guidelines consider palliative care a key aspect of metastatic and recurrent disease management (18).

During the first year after a breast cancer diagnosis, women experience significant psychological distress, including feelings of shock, emotional numbness, depression, and anxiety (44, 45). Many patients also experience cognitive alterations induced by cancer and cancer treatments (onco-brain). Additionally, the burden of systemic adjuvant treatment in breast cancer is associated with weight gain, infertility, and early menopause (46).

Fertility preservation is an important aspect of cancer care, with several techniques available: ovarian suppression, embryo cryopreserva-

tion, oocyte cryopreservation, ovarian tissue cryopreservation, and transplantation (47). In 2016, the Portuguese Society of Oncology issued oncofertility recommendations, to be implemented in Portugal, providing information on preservation of the reproductive potential in adult cancer patients based on available evidence (47). These have been implemented in specialized oncofertility centers nationwide.

Sexual function and satisfaction can also be affected by the disease and cause great personal and interpersonal suffering. Choice of the type of surgery is a key aspect for women to preserve their sexual satisfaction and adequate body image (48).

Cancer patients have a higher risk of second malignancies and subsequent tumors compared with the general population, partly due to genetic predisposition but also to toxicity of therapeutic modalities (49).

Conventional chemotherapies and some of the most recent anticancer signaling inhibitors carry a substantial risk of cardiovascular side effects that include cardiac dysfunction and heart failure, arterial hypertension, vasospastic and thromboembolic ischemia, dysrhythmia, and CT prolongation (50).

Patients desire a holistic, individualized, compassionate, and culturally sensitive dialogue with their healthcare providers, within a shared decision making process (40).

In Portugal, there is an absence of long survivor support groups, with only a few closed support groups for MBC patients and some hospital-based groups to assist patients during their treatments. 'Fundo iMM-Laço' contributes with research grants but is not enough to fulfill this unmet need.

Recently, the Portuguese National Authority of Medicines and Health Products (INFARMED) launched "Projeto Incluir" (Project "To Include") as a vehicle for a better interaction between patients and their community representatives (50). The project aims to expand the contribution of patient advocacy groups in assessing health technologies, drug stock-outs, adverse reaction notification, and counterfeit medicine identification, among others.

ABC4 foresees that patients should be able to have an active working life if they desire or need. But for that to be possible, patients should be allowed working schedule flexibility, in order to attend hospital appointments and treatments whenever necessary. This remains an unmet need, highlighting the need for changes in societal structure and behavior. The Global Alliance for breast cancer is strongly committed towards this purpose (50).

Overall, it is key to establish an effective multidimensional survivorship program, in order to develop management guidelines specific for breast cancer survivors and properly train clinicians on the best way to discuss treatment options, prognosis, and end-of-life care with their patients.

Conclusion

Breast cancer is a significant health challenge for patients, their families, and society in general. A multidimensional approach that goes beyond the clinical perspective may provide new insights and directions to study the impact of this still highly prevalent malignancy.

The undertaking of providing a comprehensive picture of the disease, in a 360-degree appraisal, although intuitively desirable, is not simple. Set to

this task, the current project proposes to analyze real-world data from a 360-degree perspective, i.e., from the medical interpretation of evidence-based data to the patient perspective on the quality and effectiveness of services and medical care provided, also including the perspective of administrators and decision-makers. Using such comprehensive approach, the full impact of breast cancer on patients and society can be analyzed.

In Europe, although the Primary Care setting is key for prevention, early detection of breast cancer, disease diagnosis, treatment, and follow-up occur mainly at the hospital setting. In Portugal, the National Health Service (NHS) is provided by public institutions, but the role of private hospitals is increasing and expanding and currently accounts for a significant proportion of breast cancer care in major cities. This first initiative - the 360 Health Analysis (H360) - consists of a multi-dimensional analysis of breast cancer in 10, mostly public, Portuguese hospitals with different socio-geographic characteristics, all of which are part of the NHS.

With this approach, the authors believe they will be able to provide very relevant clinical and non-clinical data, particularly useful for stakeholders involved in breast cancer management, and to widen the critical perspective on breast cancer research and management for future H360 studies. Ultimately, this initiative aims to assist clinical and management decisions in breast cancer towards a more patient-centered approach.

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Extended Sentinel Node Biopsy in Breast Cancer Patients who Achieve Complete Nodal Response with Neoadjuvant Chemotherapy

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ABSTRACT

Neoadjuvant chemotherapy (NAC) can eradicate axillary disease in breast cancer (BC) patients. Sentinel node biopsy (SNB) in patients with positive axilla who accomplish complete clinical response after NAC is a new opportunity for changing paradigms and decreasing the extension and the morbidity of axillary surgery. The aim of this article is to review the limits of SNB in this setting and present the current status of an expanded modification of this technique. False-negative rates (FNRs) of conventional SNB exceed the threshold of 10%, and are not acceptable. The extended SNB (ESNB) entails the removal of at least 3 lymph nodes (LNs) including the sentinel node (SN) mapped by dual tracers and a marked lymph node (LN) that was found previously metastatic. This node by node removal procedure greatly reduces the FNRs of the procedure. Despite that axillary lymph node dissection (ALND) is still the standard of care for patients with involved LNs before NAC, the ESNB is a valid option for selected patients in whom axillary positive disease is converted to negative. When ESNB is negative in such cases (immunohistochemistry included), the omission of ALND seems to be safe.

Keywords: Breast cancer, neoadjuvant chemotherapy, sentinel node biopsy

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Introduction

Neoadjuvant chemotherapy (NAC) for breast carcinoma (BC), in combination with personalized targeted therapy, allows for high rates of pathologic complete response (pCR) (1-3).

Sentinel node biopsy (SNB) is safe after successful NAC in patients with clinically-negative axilla (3-5). For BC patients with positive lymph nodes (LNs) prior to NAC the standard surgery for treating the axilla has been axillary lymph node dissection (ALND), but as NAC enables downstaging of axillary disease, SNB in patients with clinically nodes positive (cN+) axilla who accomplish complete clinical response (yc N0) is an opportunity for changing paradigms.

This article reviews the role of SNB after NAC for BC treatment and presents the current status of a modification of this technique, the extended sentinel node biopsy (ESNB), in patients with initially positive axilla who achieve favorable response with NAC.

Impact of neoadjuvant chemotherapy on nodal burden

Numerous studies have demonstrated the disappearance (on average 40%) of LNs infiltration after anthracyclines and taxane-based regimens, in association with single or dual anti-HER-2 therapy for patients with HER-2 positive (HER-2+) disease (6-11).

BC is a heterogeneous disease and the chance of nodal pathologic complete response (pCR) strongly depends on molecular parameters. For Al-Hilli et al. (12), and Mamtani et al. (13), nodal pCR varied greatly based on immunohistochemical (IMH) classification, as shown in Table 1. The overall rates of nodal pCR were, respectively, 37.7% and 49.2% according to these authors. With advancements in the understanding of tumor subtypes, NAC is increasingly focused on HER-2 + and triple negative subtypes and less frequently used in hormone receptor-positive disease.

In the preoperative phase, ensuring that NAC is effective to downstage the LNs, is based on the comparison between nodal evaluation at diagnosis and after NAC, by physical examination and ultrasonography, that is considered the imaging technique of choice to monitor the

Table 1. Different breast cancer subtypes and nodal pathologic complete response with neoadjuvant chemotherapy

	ER+, HER-2 – (%)	ER+, HER-2 + (%)	ER –, HER-2 + (%)	ER –, HER-2 – (%)
Al-Hilli et al. (12)	20.2	47.7	61.3	47.3
Mamtani et al. (13)	20.5	70.2	96.6	47.2

Table 2. Meta-analyses estimating the false-negative rate (FNR) of the sentinel node (SN) biopsy after neoadjuvant chemotherapy in node-positive patients converted to node-negative

	n	Nodal positivity at diagnosis	FNR (%)
Fu et al. (19)	2471	clinical/ultrasonographic	14* (95% CI :10%-17%)
Van Nijnatten et al. (22)	1395	microscopic	15.1** (95% CI: 12.7%-17.6%)
El Hage Chehade et al. (23)	3398	microscopic	13 (95% CI: 10.8%-15.6%)
Simons et al. (24)	2002	microscopic	17 (I ² = 38.66%, p=0.05)

*FNR: 8.7% if the SN positivity includes immunohistochemical examination

**FNR: 10.4% if at least two SNs were retrieved

Table 3. False-negative rates of sentinel node biopsy after neoadjuvant chemotherapy in cN+ axilla converted to cN – axilla

	n	Patients	False-negative rate (%)			
			Overall	Dual tracers	2 SNs	3 SNs
ACOSOG Z1071 ²⁶	756	T0-4, N1-2	12.6	10.8	21.2	9.1
SENTINA ²⁵	592 (Arm C)	N1-2	14.2	8.6	18.5	7.3
SN FNAC ²⁷	153	T0-3, N1-2	9.6	5.2	–	4.9*

*>2 SNs

involution of LNs. This procedure is simple and also helps to guide the fine-needle aspiration or core biopsy of LNs suspected of involvement prior to beginning systemic therapy. In the same ultrasound study, once the node is punctured, a marker may be placed in the lymph node (LN) to help the surgeon find it during surgery (7-16). No imaging technique, however, is precise enough accurate to predict nodal pCR in patients treated with NAC (14-18).

Usual sentinel node biopsy after neoadjuvant chemotherapy in clinically positive axilla at diagnosis

The identification rate of sentinel node (SN) after NAC is quite acceptable ($\pm$ 90%), but it is lower than the one observed in upfront surgeries, probably because of fibrotic compression over the lymphatic capillaries (19). The main limitation of SNB in this setting is its high

false negative result (FNR), estimated to be greater than 25% in initial studies (20, 21). Four meta-analyses calculated the FNR in node-positive patients converted to node-negative varying from 13% to 17% (Table 2) (19-24). In all studies, the FNR was deemed unacceptable since it was higher than 10%, the threshold adopted, based on the reasoning that it should not be greater than the rate observed in patients without NAC.

Three pivotal observational studies assessed SNB in patients with cN+ axilla who converted to ycN0 status after NAC (Table 3).

The SENTINA (SENTinel NeoAdjuvant study) was undertaken in Germany and Austria (25). In one of the study arms, 592 patients that converted from cN+ to ycN0 were treated with both SNB and axillary lymph node dissection (ALND). The SN detection rate was 80.1%, and its FNR was 14.2%. The FNR was 24.3% for women who had one SN removed, 18.5% for those who had two sentinel nodes (SNs) removed, and 4.9% for those who had at least three SNs removed. The FNR was 8.6% for patients who underwent dual SN mapping (vital dye and radiocolloid) compared with 16.0% for those who received radiocolloid alone.

The American study ACOSOG Z1071 determined the FNR of SNB after NAC, in women initially presenting with pathologically confirmed node-positive disease, when at least 2 SNs were excised (26).

Key Points

- Extended sentinel node biopsy is considered oncologically safe for patients with complete clinical response after neoadjuvant chemotherapy.
- The technique involves dual mapping sentinel node, resection of at least 3 lymph nodes, including the metastatic one marked at diagnosis.
- The omission of axillary lymph node dissection is valid option in patients with microscopically negative disease.

Positive SNs were defined as those with metastasis larger than 0.2 mm. A total of 701 women (663 cN1 and 38 cN2) were enrolled. After completion of NAC, 582 (83.0%) patients lacked palpable LNs. The SNB FNR was 12.6%, exceeding the acceptable threshold of 10%, which did not support the use of SNB in this population. Nevertheless, the authors found the following relevant factors lowering the FNR: a) the FNR was 91% when ≥ 3 SNs were examined; b) the FNR was 20.3% with single agent mapping and 10.8% when vital dye and radiocolloid were used; and c) the FNR was 11.3% when the axilla became clinically negative and 19.2% when palpable axillary LNs persisted.

In the French SN FNAC study (Sentinel Node Biopsy Following NeoAdjuvant Chemotherapy), 145 patients with biopsy-proven node-positive disease (T0-3, N1-2) underwent SNB and ALND (27). Pathological examinations using IMH were mandatory if SN was negative by hematoxylin and eosin (H&E) staining. The SN identification rate was 87.6% (127/145), and the axillary pCR was 34.5%. The FNR of SNB was 8.4%.

The usual SNB is not sufficiently accurate in this setting. The highest FNR for SNB in relation to the axillary LNs accepted is 10%, taking into account its estimated value for T1-2 N0 BC cases (28). The prognostic influence of eventual malignant cell permanence in the axillary LNs is a cause of serious concern; experimentally, it was proved in mice, that LNs are foci for systemic dissemination through fine capillaries inside them (29, 30).

Kang et al. reviewed the records of 1247 patients who had clinically axillary LN-positive status and presented negative conversion following NAC (31). Patients who underwent axillary surgery with SNB-guided decisions were compared with patients who underwent upfront ALND. Kaplan-Meier analysis showed that recurrence-free survival (axilla and distant metastases) were not significantly different between the groups (4-year recurrence-free survival: 97.8% vs. 99.0%, $p=0.14$).

Galimberti et al. (32), evaluated 147 women with clinical nodal involvement (cT1-4 and cN1-2), who converted to cN0, and were submitted to SNB. ALND was not performed if the SN was microscopically unaffected. The SN was negative in 70 (47.6%) patients and positive in 77 (52.4%) patients, that underwent ALND. After a median follow-up of 61 months. Kaplan-Meier curves were not statistically different for distant disease free survival ($p=0.54$) and overall survival ($p=0.72$) in both groups of patients.

Extended sentinel node biopsy after successful neoadjuvant chemotherapy

The first practical point for decreasing the FNR of SNB is collecting at least 3 SNs, provided the number of LNs obtained is inversely proportional to the FNR after NAC. Several authors demonstrated that it was possible to accomplish a 10% FNR, when ≥ 3 negative SNs were withdrawn (25-27). Technique matters, and the detection rate and chance to obtain at least 3 SNs are higher when dual tracer mapping was used. In contrast, random sampling of the axillary nodes is not known to affect the FNR and should not be indicated (33).

Marking nodes containing metastases before NAC and harvesting them along the dual mapped SNs (hot/blue) established ESNB as a new and more accurate method for axillary approach. The procedure entails the combination of dual SN mapping methods with the excision of the marked LN found previously involved and eventual removal of suspicious enlarged nodes. The SNs are identified by vital

dye and radiocolloid and the metastatic LN prior to NAC could be or not one of these structures; anyhow, at least 3 LNs should be retrieved.

Patient selection

Breast pCR is highly correlated with nodal status after NAC. Tadros et al. (34), in HER-2+ or triple-negative BC patients without a breast pCR, described a relative risk for positive nodal metastases after NAC of 7.4 (95% CI: 3.7-14.8), compared with those with a breast pCR. Among 237 patients (T1-2) with initial biopsy-proved N1 disease, 77 (32.4%) presented breast pCR and 160 (67.5%) had residual tumor in the breast whereas only 10.4% of the patients with breast pCR were found to have residual disease in the axilla. Conversely, in 57.5% of patients without breast pCR, metastatic LNs were detected. Thus, patients without breast pCR do not seem to be appropriate for omission of ALND after NAC.

The GANEA 2 study assessed the SNB in the neoadjuvant scenario. Among patients with a cytologically proven axillary involvement before NAC the FNR of the SNB was 11.9% (dual mapping) (35). They found that the amount of residual breast tumor allows identifying patients with a low risk of ALND involvement. For patients with negative SNB and a remaining breast tumor size less than 5.0 mm and no lymphovascular invasion, the risk of a positive complementary ALND was 3.7%.

With regard to molecular subtypes, apart from the low rates of nodal involvement with NAC in patients with luminal tumors, positive estrogen receptor (ER+) and HER-2 negative (HER-2-) the FNR of SNB in these patients is generally unacceptable. Enokido et al. (36) described the following SNB FNRs in women initially presenting with cytology-proven node positivity for each BC subtype: 42.1% for ER+, HER-2 - ; 16.7% for ER+, HER-2 +; 3.2% for negative estrogen receptor (ER-), HER-2 +; and 10.5% for ER - , HER-2 -.

Despite the paucity of data about the criteria for eligibility of cN+ patients to ESNB post-NAC, adequate patient selection is paramount for a safe procedure. In our opinion candidates for ESNB after NAC need to fulfill the following conditions:

At diagnosis: non-luminal BC subtypes (ER+HER2+; ER-HER2+; or ER-HER2 -), T1-2, cN1-2a;

After NAC: tumor complete clinical response, and conversion to a cN0 status.

Techniques

Ensuring the exact removal of the initially involved LN by malignant cells is a challenge for surgeons, because generally there is reduction in size of the downstaged LN. The utmost concerns for a valid ESNB are correct marking of the proven-positive LN and its precise excision. Thus, normally, the affected LN is tagged under ultrasound guidance, just after the nodal puncture, by inserting a metallic clip and/or a radioactive seed, and/or by injecting a charcoal suspension for tattooing.

In a landmark paper, the authors of the ACOSOG Z1071 study analyzed a subgroup of 170 patients, in whom a clip was placed in the positive LN, and the number of excised LNs was ≥ 2 (37). The clipped LN was removed separately at surgery, and radiographed to confirm that the LN contained the clip. In 107 (75.9%) cases, the marked LN was one of the SNs, and in these women the SN FNR was 6.1%. On the other hand, in 34 (24.1%) cases, the clipped LN was found in the ALND specimen, allowing a FNR of 19.0%. When the clip was

Table 4. Different methods for marking the positive axillary node

	Marker	Placement timing
Boughey et al. (37)	Titanium clip	Prechemotherapy
Donker et al. (39)	125I seed	Prechemotherapy
Caudle et al. (40)	Titanium clip and ¹²⁵ I seed	Prechemotherapy and preoperation
Choy et al. (16)	Charcoal	Prechemotherapy

not found the FNR was 14.3%. For comparison, in another subgroup of 355 patients, without clip placement, the FNR was 13.4%. It was concluded that ESNB, including the presence of the clipped LN in the removed tissue, significantly reduces the FNR.

Caudle et al. (7) performed ALND in 191 patients with biopsy-proven axillary nodes in which a clip was inserted. Nodal disease disappeared after NAC in 71 (33%) patients. In 118 patients undergoing SNB and ALND, the FNR was 10.1%. The clipped node contained metastasis in 115 patients, resulting in a FNR of 4.2% for the marked LN in relation to ALND. When the evaluation was performed for the combination of SN biopsies and clipped nodes, the FNR was markedly reduced to 1.4%. Clipped nodes were not seen in 23.1% (31/134 of patients), including six with negative SNs and metastasis in the clipped node. Accordingly, clipping positive nodes for extended SNB refines the pathologic evaluation and reduces the FNR.

Cabioglu et al. (38), in a prospective registry trial combining conventional SNB with clipped node excision, ascertained that the clipped node was the SN in 81.4% of the cases, whereas in 18.6% the clipped node was a non-SN. The possibility of clip migration was evidenced, and in 3.5% the clipped node could not be found in the specimen.

The intraoperative localization of the clipped LN is not an easy task. Therefore, other methodologies to mark the LN have been investigated, such as the placement of a Iodine-125 (¹²⁵I) seed in the biopsy-proven positive LN. The node with the seed is posteriorly excised using a hand held gamma detection probe during the surgery. Donker et al. (39) described an identification rate of the seed-containing LN of 97% with this technique.

Caudle et al. (40), from the MD Anderson Cancer Center, proposed a variation of this procedure, the Targeted Axillary Dissection (TAD) method. This methodology consists of SNB and excision of the positive LN, which was first marked by a clip prior to chemotherapy, and months later, before surgery, was additionally tagged by a ¹²⁵I seed. A gamma probe optimized to ¹²⁵I activity, which is distinct from the setting used in the SN identification with Technetium-99m (^{99m}Tc), guides the removal of the LN marked with the clip and seed. Intraoperative radiography is performed to check for the presence of both markers in the tissue sample before pathologic handling. They had a FNR of 2% with TAD versus 10.6% with SNB alone.

Diego et al. (41) used the same methodology in 30 patients, and they described intraoperative finding of blue dye or ^{99m}Tc activity in the ¹²⁵I-localized LN in 73.3% of the cases.

Another strategy, proposed by Choy et al. (16), is to inject a small volume (median 0.5 mL) of sterile black carbon suspension into the

cortex of the LN and adjacent soft tissue just after the nodal fine needle aspiration. The tattooed node is visible intraoperatively even months later. Park et al. (42) approved the diagnostic performance of SNB using the technique of charcoal tattooing of cytologic-metastatic LN at presentation. The carbon nodal injection may occur before NAC, exclusive or combined with the clip, or later, preoperatively, in nodes previously marked by a clip.

The concordance between the pathologic results for both the charcoal tattooed nodes and the nodes containing blue dye or radiocolloid was analyzed by Kim et al. (43). In 45 cases the tattooed nodes were not identified in the surgical field in only 1 (2.2%). In 25 cases (56.8%) there was concordance between the SN and the tattooed node, they were the same structure. In the final pathological results, 18 (40.0%) patients had metastatic nodes. The sensitivities of the SNB, charcoal marked node biopsy, and the combination radiocolloid and/or tattooed node biopsy, for axillary metastasis identification, were 61.1%, 66.6%, and 77.8%, respectively.

The different techniques, employed in order to facilitate the identification of the node previously containing malignant cells in the surgical field, are summarized on Table 4. All of them entail the placement of a marker under ultrasound guidance. Each method has pros and cons.

A clipped lymph node is not easily identified during the surgery, since it is not visible nor detected by a probe. A nodal radiography is mandatory to confirm the harvesting precision. Besides, we must consider that hazardous spontaneous clip migration is possible. On its turn the radioisotopic seed placing is more complex and requires interaction between the services of Nuclear Medicine and Ultrasonography. Moreover, the 5-6 months permanence of a radioactive source in the human body is theoretically undesirable, and in some countries federal laws do not allow this type of procedure. To circumvent this problem, in the TAD method the ¹²⁵I seed is placed in a second-step procedure after NAC, some days prior the surgery.

The method of node tattooing with black carbon is simple, cheap, and the ink injection could be done at the same moment of the puncture for cytology/histopathology. It is easier to find a tattooed node than a clipped one, and the excised node radiography is not needed. The sole precaution is not to inject excessive volume of carbon suspension inside the node, since it may interfere with the microscopic analysis.

The value of the isolated tumor cells and micrometastases in the sentinel node

Low-volume SN disease after NAC is not an indicator of a low risk of additional positive axillary nodes. In contrast with its role in adjuvant treatment, it is likely that isolated tumor cells (ITCs) or micrometastasis in the SN after NAC, remnants of nodal disease that were not sensitive to chemotherapy, have a different meaning, and could have a negative impact on the evolution of the patients. Of note, patients with micrometastases in the SN after NAC have high rates (12%-64%) of positive non-SNs (44-46).

In the SN FNAC trial, FNR improved from 13.3% to 8.4% when IMH had been used (27). The importance of IHC was also evident in the ACOSOG Z1071 study: the trial's FNR was 8.7% when any ITC-positive node was included compared with 12.6% without IHC (37).

For Moo et al. (46) 17% of the patients with ITCs and 64% of the patients with micrometastasis in the SN had additional nodal metastases at ALND.

A meta-analysis conducted by Fu et al. (19) estimated that the SN FNR reduced from 16.0% to 8.7%, if ITC detected by the additional IHC, was considered positive.

There are typical findings in the metastatic LNs which had negative conversion after NAC. Chemotherapy effects on the positive node include fibrosis, hemosiderin deposits, laden macrophages, increased vascularity and a foamy histiocytic infiltrate. Malignant cells may be scattered through a fibrotic LN, and cytokeratins-IMH may be useful to confirm suspicious morphology (47). In clinical practice, cytokeratin staining should be added to achieve a more accurate ESNB result when the excised LNs are negative according to H&E analysis (9, 48).

Intraoperative evaluation of SNs could prevent a second surgery by indicating immediate ALND. Rubio et al. (45), after performing SNB and completing ALND in the same patients after NAC, demonstrated that frozen sectioning of the SNs is effective, with sensitivity ranging from 78.5% for micrometastasis and ITC to 100% for macrometastasis. In the experience of the Memorial Sloan Kettering Cancer Center the FNR of the frozen section of the SN was 6.2% and minimal involvement of the SN in the final pathology was an indication for ALND (46).

Conclusion

ALND is still the standard procedure for the management of the axilla of BC patients with metastatic lymph nodes before NAC. Nevertheless, ESNB (dual SN mapping, resection of at least 3 LNs, including the metastatic one marked at diagnosis) is considered a valid option for selected patients with axillary positive disease that is converted to negative after NAC. In patients with negative microscopic findings in the excised LNs (IMH included), the omission of ALND seems to be oncologically safe. Future research studies focusing specifically on prognosis of the treated patients are needed for definitive judgement.

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Investigating the Link between Lynch Syndrome and Breast Cancer

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ABSTRACT

Objective: Lynch syndrome is an inherited genetic disorder associated with a predisposition to early-onset colorectal and endometrial cancers, but breast cancer risk in these patients is debated. The aim of this study is to evaluate breast cancer rates in a cohort of Lynch syndrome patients, as well as to identify women who may be eligible for additional breast cancer specific genetic testing or enhanced breast surveillance (contrast-enhanced magnetic resonance imaging (MRI) screening).

Materials and Methods: Using a hereditary colorectal cancer registry at a single academic institution for identification of patients with Lynch syndrome, a retrospective chart review was performed of 188 women with DNA mismatch repair (MMR) mutations. The Tyrer-Cuzick model was used to estimate breast cancer risk in patients without breast cancer.

Results: The prevalence of breast cancer differed based on mutation type ($p=0.0043$), as 27% of women with a PMS2 mutation were diagnosed with breast cancer, compared to 3%, 4%, and 9% in MLH1, MSH2, and MSH6 patients. The average age at diagnosis for women with a PMS2 mutation was 46.7 years. Additionally, 7.5% of unaffected women had an estimated lifetime risk of breast cancer greater than 20%. 46/188 (24.4%) of patients were eligible for breast specific genetic testing.

Conclusion: Our analysis suggests that Lynch syndrome patients with PMS2 mutations may be at higher risk of developing breast cancer. Additionally, the personal and family history of cancer suggests crossover in eligibility for breast specific genetic testing in a significant number of patients (16.5-24.4%). Also, many women are eligible for enhanced breast surveillance (7.5%) which would otherwise not be offered.

Keywords: Breast neoplasms, cancer screening, colorectal cancer hereditary nonpolyposis

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Introduction

Lynch syndrome is an inherited cancer-susceptibility disorder caused by pathogenic germline variants in DNA mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Historically known as hereditary nonpolyposis colorectal cancer, this syndrome is associated with increased risk for a multitude of cancers, including colorectal, endometrial, ovarian, small bowel, urothelium, biliary tract, and stomach (1–3). Lynch syndrome affects 1 in 279 individuals, and is more common than Hereditary Breast and Ovarian Cancer Syndrome caused by *BRCA1* and *BRCA2* mutations (4, 5). Lynch syndrome is also inherited in an autosomal dominant fashion. Recent studies have suggested that breast cancer may be included in the spectrum of Lynch syndrome-associated cancers, but the evidence is controversial. Cohort studies have found significantly increased age-specific incidence rate ratios of breast cancer in Lynch patients (6, 7). Case series have also shown high prevalence of breast cancer in Lynch populations, with earlier age of diagnosis compared to the general population (8). Investigators have looked at microsatellite instability, immunohistochemistry and mismatch repair gene deficiency in breast cancers of Lynch syndrome patients, suggesting that patients with Lynch syndrome are more likely to exhibit microsatellite instability and MMR protein loss compared with sporadic breast cancers (9–11). However, other studies show no association and recommend that increased surveillance is not indicated for Lynch syndrome patients (1, 12, 13).

Multigene panel testing has provided new insight, suggesting that individuals with *MSH6* and *PMS2* mutations may have a higher risk for breast cancer (14, 15). A case-control study published by Couch showed that only *MSH6* mutations were associated with a statisti-

Table 1. Mismatch repair gene distribution and characteristics in the Lynch syndrome cohort

	MLH1	MSH2	MSH6	PMS2
Cohort size	58	70	34	26
Race (% white)	94.8	90	100	92.3
Age (mean±SD)	51.8±15.8	54.7±12.8	54.2±14.0	53.8±12.5
SD: standard deviation				

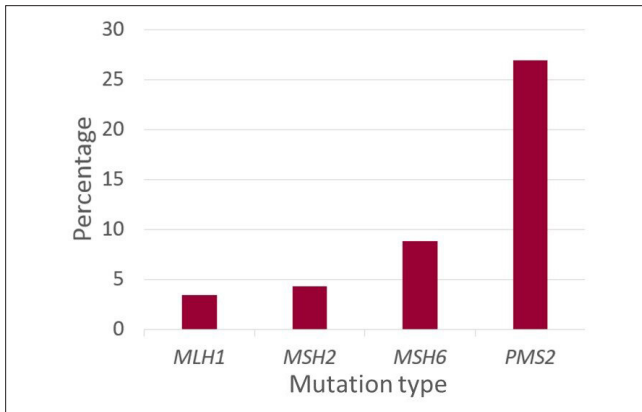


Figure 1. Percentage of women diagnosed with breast cancer by mutation type. 27% of PMS2 mutation carriers were diagnosed with breast cancer, which was greater than other mutation types ($p=0.0043$)

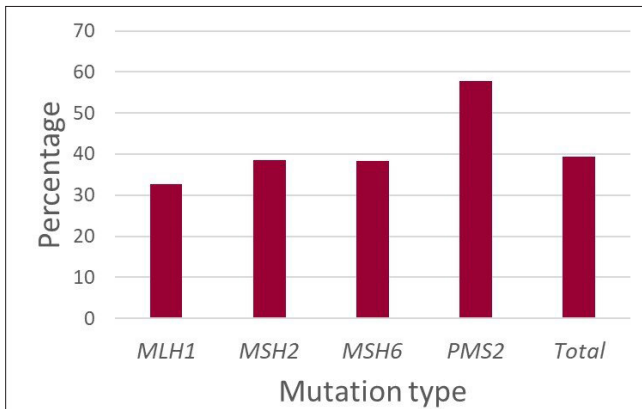


Figure 2. Percentage of women who had a family history of breast cancer, including first- and second-degree relatives. There were not significant differences between mutation type ($p>0.05$)

Key Points

- The link between breast cancer and Lynch syndrome has been debated in the literature, however no studies have looked at appropriate surveillance and risk-reducing methods in Lynch syndrome patients.
- In this cohort, patients with PMS2 mutations had a significantly higher prevalence of breast cancer compared with other mutation types.
- Many Lynch syndrome patients qualify for breast-specific genetic testing, and 7.5% of patients without breast cancer in this study qualified for enhanced surveillance for breast cancer. We may be missing an opportunity to fully screen and reduce risk in this patient population.

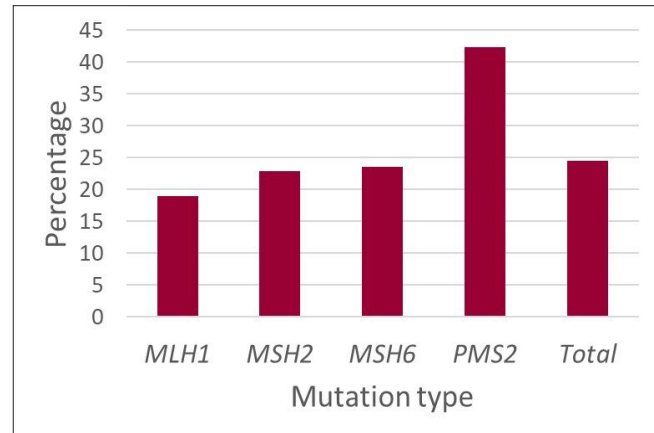


Figure 3. Percentage of women who qualified for breast-specific genetic testing, based on NCCN guidelines (v 2.2019). There were not significant differences between mutation type ($p>0.05$)

cally significantly increased risk for breast cancer with an OR of 1.93 (1.16-3.27) and PMS2 mutations were not associated with increased risk (13).

Conflicting studies have made it difficult to assess breast cancer risk in Lynch syndrome patients, and the possible mechanistic association between Lynch syndrome and breast cancer remains unclear. However, studies have not evaluated whether or not these patients are being offered appropriate surveillance and risk reducing measures based on tools used clinically to evaluate women for breast cancer risk. This study aims to address this question, as well as adding to the body of existing literature by assessing breast cancer rates by gene in our cohort. Utilizing hereditary colorectal cancer registry at a single academic institution, a cohort of 188 women with *MMR* mutations was identified. This cohort was examined for breast cancer prevalence based on mutation type, as well as qualification for breast-specific genetic testing and enhanced breast surveillance utilizing current national guidelines and clinically available risk assessment tools.

Materials and Methods

Study population

The hereditary colorectal cancer registry at a single academic institution was used to identify women who were above age 18 with germline *MMR* variants. Informed consent was obtained from patients at the time of enrolment in the registry. Institutional review board committee approval was obtained for the study. Retrospective chart review was performed utilizing the electronic medical record to select women with breast cancer from this population and extract demographic information, breast cancer characteristics, and personal and family history of other cancers.

Statistical analysis

Breast cancer risk estimations were run using the Tyrer-Cuzick model (v8) (16). The National Comprehensive Cancer Network (NCCN) Practice Guidelines-Genetic/Familial High-Risk Assessment: Breast and Ovarian, version 2.2019 was used to identify women eligible for breast-specific genetic testing (17). Descriptive statistical analyses were conducted separately for *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes. Statistical tests were performed using RProject (R Foundation for Statistical Computing, Vienna, Austria) (18). Nominal variables were assessed using 2-tailed chi-squared analyses or Fisher's exact analyses.

Results

The series included 188 women with Lynch syndrome. It included women with pathogenic variants in *MLH1* (n=58), *MSH2* (n=70), *MSH6* (n=34), and *PMS2* (n=26; Table 1). Of the 188 women, 16 had a previous diagnosis of breast cancer at the time of the study. Of the 26 women with *PMS2* mutations, 27% had a history of breast cancer which was significantly greater than women with other mutation types (p=0.0043, Figure 1). Women with *PMS2* mutations who developed breast cancer had an average age of diagnosis of 46.7 years old. Overall, 39.3% of the study population had a family history of breast cancer, incorporating first- and second-degree relatives (Figure 2).

Of the 172 Lynch syndrome patients without a previous diagnosis of breast cancer, 7.5% had an estimated lifetime risk of breast cancer (using the Tyrer-Cuzick model v8) greater than 20%, meeting criteria for screening breast magnetic resonance imaging (MRI) per NCCN, American Cancer Society, and American College of Radiology guidelines (17, 19, 20).

Patients who qualified for breast-specific genetic testing were identified using NCCN Practice Guidelines (17). Overall, 24.4% of all Lynch syndrome mutation carriers were eligible for breast specific testing (Figure 3). As pancreatic cancer and ovarian cancer overlap between the two syndromes, when excluding patients who only met criteria based on a personal or family history of these cancers, 16.5% met criteria for breast specific genetic testing.

Discussion

This study examined the association between Lynch syndrome mutation type and breast cancer, evaluated women with Lynch syndrome for their estimated lifetime risk of breast cancer development, and determined eligibility for breast-specific genetic testing. We found that the prevalence of breast cancer in *PMS2* mutation carriers was significantly higher in this cohort when compared to other mutation types. With regard to family history of breast cancer, 57.7% of women with *PMS2* mutations had a first- or second-degree relative diagnosed with breast cancer. Other studies have found a similar association (14, 21). We also found that these women were diagnosed with breast cancer at an average age of 46.7 years old, which is younger than that of the general population (22). This topic warrants future study with larger diverse multicentre cohorts of patients with Lynch syndrome studied prospectively, as breast cancer is a common disease and current data come mainly from Caucasian populations.

Many women with Lynch syndrome qualified for breast-specific genetic testing by NCCN guidelines, and 7.5% of women without breast cancer were eligible for enhanced surveillance based on the Tyrer-Cuzick risk assessment tool. This presents significant implications for carrier identification and screening. Patients with Lynch syndrome are

typically not routinely assessed for breast cancer risk in a clinical setting. However, many of these women may be eligible for screening MRI surveillance or other opportunities for breast cancer risk reduction. We may be missing an opportunity to fully assess cancer risk in these patients, which impacts screening and risk reduction strategies.

This study utilized a comprehensive registry with a large population of Lynch mutation carriers. There are some limitations, including that groups were compared without a population control, which limits the inferences that can be made about Lynch syndrome and breast cancer risk compared to that of the general population. The registry may have also included related families or family members, which was not accounted for in this study. Future directions include looking at the pathology of breast cancers with Lynch syndrome to examine the frequency of microsatellite instability (which may be important therapeutically) (23), immunohistochemistry and others, in order to determine if breast cancers in Lynch syndrome patients have specific pathologic features, further supporting the hypothesis of a genetic association and possible causation. Further, cancer specific risks for Lynch syndrome patients, including that for breast cancer, need to be clarified.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cleveland Clinic.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.S., H.P., M.K.; Design – M.S., H.P.; Supervision – H.P., S.G., M.K.; Resources – M.K., C.E., E.D.K.; Materials – M.K., B.H.; Data Collection and/or Processing – M.S., C.Y.; Analysis and/or Interpretation – M.S., H.P.; Literature Search – M.S., H.P.; Writing Manuscript – M.S., H.P.; Critical Review – C.E., B.H., E.D.K., S.G.

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Comparison of Qualitative and Volumetric Assessments of Breast Density and Analyses of Breast Compression Parameters and Breast Volume of Women in Bahcesehir Mammography Screening Project

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ABSTRACT

Objective: We aimed to compare visual and quantitative measurements of breast density and to reveal the density profile with compression characteristics.

Materials and Methods: Screening mammograms of 1399 women between May 2014 and May 2015 were evaluated by using Volpara 4th and 5th version. First 379 mammograms were assessed according to ACR BI-RADS 4th edition and compared to Volpara. We categorized the breast density in two subgroups as dens or non-dens. Two radiologists reviewed the images in consensus. Agreement level between visual and volumetric methods and volumetric methods between themselves assessed using weighted kappa statistics. Volpara data such as fibroglandular volume (FGV), breast volume (BV), compression thickness (CT), compression force (CF), compression pressure (CP) were also analyzed with relation to the age.

Results: 1399 mammograms were distributed as follows: 12.7% VDG1, 39.3% VDG2, 34.1% VDG3, 13.9% VDG4 according to the 4th edition of Volpara; 1.2% VDG1, 46% VDG2, 36.8% VDG3, 15.9% VDG4 according to the 5th edition of Volpara. The difference between two editions was 4.7% increase in dense category. 379 mammograms, according to ACR BI-RADS 4th edition, were distributed as follows: 25.9% category A, 50.9% category B, 19.8% category C, 3.4% category D. The strength of agreement between the Volpara 4th and 5th editions was found substantial ($k=0.726$). The agreements between visual assessment and both Volpara editions were poor ($k=-0.413$, $k=-0.399$ respectively). There was a 142% increase in dense group with the VDG 4th edition and 162% with the VDG 5th edition when compared to visual assessment. Compression force decreased while compression pressure increased with increasing Volpara Density Grade (VDG) (p for trend <0.001 for both). Compression thickness and breast volume decreased with increasing VDG (p for trend <0.001 for both). The FGV decreases with age and the breast volume increases with increasing age ($p<0.001$).

Conclusion: Visual assessment of breast density doesn't correlate well with volumetric assessments. Obtaining additional information about physical parameters and breast profile by the results of quantified methods is important for breast cancer risk assessments and prevention strategies.

Keywords: BI-RADS, Breast density, mammography, screening, Volpara

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Introduction

Mammographic screening showed to be an effective tool as a screening method for more than 50 years with proven efficacy in reducing breast cancer mortality (1). The sensitivity of screening mammography is variable due to the breast density differences in the screening populations. False negative rates are higher in dens breasts because of the masking effect of density. Additional methods are considered to overcome this issue (2, 3). Furthermore, women with dens breasts have four to six fold of increased risk of breast cancer compared to women with fatty breast (4). Breast Imaging and Reporting Data System (BI-RADS) of American College of Radiology (ACR) recommends the use of breast density evaluation for every woman. The fourth edition of BI-RADS lexicon, which is used in our study, categorises the breast density depending on the percentage of fibroglandular tissue (5). The fifth edition of BI-RADS (6), published in 2013, redefined the density categories excluding the numeric quartiles of percentages of the dense area and described the distribution on the basis of possibility of having an obscured lesion. Although reliability and reproducibility of visual assessments are limited by interobserver and intraobserver variability, BI-RADS system is the most used method for breast density assessment in clinical practice (7). To overcome the limitations of a visual evaluation, automated methods of volumetric assessment which are reproducible and correlate well with the BI-RADS breast density categories, have been introduced and became commercially available (8, 9). Volumetric methods also provide ad-

ditional information about physical parameters of the procedure such as compression force- pressure and fibroglandular volume which may be guide for the screening strategy.

Breast density can vary among different countries and ethnic groups (10). Our study population were part of a county screening program which was the first, population based mammographic screening project in the country (11). Knowledge about breast density and volumetric data of screening population is important for risk assessments and prevention strategies.

The aim of this study was to compare visual and quantitative measurements of breast density and to reveal the breast density profile and compression characteristics of the screened women in our study population.

Materials and Methods

This retrospective study was conducted with institutional review board approval from Ethic Committee of our university and a waiver of the need for written informed consent from the participants. All patient information and records were made anonymous and deidentified before analyses.

A set of 1399 screening mammograms, all women in the 40–69 age group, who participated in a community based mammographic screening program for the first time between May 2014 and May 2015 were assessed in the study. All digital mammographic examinations were performed with a full-field digital mammography unit (Selenia, Hologic) equipped with 24x29 cm amorphous selenium detectors with a pixel size of 70 μm . The data set was composed of standard craniocaudal and mediolateral oblique views. Our standard compression protocol states that the radiographer should compress the breast by means of the compression paddle, until blushing of the skin occurred, or as much force as tolerable if the woman verbally expresses severe pain before blushing.

All mammograms were analysed with two versions of Volpara Density™ (Volpara) software (version 1.4.2 and version 1.5.1, Matakina Technology, Wellington, New Zealand). Version 1.4.2 is optimized for the 4th edition of ACR BI-RADS. The newer version is recalibrated for the 5th edition of BI-RADS.

Volpara is a computerized algorithm that calculates X-ray attenuation at each pixel and converts the attenuation to an estimate of tissue composition to create a density map. By adding total values in the density map, the software can calculate the volume of fibroglandular tissue in the breast, and breast density is determined as the percentage of fibroglandular tissue volume. Volpara gave separate data for each breast. We took the average of them.

Absolute dens volumes were categorized for analysis, with 0–4.7% being Volpara Density Grade (VDG) 1; 4.8–7.9% being VDG 2; 8.0–

15.0% being VDG 3; and 15.1% or greater being VDG 4. Each set of mammograms presents volume of fibroglandular tissue (cm^3), breast volume (cm^3), volumetric breast density (%), and VDG. We categorized the breast density in two subgroups as dens (ACR C and D) or non-dens (ACR A and B). Dens category was defined for VDG 3 and 4, and non-dens breasts were classified as VDG 1 and 2.

The first 379 mammograms from dataset were assessed qualitatively and independently with Volpara. The study design is retrospective and comparison of the visual assessment and Volpara data was not taken into account during the real-life assessments and the readers stopped visual assessment after a few months of the Volpara installment. To that time, the radiologists reviewed each mammogram according to ACR BI-RADS 4th edition as: Category A, almost fatty (<25% glandular); category B, scattered fibroglandular densities (25–50% glandular); category C, heterogeneously dense (51–75% glandular); and category D, extremely dense (>75% glandular). Two radiologists with 5 and 8 years of experience in breast radiology assessed the images independently. Consensus was reached in cases of inter-reader discrepancy in visual density evaluation.

Other Volpara data as; fibroglandular volume (FGV), breast volume (BV), compression thickness (CT), compression force (CF), compression pressure (CP) were also analyzed with relation to the age.

Statistical analyses

A chi-square analysis was conducted for all patient data to compare dens versus non-dens assessments using the 4th edition of BI-RADS and both Volpara 4th and 5th editions. Agreement between the BI-RADS visual density categories and Volpara 4th or 5th versions were assessed using linear weighted kappa (κ) statistics. Kruskal Wallis test was used for analysing the relation between volumetric compression data and other variables. Spearman Correlation analyses were done for the compression parameters. Statistical analysis was performed using Statistical Package for the Social Sciences statistical analysis software (PASW Statistics, version 11.0. SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered indicative of a statistically significant difference. The result used in the tables was the data of 5th versions of Volpara.

Results

A set of 1399 screening mammograms, of healthy women in the 40–69 age group, who participated in the population based mammographic screening program were assessed in the study. Table 1 presents the measures of center and dispersion of measurements in the study. The examinations with 4th version of Volpara density classification were distributed as follows: VDG1: 12.7%, VDG2: 39.3%, VDG3: 34.1%, VDG4: 13.9%, with a corresponding 5th version of Volpara density classification: VDG1: 1.2%, VDG2: 46%, VDG3: 36.8%, VDG 4: 15.9%. 379 mammograms, assessed according to ACR BI-RADS 4th edition, were distributed as follows: 25.9% category A, 50.9% category B, 19.8% category C, 3.4% category D. Table 2 shows the distribution of breast density by Volpara according to different age groups. 527% of studied women had dense breast based on the VDG 5th edition assessment, there was no VDG1 breast type in women below 44 yo (Table 2).

The compression parameters are shown in Table 3. The fibroglandular volume decreases with age ($p < 0.001$), and the breast volume increases with increasing age until age 64 ($p < 0.001$). Compressed breast thickness changed with increasing age ($p < 0.001$) as well as the compression

Key Points

- Visual assessment of breast density doesn't correlate well with volumetric assessments. Dense group increases with using Volpara.
- Volpara give information about quantitative density measurements, also reports the compression parameters.
- The women in the screening program had denser breast structure compared to European women.

Table 1. Measures of center and dispersion of measurements in the study

	n	Mean	SD	Median	Min	Max
Age (Year)	1399	52.4	8.3	51.0	40	69
Max. VBD	1399	9.9	6.4	7.8	2.7	41.3
VBD	1399	9.4	5.9	7.3	2.6	38.3
BV (cm ³)	1399	892.8	433.5	835.6	118.8	3171.5
FGV (cm ³)	1399	68.0	29.7	61.7	17.9	367.8
CT (mm)	1399	57.4	10.5	57.5	25.5	88.8
CF (fN)	1399	106.9	15.2	107.9	44.5	164.6
CP (kPa)	1399	10.2	3.6	9.5	3.2	30.6

BV: breast volume; CF: compression force; CP: compression pressure; CT: compression thickness; FGV: fibroglandular volume; VBD: Volpara breast density

Table 2. Distribution of Volpara density grade (VDG) and percentages of the VDG according to age groups of healthy women

Age	VDG								n	%
	1		2		3		4			
	n	%	n	%	n	%	n	%		
≤44	0	0.0	52	19.8	120	45.6	91	34.6	263	100.0
45-49	0	0.0	114	33.7	141	41.7	83	24.6	338	100.0
50-54	6	2.1	136	46.6	121	41.4	29	9.9	292	100.0
55-59	5	2.3	140	64.2	58	26.6	15	6.9	218	100.0
60-64	2	1.5	91	70.0	34	26.2	3	2.3	130	100.0
≥65	4	2.5	111	70.3	41	25.9	2	1.3	158	100.0
Total	17	1.2	644	46.0	515	36.8	223	15.9	1399	100.0

VDG: volpara density grade

Table 3. Distribution of breast compression parameters in healthy women aged 40–69 by age groups

		Age≤44 (n=264)	Age 45-49 (n=339)	Age 50-54 (n=292)	Age 55-59 (n=218)	Age 60-64 (n=130)	Age 65 (n=159)	p
FGV (cm ³)	mean (SD)	82.8 (38.1)	75.2 (30.5)	66.5 (26.4)	58.0 (20.8)	55.6 (18.6)	55.0 (18.2)	0.0001**
	median	74.7	69.0	61.9	54.2	52.0	50.6	
BV (cm ³)	mean (SD)	766.5 (404.9)	847 (430.2)	936.7 (457.9)	962.1 (433.7)	970.3 (416.3)	961.8 (397.5)	0.001**
	median	699.4	767.3	850.5	898.3	907.9	906.1	
CT (mm)	mean (SD)	54.6 (10.9)	57.6 (11.2)	59.0 (10.8)	59 (9.8)	57.9 (8.5)	56 (8.8)	0.0001**
	median	55.3	57.5	59.4	58.8	58.6	56	
CF (fN)	mean (SD)	103.9 (15.4)	107.5 (15.4)	108.5 (16.6)	109.0 (13.8)	107.6 (13.7)	104.9 (13.7)	0.0001**
	median	104.5	107.9	109	109	107.9	105.7	
CP (kPa)	mean (SD)	10.9 (3.5)	11 (3.7)	10.4 (3.9)	9.8 (3.3)	9.2 (3)	8.2 (2.4)	0.0001**
	median	10.4	10.5	9.4	9.3	8.9	7.6	

Kruskal Wallis test. **p<0.001. BV: breast volume; CF: compression force; CP: compression pressure; CT: compression thickness; FGV: fibroglandular volume

force and pressure ($p < 0.001$) (Table 3). Compression force decreased while compression pressure increased with increasing VDG (p for trend < 0.001 for both). Compressed breast thickness and breast volume decreased with increasing VDG (p for trend < 0.001 for both)

(Table 4). Compression force was correlated with compressed breast thickness and breast volume ($r: 0.293$, $r: 0.450$; $p < 0.001$ for all), while compression pressure was negatively correlated with compressed breast thickness and breast volume ($r: -0.362$, $r: -0.751$, $p < 0.001$

Table 4. Range of breast compression parameters based on breast density measurements by VDG 5th edition in healthy women aged between 40 and 69

		Volpara 5 th				p
		VDG 1 (n=17)	VDG 2 (n=646)	VDG 3 (n=516)	VDG 4 (n=223)	
FGV (cm ³)	mean (SD)	60.2 (7.7)	57.1 (19)	71.4 (27.3)	93.3 (41.7)	0.0001**
	median	50.8	53.1	66.6	88.8	
BV (cm ³)	mean (SD)	1637 (304)	1130.2 (412.4)	754.3 (302.3)	469.3 (200.6)	0.0001**
	median	1612.8	1048.8	713.2	443	
CP (kPa)	mean (SD)	6.4 (1.5)	8.6 (2.5)	11 (3.4)	13.1 (3.9)	0.0001**
	median	6.0	8.4	10.5	12.4	
CF (FN)	mean (SD)	112.9 (18.3)	111.6 (14.5)	105.2 (13.7)	97.1 (14.8)	0.0001**
	median	116.8	111.2	105.7	97.9	
CT (mm)	mean (SD)	69.9 (7.1)	62.2 (8.6)	55.5 (8.9)	46.7 (9.2)	0.0001**
	median	69.5	61.5	55.3	46.0	

** $p < 0.001$. Kruskal Wallis test. BV: breast volume; CF: compression force; CP: compression pressure; CT: compression thickness; FGV: fibroglandular volume; VDG: Volpara density grade

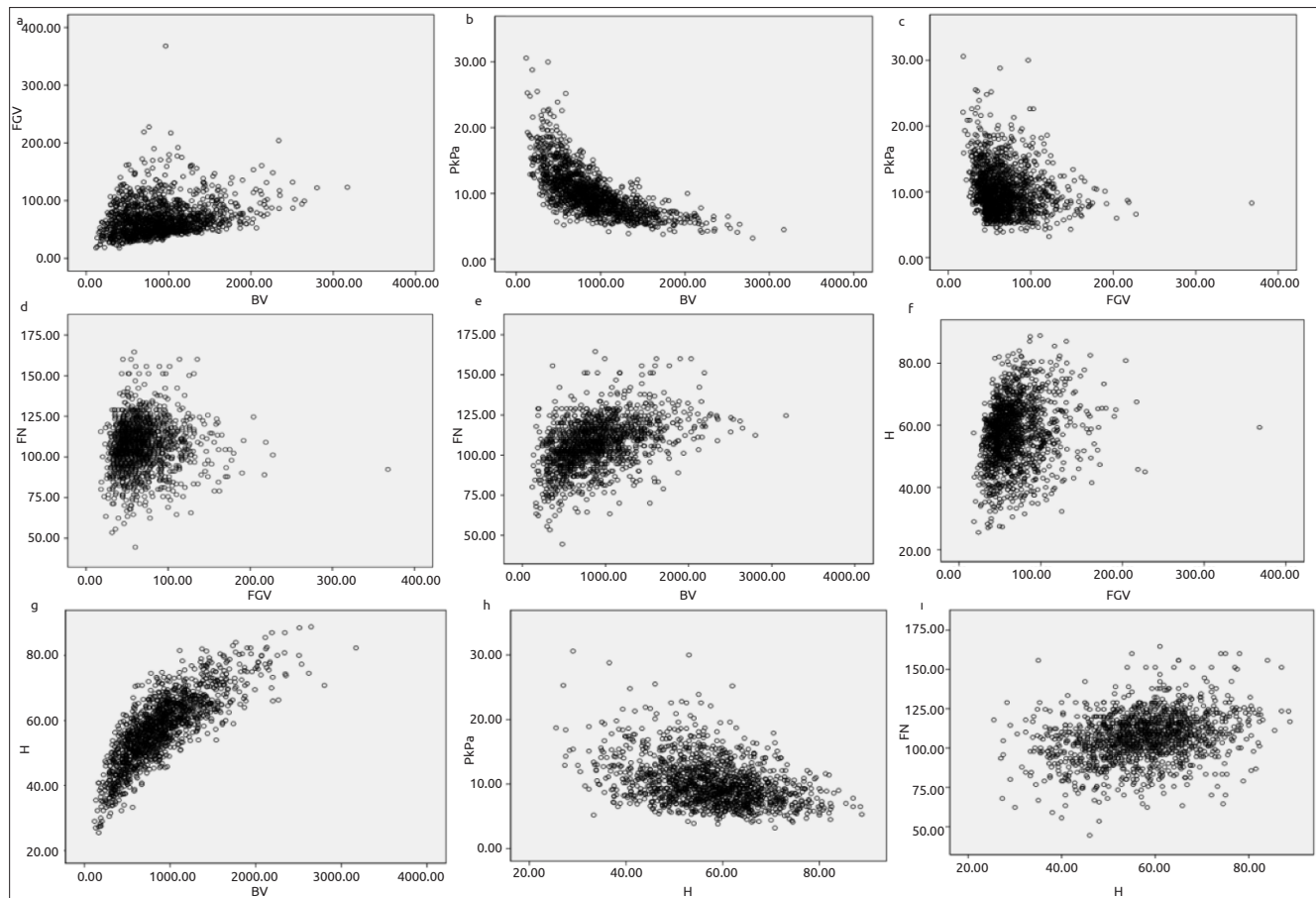


Figure 1. a-i. Breast volume- FGV correlation (a). Breast volume- Compression pressure correlation (b). FGV- Compression pressure correlation (c). FGV- Compression force correlation (d). BV- Compression force correlation (e). FGV- Breast thickness correlation (f). Breast volume- Breast thickness correlation (g). Breast thickness- Compression pressure correlation (h). Compression thickness- Compression force correlation (i)

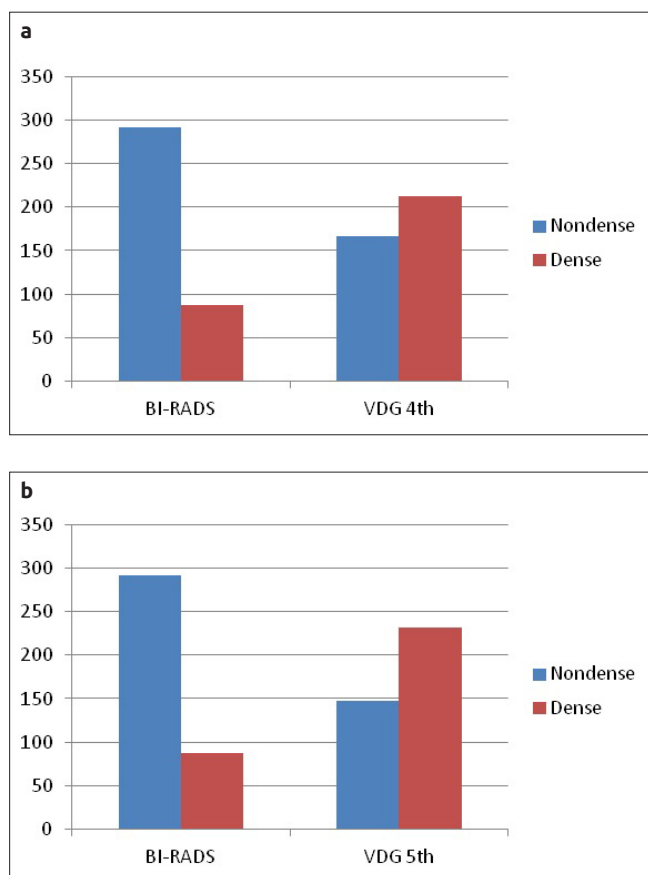


Figure 2. a, b. Comparison between BI-RADS scores and Volpara density grade (VDG) 4th version (a). Comparison between BI-RADS scores and VDG 5th version (b)

for all). Compressed breast thickness was correlated with breast volume ($r:0.820$, $p<0.001$ for all). Compression force and compressed breast thickness were positively correlated with fibroglandular volume ($r:0.103$, $r:0.237$), while compression pressure and fibroglandular volume were correlated negatively ($r:-0.204$) (Figure 1).

The strength of agreement assessed one by one between the Volpara 4th and 5th editions was calculated as substantial ($k=0.726$). The 379 mammograms that were assessed visually at the beginning of the study were divided into two categories, as dense and non-dense groups due to small number of patients. The current study showed a significant upgrade of breast density categories with a 60% increase in dens category while a 39% decrease in non-dens category when visual evaluation was compared to Volpara. The agreement between the visual assessment and both Volpara editions were poor ($k=-0.413$ with VDG 4th edition, -0.399 with VDG 5th edition). There was a 142% increase in dense group with the VDG 4th edition and 162% with the VDG 5th edition when compared to visual assessment (Figure 2).

The current study showed a significant upgrade of breast density categories with a 60% increase in dens category while a 39% decrease in non-dens category when visual evaluation was compared to Volpara. The agreement level was less than 0 indicating a poorer than chance-level prediction ($\kappa=-0.399$).

Discussion and Conclusion

The current work used two versions of Volpara automated software for breast density quantification which was found as the most reliable pro-

gram in several fully automated volumetric methods (12-15). The software was updated according to the 5th edition of ACR BI-RADS. Studies in the current literature compared the visual density assessment in itself or visual methods with automated systems (16-20). Recent studies showed 12.6 to 21.7% shift in breast density assessment from less dense to denser categories with the switch to the 5th edition. The shift of density assessment for those women to a denser group may have an impact on screening approach (16, 17). To the best of our knowledge there is no study comparing both versions of automated volumetric density assessments for ACR BI-RADS density. In our study, with the use of two versions of Volpara, the percentage of dens group increased from 48 to 52.7% but the agreement level between two versions were good ($\kappa=0.726$) which showed that both versions were compatible for assessing the density in screening settings.

The agreement level was less than 0 indicating a poorer than chance-level prediction ($\kappa=-0.399$). On the contrary there is moderate to substantial agreement in the current literature (7-9, 17]. The analyses of the factors affecting discrepancy between Volpara software and radiologist's visual assessment, showed that the difference in bilateral breast density could cause misperception (9). Bilaterally different breast density may be a challenge for radiologists which could prevent proper visual assessment of the breast density while Volpara averages each breast density per se. Previous studies reported that there was no difference affecting discrepancy with regard to age in multivariate analysis. However, it was mentioned that the disagreement between visual and volumetric assessment mostly occurred in non-dens parenchyma where scattered small amount of tissue could cause difficulties in visual evaluation (9, 19). Accordingly, our study group had a higher count of BIRADS Category B breast parenchyma in visual assessment which may be the source of this misperception.

Agreement levels changes by the radiologist's experience level with an increase parallel to the experience (7). The readers in our study were experienced (5 and 8 years of experience), however we did not evaluate the inter-reader agreement as this was not the scope of this study.

The low agreement level between visual assessment and automated breast density quantification found in this study despite the evaluation of experienced breast radiologists discourages the use of qualitative methods for density assessment particularly in screening programs. BI-RADS density assessment is based on subjective description and has a suboptimal reproducibility (5, 6).

A Japanese study which used Volpara for assessment of breast density in 666 women, showed that the proportion of Japanese women with dense breast was high. That aforementioned study, pointed out the need of an additional test in the screening program in Japan (21). On the other hand, an Indian study showed that the breast density in Indian population was less dense compared to western women and concluded that screening with mammography only was sufficient for Indian women (22). Our study showed that the women in the screening program had denser breast structure when compared to European women. According to Malmö breast tomosynthesis screening trial which is a population-based screening program with the 7500 participants in the city of Malmö between 2012-2014 years, 53% of the screened had non-dense breast while our percentages of non-dense breast was 47.2% (23).

The current study showed that the density decreased noticeably in the perimenopausal period. The study about the mammographic density

and ageing which was set from 22 countries data, and 11.000 mammograms showed decrease in mammographic density with increasing age which was most pronounced during the menopausal transition (10). Our findings were in line with this multicentered multinational study.

Volpara does not only give information about quantitative density measurements, but also reports the compression parameters which has an effect on image quality. This study showed similar change of compression parameters and breast characteristics correlated to the density increase, in line with the literature (24-26). Analyses of breast compression parameters and breast volume by VDG showed that increasing VDG was correlated with the decrease of compression force, compressed breast thickness and breast volume but increase of compression pressure. Furthermore, in the Norwegian Breast Cancer Screening Programme, it was also stratified by mammographic projections and concluded that compression force, compressed breast thickness and breast volume were lower for craniocaudal (CC) as compared to mediolateral oblique (MLO) mammograms, while compression pressure were higher. The explanation was the inclusion of a larger part of pectoral muscle in MLO projection (24).

Amongst the parameters which were compared in our study, one of the strongest findings was the negative correlation between compression pressure and breast volume and the other being the positive correlation between breast volume and compressed breast thickness. Due to the fact that the relation between compression pressure and compression force is a weak one, the perception of pressure that women with smaller breasts may have, independent from the compression force, can be higher than those with large breasts. Furthermore, the compression thickness is firstly affected by breast volume rather than the fibroglandular tissue density per se. On the other hand, in women with larger breasts, compression force increases parallel to compression thickness on the other hand compression pressure decreases. Studied women in our study have lower breast volume than European women and the median compression force is lower but median compression pressure is similar (21). Asian women had the highest compression pressure because of smaller breast volume (27). Compression pressure is relevant with pain and discomfort which affects the screening behavior directly (28). Supervision of compression pressure can be an advantage in understanding and monitoring insufficient or excessed compression. By this way the technical parameters could be improved, and negative experience caused by pain due to faulty compression could be minimized in some cases.

We had some limitations in this study. First, the number of visual assessment cases were low. We have recorded the visual assessments in the beginning of the study when Volpara was initialized. But after the first few months the visual assessments were no longer recorded and Volpara was used for data keeping and recording. The study design is retrospective, and the shortage of visual cases was not noticed before the analysis. However, the number of recorded cases is 379 and we believe that this cohort is good enough to make a comparison with the automated assessments. Second, it is a single-site study and all images were acquired with a single mammographic system and a single technician.

In conclusion, the breast density, which is dependent on personal and geographic factors, should be assessed precisely since it is an essential tool for individual and population-based screening. As shown in our study, the visual assessment of breast density is a subjective method and it does not correlate well with the objective volumetric assessments.

Volumetric methods also provide additional information about physical parameters of the procedure such as compression which may be informative for the screening behavior of the targeted women.

Also knowing the information about physical parameters of the procedure such as compression gives us the opportunity to understand the screening features of the targeted women.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.A., A.N.O., V.O.; Design – E.A., A.N.O., A.A.G.; Supervision – E.A., V.O.; Resources – V.O., N.C., S.O.G., B.O., E.A.; Materials – A.N.O., N.C., S.O.G., B.O.; Data Collection and/or Processing – E.A., A.N.O., N.C., S.O.G., B.O.; Analysis and/or Interpretation – E.A., A.A.G.; Literature Search – A.A.G., E.A.; Writing Manuscript – A.A.G., E.A.; Critical Review – A.A.G., E.A., A.N.O.

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The Correlation of Magee Equations™ and Oncotype DX® Recurrence Score From Core Needle Biopsy Tissues in Predicting Response to Neoadjuvant Chemotherapy in ER+ and HER2- Breast Cancer

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ABSTRACT

Objective: Oncotype DX® recurrence score (RS) can be predicted from Magee Equations™ (MS) postoperatively. The aim of this study is to investigate correlation of MS with RS from pretreatment core needle biopsy (CNB) tissues, and their clinical usefulness in prediction of response to neoadjuvant chemotherapy (NCT) in estrogen receptor-positive and human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer (BC).

Materials and Methods: Pretreatment CNB tissue samples from 60 patients with ER+/HER2- invasive BC were analyzed for MS and RS correlation. MS and RS were categorized as follows: low (<18), intermediate (18–30), and high (≥ 31). Percentage Tumor size Reduction (%TR) was used to assess tumor response to NCT, and substantial %TR was defined as at least 50% reduction (≥50%TR). Correlation between MS and RS, and predictive factors for the ≥50%TR achievement were assessed.

Results: MS and RS represented a strong correlation (Spearman's correlation; $r=0.58$, $p<0.0001$) as a continuous variable. As a categorical variable, the concordance between MS and RS was 43.3%, and it increased to 80% ($r=0.61$, $p=0.003$) with the exclusion of the intermediate risk categories. Although, there was pathologic complete response (pCR), MS showed the highest predictive power for the ≥50% TR achievement, none of the factors were statistically significant ($p\geq0.07$).

Conclusion: Our study demonstrated that there was a strong correlation between MS and RS from pretreatment biopsy tissue samples in ER+ and HER2- invasive BC.

Keywords: Breast cancer, Magee Equations™, Oncotype DX® recurrence score, pretreatment biopsy, neoadjuvant chemotherapy

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Introduction

Oncotype DX® (Genomic Health, Redwood City, CA, USA) is a commercially available reverse transcriptase-polymerase chain reaction-based assay that provides a recurrence score (RS) which ranges from 0 to 100 based on the expression of 21 genes, using RNA extracted from formalin fixed paraffin embedded (FFPE) tumor tissues. It classifies patients into low-, intermediate- and high-risk of recurrence for women with hormone receptor positive (HR+) early stage breast cancer (BC) who are treated with adjuvant endocrine therapy. More importantly, Oncotype DX® can predict the magnitude of chemotherapy (CT) response and identify HR+ early stage BC patients who will benefit from CT (1-5). However, two considerable drawbacks of Oncotype DX® are its high cost and the time required for processing of the specimens.

Although several guidelines recommend Oncotype DX® use for lymph node negative HR+ early stage BC (6-9), considering its cost and time, clinicians should identify patients who are unlikely to benefit from Oncotype DX® testing even when the test is available. Additionally, Oncotype DX® assay is not currently reimbursed/readily available in most of countries. Efforts have been put forth to determine if routinely available pathologic parameters could predict RS. Some studies have shown that estrogen receptor (ER) levels, progesterone receptor (PR) levels, human epidermal growth factor receptor 2 (HER2) score, Ki67, Nottingham grade, tubule formation, mitosis and nuclear pleomorphism had a correlation with RS (10-16). Previous studies from our group showed that RS could be predicted by Magee Equations™ in combination with standard morpho-immunohistological variables from surgical pathology (17, 18). The correlation between RS and Magee Equations™ score (MS) seems appealing given its simplicity and potential cost savings (19-21).

While neoadjuvant chemotherapy (NCT) have several advantages including to monitor response to treatment and shrinks the tumor, some studies questioned the benefit of NCT for patients with HR+ BC overall. These studies showed that pathological complete response (pCR) was less likely to occur in luminal patients and did not confer with a survival benefit (7, 22-24). However, the main objective of NCT for HR+ cancers is to increase breast conserving surgery (BCS) rate. In addition, there is a subset of HR+ BC patients who benefit from NCT (25) such as luminal B patients. RS has been proposed to also select HR+ HER2- BC patients who will benefit from NCT. The correlation between multi-gene assays such as Oncotype DX® RS from pretreatment biopsy tissue and tumor response to neoadjuvant therapy has been studied previously (26-34).

MS from post-surgical pathology and Oncotype DX® RS are highly concordant and this encourages us to evaluate the possibility of similar association from pretreatment biopsy tissue samples. There has been no study to identify the correlation between MS and Oncotype DX® RS from pretreatment tissue samples. If there is a significant correlation between these two calculations and Oncotype DX® is unavailable, MS may give additional information for decision making of NCT to clinicians with no cost.

The aim of this study is to investigate the correlation of MS with RS from pretreatment core needle biopsy tissues and its clinical usefulness in prediction of response to neoadjuvant chemotherapy in ER+ and HER2- invasive BC.

Materials and Methods

Patient selection and clinicopathological data

Clinicopathological data was collected retrospectively for 71 female patients with ER+/HER2- invasive carcinoma of the breast diagnosed with core needle biopsy (CNB) and treated with NCT. All patients were ≥18 years of age without prior history of any cancer including BC. Patients were diagnosed with T1-3 N0-1 M0 tumor, in which the tumor size was recorded based on preoperative images. All patients had unifocal tumors. Pathological data required for MS calculation such as H-scores for ER and PR, HER2, and tumor size were obtained from pretreatment slide review or medical record. These data were blinded to RS evaluation.

Score assessment

Both MS and RS were obtained from pretreatment CNB tissues. Pretreatment paraffin-embedded tissue samples were sent to Genomic Health,

Inc. for Oncotype DX® RS. MS was calculated from Magee Equations™ (<http://path.upmc.edu/onlineTools/mageeequations.html>). The recurrence score risk categories were as follows: low (<18), intermediate (18–30), and high (≥31). We also investigated low- and midrange-risk groups as follows: low (<11), intermediate (11–25), and high (>25) (35-37).

Response assessment

All patients received standard NCT. Pathologic complete response (pCR) was defined as complete absence of viable invasive tumor cells both in the breast and lymph nodes on pathologic examination. We used Percentage Tumor Size Reduction (%TR) to assess tumor response to NCT in this study. %TR was based on pretreatment size (the largest dimension) and pathology evaluation of the resected specimen. The pretreatment tumor size was abstracted from clinical charts as a maximum dimension (unidimensional measurement). Imaging modality considered for tumor size measurements was selected in the following preferential order: Magnetic resonance imaging, ultrasound, mammogram or physical examination. The post-treatment tumor size was defined as the product of: maximum dimension of tumor-bed (or area of fibrosis)* percentage cellularity (compared with pretreatment biopsy) of the tumor-bed (or area of fibrosis) by microscopic exam. %TR was calculated as the difference between the pre- and post-treatment tumor size divided by pre-treatment tumor size, multiplied by 100 (available at <http://path.upmc.edu/onlineTools/ptvr.html>). Substantial %TR was defined as at least 50% reduction in tumor size (≥50%TR).

Statistical analysis

We assessed the correlation of MS with RS and predictive factors for clinicopathological response to NCT. Categorical comparisons between the categories were tested by the Pearson Chi-Square test. Correlations between MS and RS were determined using the Spearman's correlation coefficient both as continuous and categorical variables. The predictive power of variables on the ≥50%TR achievement was assessed based on multiple logistic and linear regression analyses. The Area Under the ROC (Receiver Operating Characteristic) Curve (AUC) values were calculated by plotting cumulative distribution function of sensitivity vs. '1-specificity'. The p-values were derived from two-tailed tests, and p<0.05 was considered significant. All statistical tests were performed using SAS/STAT version 9.3 (SAS Institute, Inc., North Carolina, USA).

Results

Pretreatment core biopsy samples were obtained and sent for Oncotype DX® testing from 71 patients. Two samples failed RNA extraction and the remaining 69 patient samples were processed by RT-PCR. There was no PCR failure, however, 9 samples were identified as HER2 positive by RT-PCR. The final sample size analyzed was 60 cases.

A summary of clinicopathologic features of the study is detailed in Table 1. The mean patient age was 52±13 years. The mean pre-NCT tumor size was 48±36 mm. The median %TR was 42% (range 0–97%) and ≥50%TR was observed in 27 (45%) patients. There was neither pathological complete response nor disease progression.

Table 2 shows the categorical distribution of MS and RS. The 21-gene assay demonstrated a low RS (<18) in 27 (45%), intermediate RS (18–30) in 10 (17%) and high RS (≥31) in 23 (38%) tissues. Magee Equations™ demonstrated a low MS in 16 (27%), intermediate MS in 40 (67%) and high MS in 4 (7%) tissues.

Key Points

- Guidelines recommend Oncotype DX® use for lymph node negative HR+ early stage breast cancer.
- Oncotype DX® assay is expensive and it is not currently reimbursed/readily available in most of the countries.
- Previous studies from our group showed that recurrence score could be predicted by Magee Equations™.
- Magee Equations™ is a simple method that takes no additional cost and waiting time.
- The present study demonstrated that there was a strong correlation between Magee Score and Recurrence Score from pretreatment biopsy tissue samples in ER+ and HER2- invasive breast cancer.
- Magee Score from pretreatment biopsy tissue can be a useful decision-making tool in the neoadjuvant setting, especially for low- or high-Magee Score patients.

Correlation between MS and RS

The mean MS was 22.0 compared with 27.7 for RS (Table 1). As a continuous variable, MS significantly correlated with RS (Pearson's correlation; $r=0.58$, $p<0.0001$). When analyzed as categorical variables, the overall concordance between MS and RS was 43.3% (Table 2). The Pearson's correlation coefficient between MS and RS was 0.38 ($p=0.001$). One-step discordance was 50% (30/60), and two-step discordance was 6.6% (4/60). With the exclusion of the intermediate risk categories for both MS and RS, the concordance between the two variables increased to 80% ($r=0.61$, $p=0.003$).

When MS fell in the intermediate category, RS was either the low or intermediate category in 63% (25/40) of the cases. Focusing on

the intermediate MS category, median MS for the low/intermediate RS category was 21 (range 18-31), and median MS for the high RS category was 25 (20-31). With 15 cases represented the lower range of the intermediate MS category (score of 18-21), 14 cases (93%) were reported as the low/intermediate RS category, and only 1 case (7%) was reported as the high RS category. Additionally, in the intermediate MS category, median PR H-score for the low/intermediate RS category is 120 (0-300), and median PR H-score for the high RS category is 23 (2-200). With 11 cases presented PR ≤ 23 in the intermediate MS category, 8 cases (73%) grouped to the high RS category, and 3 cases (27%) case grouped to the low/intermediate RS category.

Table 1. Summary of clinicopathologic features (n=60)

	Total		<50%TR (n=33)		≥50%TR (n=27)	
	Mean	(range)	Mean	(range)	Mean	(range)
Recurrence score	27.7	(3.3-69.9)	25.6	(6.0-69.9)	30.4	(3.3-66.6)
Magee score	22.0	(10.2-39.0)	20.6	(10.2-34.9)	23.7	(13.6-39.0)
Ki67	42.2	(5.0-85.0) ^a	35.0	(5.0-60.0) ^b	50.4	(8.0-85.0) ^c
ER (H-score)	234.7	(216.2-253.1)	257.7	(130-300)	206.5	(35-300)
PR (H-score)	131.6	(0-300)	149.8	(0-300)	109.3	(0-300)
Tumor size (cm)	4.8	(1.0-23.0)	4.7	(1.0-14.0)	5.0	(2.0-23.0)
Nottingham Score	6.6	(5.0-9.0)	6.6	(5.0-9.0)	6.5	(5.0-9.0)

^an=15, ^bn=8, ^cn=7

Table 2. Comparison between numbers of low, intermediate and high-risk categories based on Oncotype DX® recurrence score (RS) and Magee score (MS) (n=60)

MS	RS			
	Low (<18)	Intermediate (18-30)	High (≥31)	Total
Low risk (<18)	12 (20%)	0	4 (7%)	16 (27%)
Intermediate risk (18-30)	15 (25%)	10 (17%)	15 (25%)	40 (67%)
High risk (≥31)	0	0	4 (7%)	4 (7%)
Total	27 (45%)	10 (17%)	23 (38%)	60 (100%)

Pearson's correlation: 0.38 (± 0.12). Table Likelihood Chi-Square $p=0.001$. Concordance: 43.3% (26/60); one-step discordance: 50% (30/60); two-step discordance: 6.6% (4/60).

Table 3. Comparison between numbers of low (<11), midrange (11-25) and high-risk (>25) categories based on Oncotype DX® recurrence score (RS) and Magee score (MS) (n=60)

MS	RS			
	Low (<11)	Intermediate (11-25)	High (≥25)	Total
Low risk (< 11)	1 (2%)	0	0	1 (2%)
Intermediate risk (11-25)	6 (10%)	21 (35%)	15 (25%)	42 (70%)
High risk (≥25)	1 (2%)	4 (7%)	12 (20%)	17 (28%)
Total	8 (13%)	25 (42%)	27 (45%)	60 (100%)

Pearson's correlation: 0.35 (± 0.12). Table Likelihood Chi-Square $p=0.04$. Concordance: 56.7% (34/60); one-step discordance: 41.7% (25/60); two-step discordance: 1.7% (1/60).

In order to investigate the low and midrange risk categories, we used the other cutoff as follows: low (<11), intermediate (11–25), and high (>25) (Table 3). Oncotype DX® assay demonstrated a low RS (<11) in 8 (13%), intermediate RS (11–25) in 25 (42%) and high RS (>25) in 27 (45%) samples (Table 3). Magee Equations™ demonstrated a low MS (<11) in 1 (2%), intermediate MS (11–25) in 42 (70%) and high MS (>25) in 17 (28%) tissues. By using this cutoff, the concordance between MS and RS as a categorical variable was increased to 56.7%. One-step discordance was 41.7% (25/60), and two-step discordance was 1.7% (1/60). With the exclusion of the intermediate risk categories for both MS and RS, the concordance further increased to 92.9%.

Correlation between MS and RS in the patients achieved ≥50%TR

Twenty-five percent (4/16) of the low MS category patients, 50% (20/40) of the intermediate MS category patients, and 75% (3/4) of the high MS category patients achieved ≥ 50%TR, compared with

37% (10/27) of the low RS category patients, 60% (6/10) of the intermediate category RS patients and 48% (11/23) of the high RS category patients achieved ≥ 50%TR (Table 4, 5). Focusing on the ≥50%TR achieved patients, the correlation between MS and RS was marginally significant (Table 4; $r=0.42$, $p=0.05$). The concordance between MS and RS was 44.4%. One-step discordance was 51.9% (14/27), and two-step discordance was 3.7% (1/27). With the exclusion of the intermediate risk categories for both MS and RS, the concordance increased to 86% ($r=0.75$, $p=0.002$).

We also investigated the low and midrange risk categories (Table 5). Oncotype DX® assay demonstrated a low RS (<11) in 2 (7%), intermediate RS (11–25) in 11 (41%) and high RS (>25) in 14 (52%) samples. Magee equation demonstrated a low MS (<11) in 0 (0%), intermediate MS (11–25) in 16 (59%) and high MS (>25) in 11 (41%) tissues. In this cutoff, the concordance between MS and RS as a cat-

Table 4. Comparison between numbers of low, intermediate and high-risk categories based on Oncotype DX® recurrence score (RS) and Magee score (MS) among samples with tumor volume reduction ≥50% (n=27)

MS	RS			Total
	Low (<18)	Intermediate (18-30)	High (≥31)	
Low risk (<18)	3 (11%)	0	1 (4%)	4 (15%)
Intermediate risk (18-30)	7 (26%)	6 (22%)	7 (26%)	20 (74%)
High risk (≥31)	0	0	3 (11%)	3 (11%)
Total	10 (37%)	6 (22%)	11 (41%)	27 (100%)

Pearson's correlation: 0.42 (± 0.16). Table Likelihood Chi-Square $p=0.05$. Concordance: 44.4% (12/27); one-step discordance: 51.9% (14/27); two-step discordance: 3.7% (1/27).

Table 5. Comparison between numbers of low (<11), midrange (11-25) and high-risk (>25) categories based on Oncotype DX® recurrence score (RS) and Magee score (MS) among samples with tumor volume reduction ≥50% (n=27)

MS	RS			Total
	Low (<11)	Intermediate (11-25)	High (≥25)	
Low risk (<11)	0	0	0	0 (0%)
Intermediate risk (11-25)	1 (4%)	7 (26%)	8 (30%)	16 (59%)
High risk (≥25)	1 (4%)	4 (15%)	6 (22%)	11 (41%)
Total	2 (7%)	11 (41%)	14 (52%)	27 (100%)

Pearson's correlation: 0.01 (± 0.19). Table Likelihood Chi-Square $p=0.91$. Concordance: 48.1% (13/27); one-step discordance: 48.1% (13/27); two-step discordance: 3.7% (1/27).

Table 6. Comparison between 50%TR achievement and Oncotype DX® recurrence score (RS) and Magee score (MS) categories (focused on low and midrange risk categories)

	RS categories				MS categories			
	Low <11	Intermediate 11-25	High >25	p	Low <11	Intermediate 11-25	High >25	p
<50%TR (n=33)	6 (18%)	14 (42%)	13 (39%)	0.20	1 (3%)	26 (79%)	6 (18%)	0.04
≥50%TR (n=27)	2 (7%)	11 (41%)	14 (52%)		0	16 (60%)	11 (40%)	
Total	8 (13%)	25 (42%)	27 (45%)		1 (2%)	42 (70%)	17 (28%)	

Table 7. Univariate analysis of predictive factors for tumor volume reduction $\geq 50\%$ (n=60)

	Model P ^a	AUC (95% CI) ^b	AIC
Recurrence score categories (<18, 18-30, ≥ 31)	0.43	0.56 (0.42, 0.69)	86.90
Magee score categories (<18, 18-30, ≥ 31)	0.13	0.63 (0.52, 0.75)	83.95
Low risk Magee score category (<18)	0.07	0.61 (0.50, 0.72)	82.90
ER (H-score <100, ≥ 100)	0.97	0.59 (0.52, 0.67)	78.03
PR (H-score <120, ≥ 120)	0.12	0.60 (0.48, 0.73)	84.05

^aLogistic regression modeling tumor volume reduction $\geq 50\%$ as the outcome. ^b95 % Wald Confidence Intervals
AUC: Area Under the ROC (Receiver Operating Characteristic) Curve, AIC: Akaike Information Criterion

egorical variable was increased to 48.1%. One-step discordance was 48.1% (13/27), and two-step discordance was 3.7% (1/27). With the exclusion of the intermediate risk categories for both MS and RS, the concordance increased to 85.7%. Table 6 shows comparison between 50%TR achievement and RS (p=0.20) and MS (p=0.04) categories, focused on low and midrange risk categories.

Predictive factors for the $\geq 50\%$ TR achievement

Predictive factors for the $\geq 50\%$ TR achievement from univariate analysis are listed in Table 7. Although MS showed the highest predictive power, none of the factors such as RS, MS, ER and PR were statistically significant. The AUC values for RS, MS, ER and PR were 0.56, 0.63, 0.59, 0.60, respectively. Focusing on the low risk MS category, it did not lead to a significant improvement as a predictive factor (p=0.07, AUC=0.61). Low level of ER H-score (<100) was not a statically significant factor for the $\geq 50\%$ TR achievement, whereas all patients who had low level (<100) of ER H-score (n=5, the median MS=30 [range 21.5–39]) achieved $\geq 50\%$ TR.

Discussion and Conclusion

Patients must pay out of pocket for Oncotype DX® test in most of the countries as the insurance companies don't reimburse this high-cost test. In this study, we investigate the correlation between MS and RS from pretreatment biopsy tissue samples. In a continuous variable analysis, MS correlated significantly with RS. As a categorical variable, the Pearson's correlation coefficient between MS and RS dropped (Table 2). With the exclusion of the intermediate risk categories for both MS and RS, the concordance increased to 80%, and MS and RS showed strong correlation. Therefore, one can conclude that if MS is clearly in the high or low categories, it is predictive of the RS categories with 80% certainty.

MS tends to report more intermediate risk category patients than Oncotype DX® testing. Focusing on the intermediate MS category in our study, with 15 patients represented the lower range of the intermediate MS category (score of 18–21), 14 cases (93%) were reported as the low/intermediate RS category and only 1 case (7%) was reported as the

high RS category. Therefore, patients who represent the lower range of the intermediate MS category (score of 18–21) can be categorized into the low/intermediate risk RS with an over 90% possibility. In addition, with 11 cases presented PR H-score ≤ 23 in the intermediate MS category, 8 cases (73%) grouped to the high RS category, and 3 cases (27%) grouped to the low/intermediate RS. Therefore, when MS is calculated as the intermediate group, low PR H-score patients may be grouped into the high RS category with an over 70% possibility. Others have also found similar strong correlations of lower PR scores with higher RS similar to our findings (10, 12, 13, 15–17).

Management for patients with intermediate risk disease by Oncotype DX® testing is published recently (37). Adjuvant endocrine therapy and CT had similar efficacy in women with HR (+), HER2-, axillary node negative BC who had RS between 11 and 25, although some benefit of CT was found in some women 50 years of age or younger. To investigate the low and midrange risk categories, we also used cut-off as low (<11), intermediate (11–25), and high (>25). By using this cutoff, the concordance between MS and RS as a categorical variable was increased to 56.7%. With the exclusion of the intermediate risk categories for both MS and RS, the concordance further increased to 92.9%. From these results, MS > 25 may be another cut off for predicting the high RS category (Table 3).

Focusing on the $\geq 50\%$ TR achieved patients, the correlation between MS and RS was marginally significant (Table 3). The concordance between MS and RS was 44.4% due to one-step discordance. Excluding the intermediate categories for both MS and RS, the concordance increased to 86%, and MS and RS presented very strong correlation. According to this fact, when MS is in the high or low categories, it may predict the RS categories with 86% certainty for the achievement of $\geq 50\%$ TR. The same was true of for the cutoff as low (<11), intermediate (11–25), and high (>25) (Table 3), and statistically significant correlation was found between 50%TR achievement and MS categories in terms of this cutoff (Table 3).

A number of conflicting results have been published on the usefulness of RS in predicting response to neoadjuvant therapy (26–34). Although two reports showed there was no statistically significant association between tumor response and RS (26, 27), some studies support the correlation between RS and tumor response to neoadjuvant systemic therapy (28–34). In univariate analyses of predictive factors for the $\geq 50\%$ TR achievement from our study (Table 7), none of the models were statistically significant. However, the MS gave the best predictive power; 25% (4/16) of the low MS category patients and 75% (3/4) of the high MS category patients achieved $\geq 50\%$ TR, compared with 37% (10/27) of the low RS category patients, and 48% (11/23) of the high RS category patients achieved $\geq 50\%$ TR (Table 2, 4). Especially, in terms of predictive value of the $\geq 50\%$ TR achievement, there is a possibility that MS can be superior to RS. Since small number of patients in our study may have affected not to reach statistical significance in MS and tumor response correlation, further larger studies are needed. Changing focus on another pathological factor for the $\geq 50\%$ TR achievement, there was a trend that low level of PR H-score (<120) had the predictive power, but there was not significant. Although low level of ER H-score (<100) was not a statically significant factor for the $\geq 50\%$ TR achievement probably due to smaller sample size, all patients who had low level of ER H-score (<100) (n=5) achieved $\geq 50\%$ TR. These results are consistent with previous studies (28, 29).

Farrugia et al. (38) investigated an association between pCR after NCT and MS. They reported that pCR rate increased with higher MS, but this study had no genomic test. They concluded that MS can predict pCR, but this finding should be tested in a bigger study.

Some studies have been reported the association between RS and tumor response to neoadjuvant therapy, nevertheless, RS is not available for patients in almost most countries. Under such a situation, our results assure that MS gives an additional information in patient for NCT, especially for low or high MS score patients. The low or high MS categories are predictive of the RS categories with 80% certainty, and they may predict the RS categories with 86% certainty for the achievement of $\geq 50\%$ TR. When MS is calculated to the intermediate risk category, patients who represented the lower range of the intermediate MS category (score of 18–21) can be categorized into the low/intermediate risk RS with an over 90% possibility, and low PR H-score may categorize the intermediate MS risk patients into the high RS category.

From our results, one can be speculated that the high MS category calculated from pretreatment biopsy tissue may enable us to predict high tumor response to chemotherapy. On the other hand, the low MS category may give small benefit of NCT, and initial surgery or neoadjuvant hormone therapy may be recommended. Since none of factors including MS were not significantly correlated with tumor response in this small study, further studies are needed to determine whether MS can be a predictive marker for tumor response in neoadjuvant settings or not.

Our study has some limitations. At first, this is a small sample study from single institution. It was noteworthy that this result was achieved using limited amount of tissues obtained from pretreatment core needle biopsy. The second, we used an original method to evaluate tumor response (Magee Method; <http://path.upmc.edu/onlineTools/ptvr.html>). We cannot deny that different results will be come out with other assessment methods for tumor response.

The present study demonstrated that there was a strong correlation between MS and RS from pretreatment biopsy tissue samples in ER+ and HER2- invasive BC. Magee equation is a simple method that takes no additional cost and waiting time. When Oncotype DX® testing is not available readily, MS from pretreatment biopsy tissue can be a useful decision-making tool in the neoadjuvant setting, especially for low- or high-MS patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Pittsburgh Institutional Review Board (IRB#:PRO09080144, August 3, 2010).

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Breast Cancer Detection in Qatar: Evaluation of Mammography Image Quality Using A Standardized Assessment Tool

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ABSTRACT

Objective: Compared with other countries in the Middle East, Qatar has one of the highest breast cancer incidence and mortality rates. Poor quality mammography images may be associated with advanced stage breast cancer, however there is limited information about the quality of breast imaging in Qatar. Our purpose was to evaluate the clinical image quality of mammography examinations performed at a tertiary care center in Doha, Qatar using a standardized assessment tool.

Materials and Methods: Bilateral mammograms from consecutive patients from a tertiary care cancer center in Doha, Qatar were obtained. Proportions of examinations deemed adequate for interpretation were estimated. Standardized clinical image quality assessment form was utilized to evaluate image quality components. For each image, image quality components were given grades on a 1-5 scale (5- excellent, 4- good, 3- average, 2- fair, 1- poor). Mean scores with 95% confidence intervals were estimated for each component.

Results: Consecutive sample of 132 patients was obtained representing 528 mammographic images. Overall, 99.2% of patients underwent examinations rated as acceptable for interpretation. Mean scores for each image quality component ranged from 4.045 to 5.000 (lowest score for inframammary fold). Image quality component scores were 93.0% excellent, 5.2% good, 1.1% average, 0.6% fair, and 0.1% poor.

Conclusion: Overall image quality at a tertiary care center in Doha, Qatar was acceptable for interpretation with minimal areas identified for improvement.

Keywords: Breast cancer, diagnostic imaging, Qatar, mammography, Middle East

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Introduction

Compared with other countries in the Middle East, Qatar has one of the highest breast cancer incidence and mortality rates (1). In a retrospective review of 268 breast cancer patients in Chicago, Rauscher et al. found that lower image quality scores were associated with late stage breast cancer diagnoses, even after adjusting for patient and practice related characteristics (2). There is limited information about mammography image quality in Qatar. Our purpose was to evaluate the clinical image quality of mammography examinations performed at a tertiary care center in Doha, Qatar using a standardized assessment tool.

Materials and Methods

Ethics committee and institutional review board (IRB) approval was obtained for our retrospective study. Informed consent was not required for retrospective review of previously collected images. This study was supported by a grant from the Qatar National Research Fund (QNRF), project number NPRP9-189-3-031.

Study results were reported using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (3).

Study design

Our study design involved retrospective evaluation of consecutive images performed from October 2018 to January 2019.

Data sources/measurement

Clinical image quality of mammography images was evaluated using Hologic SecureView Dx viewing software (Hologic Inc., Marlborough, MA, United States). Images were acquired using Hologic Selena Dimensions 2D and 3D mammography units installed in 2016 (Hologic Inc., Marlborough, MA, United States). Initial evaluation of clinical image quality was performed by the interpreting radiologist. External review of clinical image quality review was subsequently performed by a breast imaging faculty member with 4 years of experience in breast imaging. Review was blinded to final assessment, whether or not examination was technically recalled, and the technologist performing the examination.

Setting

Mammography images were acquired from two sites associated with a tertiary care center in Doha, Qatar. The tertiary care center is the main provider of secondary and tertiary healthcare in Qatar (4). At both sites, women present for diagnostic mammography.

Participants

Images from consecutive patients from two different imaging sites was obtained from October 2018 to January 2019 was included.

Study size

The study size was based on available number of eligible adult patients presenting to the two sites.

Variables

Dependent variables

Outcomes for the study included subjective binary assessment as to whether or not the examination was technically adequate for clinical interpretation (Adequate vs Not Adequate for Interpretation) as well as outcomes from standardized assessment form. Standardized image quality assessment was derived from recommendations produced by a working group of the National Health Service Breast Screening Programme (NHSBSP) Clinical and Professional group for Radiography, developed for the National Health Service in the UK (5). The standard image quality assessment form involved subjective assessment of the following items (Figure 1): Correct patient ID & Markers, Appropriate

exposure, Adequate compression to hold breast firmly - no movement, Image sharp, No artefacts obscuring image, No obscuring skin folds, Nipple in profile, Pectoral muscle to nipple level, Pectoral muscle at appropriate angle, IMF shown clearly, Medial border demonstrated, Back of breast clearly shown with some medial central & lateral, Some axillary tail shown. Appropriate exposure refers to subjective reader perception of exposure (standardized quality assessment form does not include quantitative benchmarks or reference levels for radiation dose). For each item, each image (RMLO, LMLO, RCC, LCC) was given a 1-5 score (1- poor, 2- fair, 3- average, 4- good, 5- excellent). For patients who had repeat views, each image quality component was evaluated on the best possible view obtained for the evaluation of each specific component of image quality.

Independent variables

Independent variables included imaging site, age and breast density (categorized as dense ("The breasts are heterogeneously dense, which may obscure small masses", "The breasts are extremely dense, which lowers the sensitivity of mammography") vs not dense ("The breasts are almost entirely fatty", "There are scattered areas of fibroglandular density").

Statistical analysis

Proportion of examinations considered as adequate were estimated, stratified by imaging site and breast density. For each component of clinical image quality for each image, means and 95% confidence intervals were estimated. Multiple variable linear regression analyses were conducted to evaluate the association between image quality parameters and imaging site, age and breast density. Analyses were conducted using STATA 11 (StataCorp, College Station, TX, United States). Two-tailed p values less than 0.05 were considered statistically significant.

Results

A total of 528 images were obtained from 2 sites from 132 unique patients (90 patients from one site and 42 patients from the other site). All of the examinations (100%) in our study were initially interpreted as technically adequate by the interpreting radiologist. External review of these examinations found 99.2% (131/132) of patients undergoing technically adequate examinations for clinical interpretation. The one discrepant examination was one in which image quality was considered as not adequate for interpretation was rated as inadequate secondary to the sharpness of the LMLO image (rated as poor in the standardized image quality assessment form).

Quantitative ratings for each of the image quality components from external review are presented in Table 1 with 95% confidence intervals. Mean scores for each image quality component ranged from 4.045 to 5.000 with a few of the indicators having perfect image quality scores (Correct Patient ID, Medial border demonstrated, Back of breast clearly shown with some medial central & lateral, Some axillary tail shown). Overall 93.0% of the image quality component scores were excellent (5,404/5,808), 5.2% were good, (304/5,808), 1.1% were average (66/5,808), 0.6% were fair (33/5,808) and 0.1% were poor (1/5,808). Image quality component with the lowest score was inframammary fold (mean 4.083) with 40.9% of the images with excellent scores, 35.6% of the images with good scores, 14.4% of the images with average scores, 9.1% of the images with fair scores and 0.0% of the images with poor scores.

Key Points

- 99% of studies conducted at a tertiary care cancer center in Doha, Qatar were deemed adequate for interpretation, results that are comparable to academic centers in the United States and Europe.
- Using our standardized quality improvement instrument, we found that visualization of the inframammary fold was the most commonly identified area for improvement.
- Standardization of performance and evaluation of mammography images will be essential to maintaining and improving the quality of screening and diagnostic breast imaging.

MAMMOGRAPHIC IMAGE ASSESSMENT																														
Dates of Assessment:																		Static/ Mobile												
Assessor(s):														Clinic Code				Date Taken				Mammographer								
Case No.	View	Correct patient ID & Markers		Appropriate exposure		Adequate compression to hold breast firmly - no movement		Image sharp		No artefacts obscuring image		No obscuring skin folds		Nipple in profile		MLO's						CC's						Symmetrical Images	Whole breast imaged	Comments
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L			
1	MLO																													
	CC																													
2	MLO																													
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9	MLO																													
	CC																													
10	MLO																													
	CC																													

Notes: No less than 50 exams should be reviewed in total, preferably 5 per mammographer. No patient identifying numbers should be used.
To view trends easily only place an X in boxes where criteria are NOT met

Figure 1. Standardized image quality assessment form

Discussion and Conclusion

In our study, 99% of studies conducted at a tertiary care center in Doha, Qatar were deemed adequate for interpretation, results that are comparable to high volume academic centers in the United States and Europe (6, 7). With adequate image quality performance, our results suggest that image quality may not be an explanation for higher rates of advanced stage breast cancer in Qatar.

As the country develops additional capacity and awareness for mammography screening, it will be important to continuously monitor image quality. Using our standardized instrument, we identified a few specific areas for improvement, specifically the inframammary fold. NHS Breast Screening Guidance for breast screening mammographers states that the inframammary angle should be clearly demonstrated without overlapping chest wall tissue. This positioning ensures that the breast has been lifted and that the postero-inferior part of the breast has been adequately imaged. Previously published studies have suggested that the inframammary fold is one of the most commonly cited reasons for technical recalls (8). Writing in the Society of Breast Imaging Newsletter, Louise C. Miller provided several suggestions for improving visualization of the IMF and reducing skin folds (9). To improve visualization of the IMF, the IMF should be placed onto the image receptor. To reduce folds, technologists may utilize several corrective actions including smoothing lateral and inferior breast tissue before lifting the breast up and out, maintaining the up and out position throughout breast compression, and having the patient lift her contralateral breast up and back. In addition to the IMF, usage of a

standardized instrument can help facilitate comprehensive longitudinal monitoring of components of clinical image quality.

High performance quality control for breast images includes not only evaluation of image quality of clinical images but also breast phantoms. Phantoms quantitatively evaluate the capacity of mammographic systems to image structures, similar to those found clinically. Gürdemir and Aribal used the American College of Radiology (ACR) phantom to assess the image quality of mammography units in Istanbul (10). The ACR phantom contains 16 objects that mimic structures seen clinically (spiculations, microcalcifications and small masses). Images from 38% of the imaging units had unacceptable quality scores. In our study, we found that 99% of studies had acceptable image quality study, however our study focused on clinical image quality evaluation. Future studies should be conducted including breast phantoms to evaluate whether or not imaging units in Qatar can identify structures that mimic early breast cancers.

Standardization of performance and evaluation of mammography images has been associated with improvements in image quality (6). The International Atomic Energy Agency (IAEA) convened a group of breast imagers, medical physicists and radiographers to evaluate and improve image quality in 15 countries (Bosnia and Herzegovina, Costa Rica, Egypt, India, Kenya, the Frmr. Yug. Rep. of Macedonia, Mexico, Nigeria, Pakistan, Philippines, Slovenia, Turkey, Uganda, United Kingdom and Zambia) (11, 12). After performing a baseline evaluation in these countries, the IAEA recommended several key interventions to foster high quality imaging practices. Among these interven-

Table 1. Quantitative evaluation of image quality components

Parameter	RMLO*	LMLO*	RCC*	LCC*
Correct Patient ID	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
Exposure	4.992 (4.977, 5.007)	5 (5, 5)	4.992 (4.977, 5.007)	5 (5, 5)
Compression	4.970 (4.940, 4.999)	4.970 (4.933, 5.006)	4.992 (4.977, 5.007)	5 (5, 5)
Sharpness	4.902 (4.846, 4.957)	4.833 (4.745, 4.921)	4.939 (4.888, 4.990)	4.788 (4.717, 4.859)
Artefacts	4.985 (4.964, 5.006)	4.992 (4.977, 5.007)	5 (5, 5)	5 (5, 5)
Skin Folds	4.758 (4.684, 4.832)	4.742 (4.664, 4.821)	4.977 (4.952, 5.003)	4.795 (4.726, 4.865)
Nipple	4.879 (4.794, 4.964)	4.894 (4.806, 4.982)	4.909 (4.840, 4.978)	4.856 (4.758, 4.954)
Pectoralis	4.841 (4.762, 4.920)	4.879 (4.815, 4.943)		
Pectoralis Angle	4.917 (4.860, 4.973)	4.955 (4.913, 4.996)		
IMF*	4.045 (3.874, 4.217)	4.121 (3.963, 4.279)		
Back of Breast Shown			5 (5, 5)	5 (5, 5)
Axillary Tail Shown			5 (5, 5)	5 (5, 5)
Medial border			5 (5, 5)	4.992 (4.977, 5.007)

LCC: left craniocaudal; LMLO: left mediolateral oblique; RCC: right craniocaudal; RMLO: right mediolateral oblique

tions, the IAEA recommended additional training in mammography positioning for technologists and performance measurements and dosimetry for medical physicists. Implementation of these recommendations and several others were associated with improved breast imaging quality, capability and expertise. The improvements were particularly pronounced in diagnostic imaging centers, similar to the two sites associated with the tertiary care center where our study was performed. While our study focused on radiography, these types of multi-pronged, collaborative initiatives will be essential to maintaining and improving the quality of screening and diagnostic breast imaging.

Limitations of our study include image quality evaluation performed by one reader and selection of study participants from two sites associated with one center. Our study was limited as external image quality evaluation was performed by just one reader. Though readings by multiple readers would provide more optimal evaluation of image quality parameters, results from the overall readings by one reader were similar to previously published evaluations of clinical image quality, suggesting that double reading may not have significantly changed overall conclusions. Our study was also limited by the utilization of two sites associated with one center. While there are other sites that perform mammography screening, our study site is the site that provides tertiary cancer care for patients in Qatar. Finally, our study was performed at diagnostic mammography sites. To develop a comprehensive picture of overall image quality, our study would also need to include screening sites. Unfortunately, implementation of breast cancer screening in Qatar has been limited (13). While widespread implementation of mammographic screening plays a critical role in reducing breast cancer mortality, expanding access to diagnostic mammography may facilitate access to high quality, effective treatment in women with later stage breast cancers (14).

In conclusion, 99% of studies conducted at a tertiary care cancer center in Doha, Qatar were deemed adequate for interpretation, results that are comparable to high performance academic centers in the United States and Europe.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hamad Medical Corporation (project number NPRP9-189-3-031).

Informed Consent: Informed consent was not required for retrospective review of previously collected images.

Peer-review: Externally peer-reviewed.

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Clinicopathological Characteristics, Treatment and Outcome of 123 Patients with Synchronous or Metachronous Bilateral Breast Cancer in a Swiss Institutional Retrospective Series

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ABSTRACT

Objective: To evaluate the prognosis, the patient and tumor characteristics, and the treatment of bilateral breast cancer (BBC) and to compare synchronous (sBBC) and metachronous BBC (mBBC).

Materials and Methods: For this retrospective study, data from 123 consecutive BBC patients (56 sBBC and 67 mBBC) that were presented at the Sion Hospital tumor board between 2007 and 2018 were collected retrospectively.

Results: Mean follow-up was 85 months. 2nd tumors in both groups were more often diagnosed radiologically. Mean time interval between mBBC was 115 months. A shorter interval was positively correlated with a negative hormonal receptor (HR) status and higher grade for the 2nd tumor. There was no difference in overall survival (OS) and relapse-free survival (RFS) between sBBC and mBBC. OS was longer if both tumors were hormonal receptor (HR) positive. mBBC exhibited a higher local recurrence rate than sBBC ($p=0.03$).

Conclusion: sBBC and mBBC patients did not show any difference in OS or RFS, although mBBC patients were more prone to local relapses.

Keywords: Bilateral breast cancer, contralateral breast cancer, synchronous, metachronous, survival, local relapse

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Introduction

Breast cancer is the second most frequent cancer in women and the fifth cause of female malignancy-related deaths worldwide (1). In our population, according to the most recent report of the regional tumor registry, breast cancer was the first female cancer (32% of newly diagnosed cancer cases, with a mean range of 249 new cancers/year between 2011 and 2015 and the second in terms of specific mortality (16% of all cancer-related death in women) (2).

Breast cancer survivors are at risk of developing a second primary malignancy, the most common being a second ipsilateral or contralateral breast cancer (3). Reported incidence of bilateral breast cancer (BBC) varies from 1.4% to 11.8% of all breast cancer cases (4, 5). The availability and adherence to the screening programs, increasing use of modern imaging methods such as digital tomosynthesis, elastography and MRI, progress in systemic and loco-regional treatments and growing life expectancy result in an increasing BBC incidence.

The time interval between the index and the 2nd tumor classifies BBC into synchronous (sBBC) and metachronous (mBBC). According to the World Health Organization (WHO), synchronous tumors are diagnosed at the same time as the index tumor or in the three following months. The contralateral tumor is deemed metachronous if diagnosed three months or more after the index tumor. Some authors extend this cutoff to 6 or even 12 months (6, 7).

Circulating breast cancer cells may be detected in 20 to 25% of patients with localized disease at the time of diagnosis raising the question of the *de novo* vs. metastatic origin of the contralateral 2nd tumor (8, 9). However, genomic analyses indicate that only a small proportion (6%) of contralateral breast cancers are metastasis of the index tumor (10). Controversies persist about the impact of contralateral

breast cancer on survival and how the time interval between the index and the 2nd tumor influences the prognosis of these patients with conflicting reports (11-19). So far, there are no specific recommendations for the treatment of BBC despite the fact that their prognosis seems poorer than unilateral tumors (5, 11, 14, 15, 18-20). Systemic treatments are usually guided by the sBBC tumor with the worse prognosis, while mBBC tumors tend to be treated like independent unilateral breast cancer.

We hereby report the analysis of 123 sBBC and mBBC patients treated and followed-up in our Institution aiming at identifying differences in epidemiological, clinical and pathological characteristics and at comparing outcomes.

Materials and Methods

Information on patients with BBC, who were treated for at least one tumor and followed-up in our Institution, was retrospectively collected by systematically screening tumor board registers between January 1st, 2007 and December 31st, 2018. Data were gathered from the medical files of the institution or general practitioners when follow-up data were incomplete. The study was approved by the local ethics committee (protocol number 2018-02320).

Patients were divided in two groups based on the time interval between the surgical resection of the contralateral breast tumor. Following the WHO classification for BBC, all 2nd contralateral breast cancers detected within 3 months from the diagnosis of first tumor were considered as sBBC. The one with the larger diameter was considered the index tumor. All contralateral breast tumors diagnosed after 3 months were considered mBBC.

The family history of patients was considered positive when a first- or second-degree relative had breast cancer. Age at both first and second cancer diagnosis, tobacco smoking and alcohol consumption, diagnostic tool (clinical examination, mammography, ultrasonography or MRI), histological tumor characteristics and type of surgery and adjuvant/ neoadjuvant treatments were recorded.

Histological type and grade (Elston and Ellis), multicentricity, lymph node status, pathological stage, HR status, Her-2/neu expression were extracted from pathology reports. Tumors were classified according to the International classification of Disease for Oncology as *in situ*, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), mixed IDC/ILC or other type. Tumors (T) were classified as smaller than or equal to 2 cm (T1), T2-3 or T4. The expression of HR and Her-2/neu was evaluated immunohistochemically. Her-2 was considered positive with a 3+ expression and negative when absent or with a 1+ expression. FISH evaluation classified further Her-2/neu status in positive or negative for intermediate 2+ tumors. Axillary node involve-

ment was categorized as negative or positive (N0 or N1-3) and the axillary surgery in sentinel node biopsy and classical lymphadenectomy. Breast surgery was categorized as none, conservative (lumpectomy) or radical (mastectomy). Adjuvant radiotherapy and systemic therapy (chemotherapy or hormonotherapy) were recorded if performed.

The two groups (sBBC and mBBC) were compared for patient and tumor characteristics and the following outcomes: disease-free survival (DFS), overall survival (OS), specific mortality, and locoregional and

Table 1. Patient characteristics

	Synchronous (%)	Metachronous (%)	Total (%)	p
Total	56 (100)	67 (100)	123 (100)	
Age				0.6
Mean (min-max)	63 (28-90)	62 (42-86)	63 (28-90)	
≤40	3 (5)	0 (0)	3 (2)	
41-50	11 (20)	12 (18)	23 (19)	
51-60	7 (13)	14 (21)	21 (17)	
>60	35 (63)	41 (61)	76 (62)	
Family History				0.99
Yes	26 (46)	35 (52)	61 (50)	
No	23 (41)	31 (46)	54 (44)	
Unknown	7 (13)	1 (1)	8 (7)	
Menopause				0.002
Yes	41 (73)	62 (93)	103 (84)	
No	15 (27)	4 (6)	19 (15)	
Man	0 (0)	1 (1)	1 (1)	
Marital status				0.6
Single	4 (7)	3 (4)	7 (6)	
Married	21 (38)	38 (57)	59 (48)	
Divorced	5 (9)	5 (7)	10 (8)	
Widowed	3 (5)	6 (9)	9 (7)	
Unknown	23 (41)	15 (22)	38 (31)	
Alcohol				0.21
Yes	8 (14)	20 (30)	28 (23)	
No	23 (41)	31 (46)	54 (44)	
Unknown	25 (45)	16 (24)	41 (33)	
Smoker				0.65
Yes	11 (20)	19 (28)	30 (24)	
No	25 (45)	35 (52)	60 (49)	
Unknown	20 (36)	13 (19)	33 (27)	
Pregnancies				0.34
Yes	37 (66)	52 (78)	89 (72)	
No	15 (27)	14 (21)	29 (24)	
Unknown	4 (7)	1 (1)	5 (4)	

Key Points

- No difference in global and recurrence-free survival was observed between sBBC and mBBC patients.
- Metachronous BBC patients had a higher rate of loco-regional relapse than sBBC. Most loco-regional relapses were due to the 2nd tumors in mBBC patients.
- Metachronous BBC were more frequently hormone receptor-negative than sBBC.

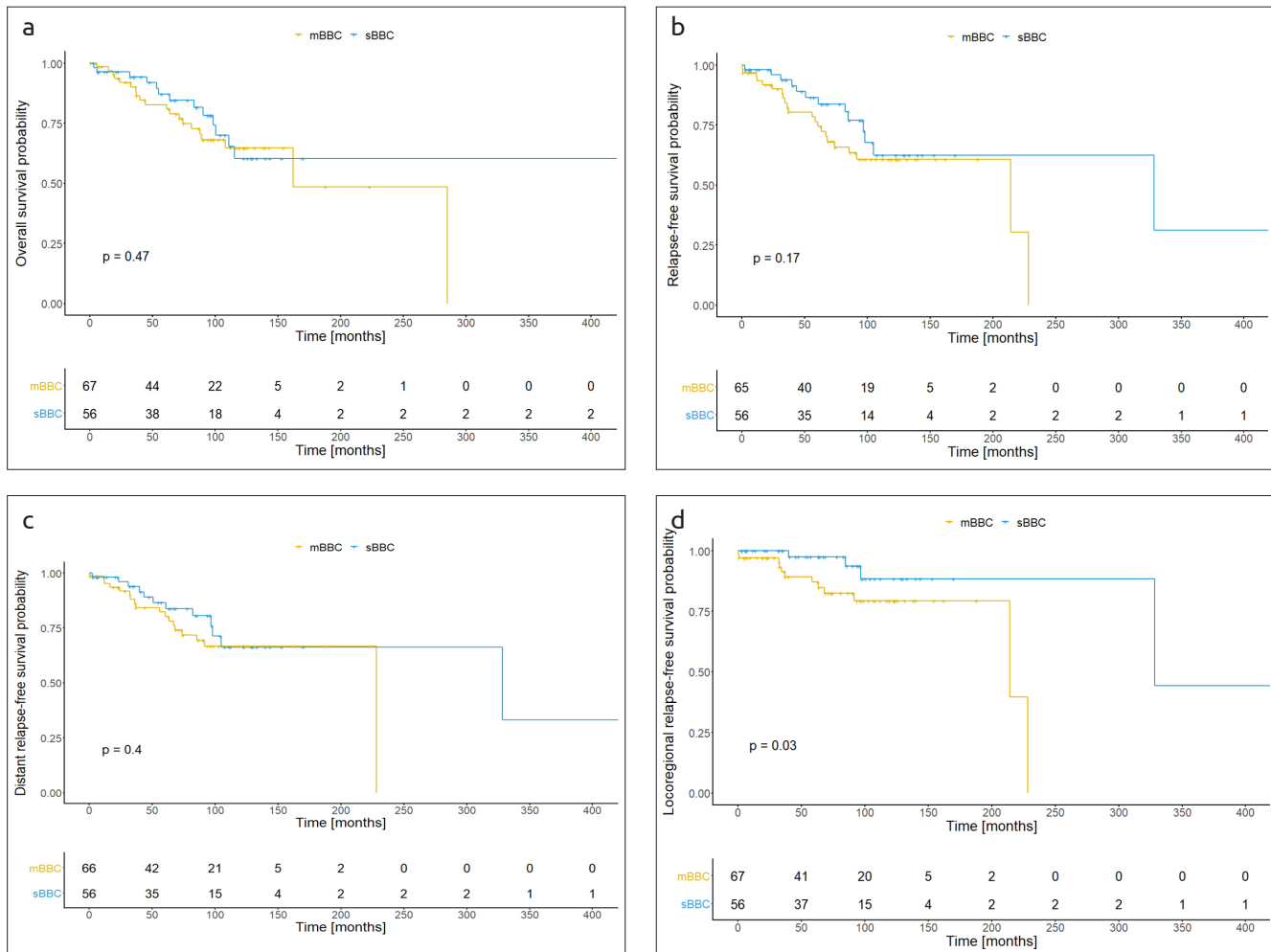


Figure 1. a-d. Survival analyses of sBBC and mBBC patients. (a) Overall survival. (b) Relapse-free survival (c) Distant relapse-free survival. (d) Loco-regional relapse-free survival

distant recurrence-free survival. Survival was calculated from the date of the second intervention (or the first if sBBC) until the date of death (OS) or relapse (DFS) with censoring for loss of follow up.

Statistical analysis

Data were analyzed by R version 3.5.3 (Lucent Technologies, USA), considering p values <0.05 as significant. All continuous variables were described by their mean and range and were analyzed using the Kruskal-Wallis test. Categorical variables were compared using the Chi-square test after exclusion of missing values. Survival curves were computed using the survival R package (version 2.44) by means of the Kaplan-Meier method and compared using the log rank test. Univariate and multivariate survival analyses were performed with Cox proportional hazard models. Agreement between tumor characteristics for each patient were analyzed using Cohen's kappa statistics.

Results

Population description

We identified 123 patients, 122 female and 1 male. Fifty-six (45.5%) were diagnosed with sBBC and 67 (54.5%) with mBBC. The mean time interval between mBBC was 115.5 months (min 13 months, max 288 months, SD 68.8). The median time interval was 111 months. The mean age of sBBC patients was 63, whereas for mBBC the mean age is 53 for the index tumor and 62 for the 2nd tumor. Patient inclu-

sion by date of surgery of the 2nd tumor is plotted in Supplementary Figure S1. The mean follow-up time was 82 months for mBBC patients, 89 months for sBBC and 85 months for the entire cohort.

Patients' characteristics are summarized in Table 1. They did not show any difference at inclusion except for the menopausal status, as mBBC patients were more frequently menopausal compared to the sBBC population ($p=0.002$). Sixty-one out of 123 patients (49.6%) had a positive family history without significant differences between the groups.

Tumor characteristics

The tumor characteristics are compared in Table 2. No significant difference between the histological types of the 1st and 2nd tumors were observed for sBBC and mBBC. In both groups, most of the tumors were invasive ductal carcinomas. Second tumors of sBBC patients were more frequently well differentiated than mBBC 2nd tumors ($p<0.001$). Conversely, a higher prevalence of poorly differentiated tumors was observed in mBBC 2nd tumors compared to 2nd sBBC ($p<0.001$).

Second sBBC tumors were more often diagnosed radiologically than index tumors ($p<0.001$). Although there was a similar tendency in the mBBC cohort, the difference was not significant ($p=0.08$). Second sBBC tumors were more often of small size (T1) compared to sBBC index tumors ($p=0.002$) and to the mBBC 2nd tumors ($p=0.04$). They

Table 2. Tumor characteristics

	Synchronous (%)		Metachronous (%)		p (x ²)
	Index	2 nd tumor	Index	2 nd tumor	
Total (%)	56 (100)	67 (100)			
Histology					0.74
<i>In situ</i> only	4 (7.1)	9 (16.1)	3 (4.5)	4 (5.9)	
Invasive ductal	35 (62.5)	33 (58.9)	44 (65.7)	44 (65.7)	
Invasive lobular	9 (16.1)	9 (16.1)	12 (17.9)	13 (19.4)	
Invasive mixt	5 (8.9)	3 (5.3)	4 (5.9)	3 (4.5)	
Other	1 (1.8)	1 (1.8)	2 (3)	3 (4.5)	
Unknown	2 (3.6)	1 (1.8)	2 (3)	0	
Grade					< 0.001
1	16 (28.6)	24 (42.8)	17 (25.4)	7 (10.4)	
2	25 (44.6)	24 (42.8)	26 (38.8)	35 (52.3)	
3	12 (21.4)	4 (7.2)	17 (25.4)	23 (34.3)	
Unknown	3 (5.4)	4 (7.2)	7 (10.4)	2 (3)	
Multifocal					0.24
Yes	18 (32.2)	14 (25)	15 (22.4)	12 (17.9)	
No	35 (62.5)	41 (73.2)	49 (73.1)	55 (82.1)	
Unknown	3 (5.3)	1 (1.8)	3 (4.5)	0	
pT					0.037
T1 (≤2 cm)	34 (60.7)	49 (87.5)	39 (58.2)	49 (73.1)	
T2-3	17 (30.6)	5 (8.9)	22 (32.8)	15 (22.4)	
T4	2 (3.6)	1 (1.8)	3 (4.5)	2 (3)	
Unknown	3 (5.3)	1 (1.8)	3 (4.5)	1 (1.5)	
pN					0.01
N-	33 (58.9)	45 (80.4)	38 (56.7)	42 (62.7)	
N+	20 (35.8)	6 (10.7)	21 (31.3)	20 (29.8)	
Unknown	3 (5.3)	5 (8.9)	8 (12)	5 (7.5)	
Hormonal receptors					0.02
ER+ / PR+	45 (80.4)	43 (76.7)	42 (62.7)	39 (58.2)	
ER- / PR-	6 (10.7)	2 (3.6)	15 (22.4)	18 (26.9)	
ER+ / PR-	3 (5.3)	4 (7.2)	5 (7.5)	9 (13.4)	
ER- / PR+	0	1 (1.8)	1 (1.5)	0	
Unknown	2 (3.6)	6 (10.7)	4 (5.9)	1 (1.5)	
HER-2 status					0.47
Positive	7 (12.5)	4 (7.2)	3 (4.5)	11 (16.4)	
Negative	39 (69.6)	36 (64.3)	19 (28.3)	39 (58.2)	
Unknown	10 (17.9)	16 (28.5)	45 (67.2)	17 (25.4)	

also exhibited a less frequent axillary lymph node invasion compared to sBBC index tumors ($p<0.001$) and mBBC 2nd tumors ($p=0.01$). HR-negative tumors were more prevalent in the mBBC cohort than in the sBBC cohort ($p<0.001$).

Histological type concordance between the index and 2nd tumors was 58.5% ($\kappa=0.175$, $p=0.033$) for the mBBC group, and 48.1% ($\kappa=0.095$, $p=0.249$) for the sBBC group. Histological grade concordance was 27.6% ($\kappa=-0.124$, $p=0.173$) for mBBC patients, and

Table 3. Surgical treatments

	Synchronous (%)		Metachronous (%)		p (x ²)
	Index	2 nd tumor	Index	2 nd tumor	
Total	56 (100)	67 (100)			
Breast surgery					0.13
Conservative	28 (50)	31 (55.3)	47 (70.2)	40 (59.7)	
Mastectomy	28 (50)	25 (44.6)	20 (29.8)	27 (40.3)	
Margins					0.90
R0	46 (82.1)	47 (83.9)	53 (79.1)	55 (82.1)	
R1	10 (17.9)	8 (14.3)	13 (19.4)	11 (16.4)	
Unknown	0	1 (1.8)	1 (1.5)	1 (1.5)	
Second surgery					0.24
No	47 (83.9)	53 (94.6)	60 (89.6)	62 (92.5)	
Yes	9 (16.1)	3 (5.4)	7 (10.4)	5 (7.5)	
Axillary surgery					<0.001
Sentinel node	30 (53.5)	39 (69.6)	11 (16.4)	38 (56.7)	
Axillar lymphadenectomy	23 (41.1)	10 (17.9)	51 (76.1)	25 (37.3)	
None	3 (5.4)	6 (10.7)	4 (6)	4 (6)	
Unknown	0	1 (1.8)	1 (1.5)	0	

Table 4. Radiotherapy and systemic treatments

	Synchronous (%)	Metachronous (%)		p (x ²)
		Index	2 nd tumor	
Total	56 (100)	67 (100)		
Radiotherapy				0.13
Yes	43 (76.8)	55 (82.1)	45 (67.2)	
No	13 (23.2)	12 (17.9)	22 (32.8)	
Hormonotherapy				0.047
Yes	49 (87.5)	47 (70.2)	44 (65.7)	
No	7 (12.5)	19 (28.3)	19 (28.3)	
Unknown	0	1 (1.5)	4 (6)	
Chemotherapy				0.008
Yes	17 (30.3)	38 (56.7)	25 (37.3)	
No	39 (69.7)	28 (41.8)	38 (56.7)	
Unknown	0	1 (1.5)	4 (6)	

56.9% (kappa 0.308, $p=0.0023$) for sBBC patients. Considering all combinations of estrogen and progesterone receptor expression, HR status concordance was 60% (kappa -0.016, $p=0.846$) for the mBBC cohort, and 90.7% (kappa 0.462, $p>0.001$) for the sBBC cohort.

Treatment

Types of breast surgery did not differ among groups or between index and 2nd tumors (Table 3). Sentinel lymph node biopsies were

less prevalent among mBBC index tumors ($p<0.001$ vs. sBBC index tumor; $p<0.001$ vs. mBBC 2nd tumors). Conversely, axillary lymphadenectomy was more often performed for the mBBC index tumor ($p=0.01$ vs. sBBC index tumor; $p=0.002$ vs. mBBC second tumor). Axillary lymphadenectomy was also more prevalent for the 2nd tumor among mBBC patients compared to sBBC patients ($p=0.0496$). No significant difference in adjuvant radiotherapy was observed (Table 4). Adjuvant hormonotherapy was less prevalent in the mBBC cohort than in sBBC ($p=0.03$). Conversely, mBBC patients received more chemotherapy for their index tumor compared to sBBC patients ($p=0.003$). They also received significantly more chemotherapy for their index tumor than for their 2nd tumor ($p=0.04$).

Outcome

5- and 10-year OS were 87.1% and 60.4% respectively in the sBBC cohort; 82.8% and 64.7% in the mBBC cohort (Figure 1a). 5- and 10-year DFS were 86.4% and 62.4% respectively for sBBC patients; 76.8% and 61.5% for mBBC patients (Figure 1b).

Distant RFS did not show any significant difference between the two groups with 5- and 10-year rates of 86.4% and 66.2% respectively for the sBBC cohort and 82.2% and 66.7% for the mBBC cohort (Figure 1c). Loco-regional RFS was significantly higher in the sBBC group with 5- and 10-year rates of 97.6% and 88.5% compared with the mBBC group with 87.1% and 79.4% rates respectively (Figure 1d). mBBC loco-regional relapses were more frequently observed on the side of the 2nd tumor (8/11) vs. the index tumor (2/11); data were missing for 1 loco-regional relapse.

Of all 17 loco-regional relapses, 13 occurred in the breast only, 3 in the axilla, and 1 in both breast and axilla. Among the 4 axil-

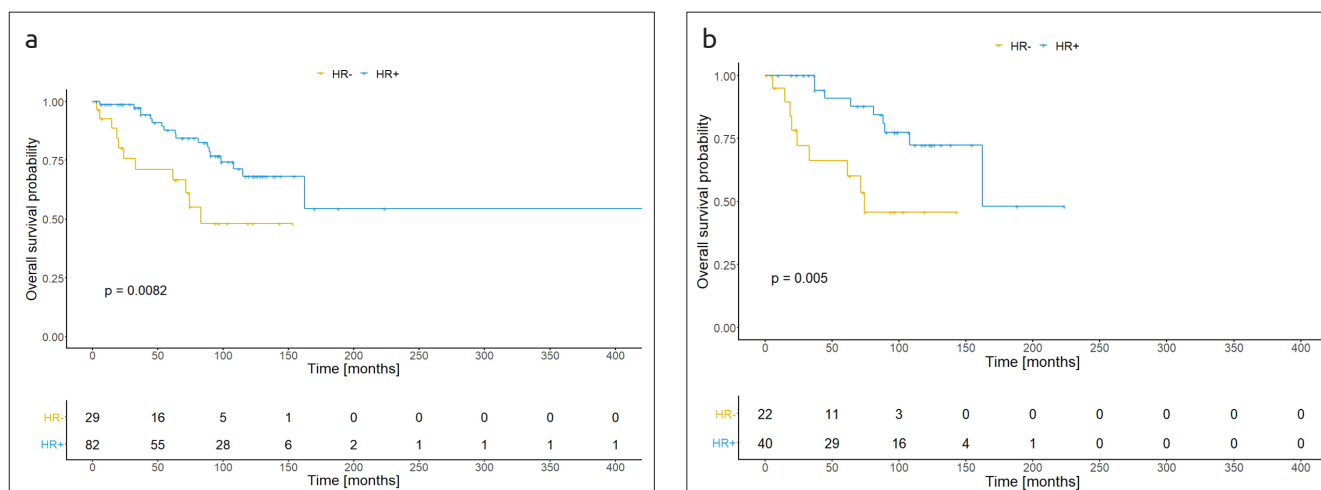


Figure 2. a, b. Survival analyses by HR status (HR-: either or both tumors HR-negative; HR+: both tumors HR-positive). (a) Whole population. (b) mBBC

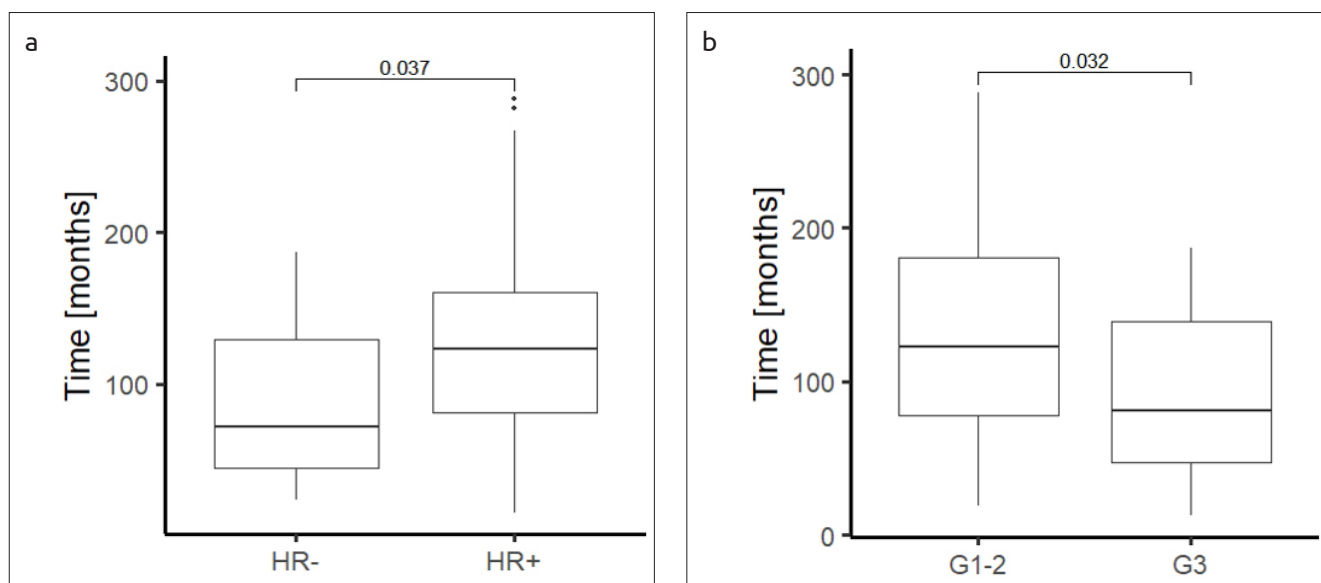


Figure 3. a, b. Correlation of time interval between mBBC tumors with HR status (a) and grade (b) of the 2nd tumor

lary relapses, 3 patients had previously underwent axillary lymphadenectomy and one had no previous axillary surgery. One out of 12 patients with breast relapses and complete pathological data had an R1 status with positive margins ≤ 1 mm. One patient had a loco-regional relapse of the index tumor before developing the contralateral one.

OS was increased for patients with both tumors being HR-positive compared to those with at least one HR-negative tumor (Figure 2a; Supplementary Figure S2). The same difference was observed for mBBC patients and remained statistically significant (Figure 2b). There were only a few HR-negative tumors within sBBC patients, and no such difference could be detected.

The time interval between mBBC tumors was not predictive of OS (hazard ratio 1.00, $p=0.73$) or RFS (hazard ratio 1.00, $p=0.86$) and was independent of nodal status ($p=0.339$). It was however correlated with the HR status of 2nd tumors, as HR-positive tumors occurred after a significantly longer interval (Figure 3a). A short time interval was associated with 2nd tumors of higher grade (Figure 3b).

Discussion and Conclusion

We analyzed clinical and pathological characteristics of patients with BBC and their outcomes over a 12-year period.

Patients' characteristics were well balanced between the sBBC and mBBC groups except for the menopausal status which was more prevalent among mBBC patients. This observation might be linked to prior systemic treatments (chemotherapy) of the index tumor, rather than age which was similar in both populations.

Standard preoperative assessment of the patients in our series includes mammography and breast ultrasound. Since 2010, breast MRI was widely introduced in the Wallis region, enhancing the diagnosis of subclinical tumors. This advancement partially explains the higher rate of radiological diagnosis for the sBBC contralateral tumors. The high rate of radiological diagnosis among mBBC and the mean interval of nearly 10 years between tumors occurrence underlines the importance of long term follow up in patients with breast cancer.

Tumor characteristics showed differences between the sBBC and mBBC groups. The fact that 2nd sBBC tumors were smaller and more often well differentiated and node-negative compared to mBBC 2nd tumors might be due to the definition of the sBBC index tumor (i.e. larger size). In contrary to previous publications (16, 21, 22), we did not observe any higher prevalence of invasive lobular carcinomas in sBBC patients.

Most patients had HR-positive tumors and underwent adjuvant hormonal therapy. A higher prevalence of HR-negative tumors was observed in the mBBC group compared to sBBC in accordance with prior published series (22, 23). This difference is probably expected for the 2nd tumor as most mBBC patients benefited from prior hormone therapy. However, mBBC index tumors were also enriched in HR-negative tumors vs. sBBC, possibly reflecting a different biology and a younger age at diagnosis. Also, HR-positive patients benefited from hormone therapy, which significantly reduces contralateral breast cancer incidence. Indeed, our data showed a shorter time interval between mBBC tumors to be correlated with a higher prevalence of HR-negative tumor and a higher grade. Although there was no correlation between the more aggressive tumor biology and survival in our series, larger studies have shown that a shorter time interval between mBBC tumors carries a worse prognosis and our series may be too small to reflect this difference (14, 24).

The concordance of histological subtypes between index and 2nd tumors was significant only in the mBBC group. Conversely, tumor grade and HR status concordances were only significant for sBBC patients. Our data confirms a particularly high level of concordance (90.7%) for HR status, in line with previously published studies (25–27). As previously suggested, this observation likely reflects the common environment where sBBC tumors developed. In contrast mBBC tumors show a lower and non-significant level of HR status concordance because of multiple intercurrent factors such as anti-hormone treatment, previous chemotherapy, age, menopausal status and possible lifestyle modifications as the result of the prior cancer diagnosis and adverse effects of treatments for the index tumor.

Previous reports showed a more aggressive breast surgery for sBBC compared to mBBC (15, 28–30). In our series, no such difference was observed. Radical lymphadenectomy accounted for the majority of axillary surgery for mBBC index tumors. However, most of these were performed before sentinel node biopsy was progressively introduced in our institution since 2004 and therefore do not reflect a more aggressive therapeutic approach. Axillary surgery for mBBC 2nd tumors was significantly more aggressive than for sBBC 2nd tumors. This observation is in line with the lesser axillary node involvement of sBBC 2nd tumors.

Chemotherapy was used more often for the index tumor of mBBC patients, probably reflecting their younger age and their treatment prior to the de-escalation of systemic therapies with the introduction of predictive molecular tests. Conversely, hormone therapy was less often prescribed to mBBC patients, reflecting their higher rate of HR-negative tumors compared to sBBC patients.

There was no difference in overall or relapse-free survival between mBBC and sBBC patients in our series. There is no consensus in the literature regarding the outcome of BBC. Most studies showing a survival difference between sBBC and mBBC patients used national registries with a longer follow up (14, 22).

Our data showed a higher rate of loco-regional recurrence in mBBC patients that is consistent with previous reports (15). Most of loco-regional relapses were due to the 2nd tumors, which might be explained by two factors: a higher grade and therefore more aggressive 2nd tumors and a potential selection bias toward a favorable index tumor biology as, by definition, mBBC patients survived until the diagnosis of the contralateral tumor.

The strengths of our study are the nearly complete follow up data, and the homogeneity of patient care and diagnostic procedures given its unicentric design. Its weaknesses include its retrospective nature over a long period of time with evolving treatments and the small number of patients compared to large registry-based series.

In our series, no significant difference of survival between sBBC and mBBC patients was observed, although mBBC patients showed a higher loco-regional relapse rate. In both groups the 2nd tumor was more often diagnosed radiologically highlighting the importance of contralateral breast imaging and the need of a long term radiological follow up of breast cancer patients. Both index and contralateral mBBC tumors were more frequently HR-negative than sBBC, probably reflecting a different biology and the consequences of treatments and lifestyle modifications following the index tumor.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Canton de Vaud (CER-VD; 2018-02320).

Informed Consent: Written informed consent was waived by the Ethics committee for patients until 2017. General informed consent was obtained for all other patients.

Peer-review: Externally peer-reviewed.

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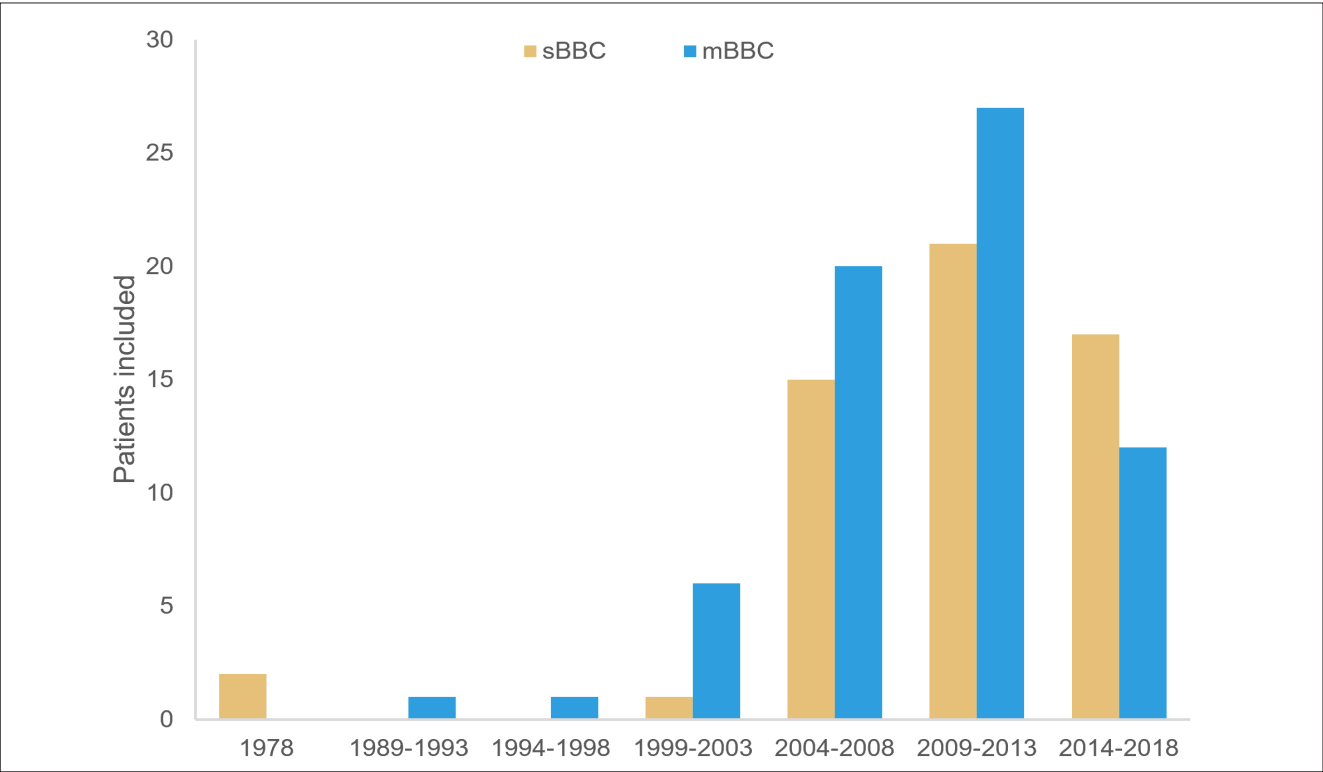


Figure S1. Number of patients by date of 2nd tumor surgery

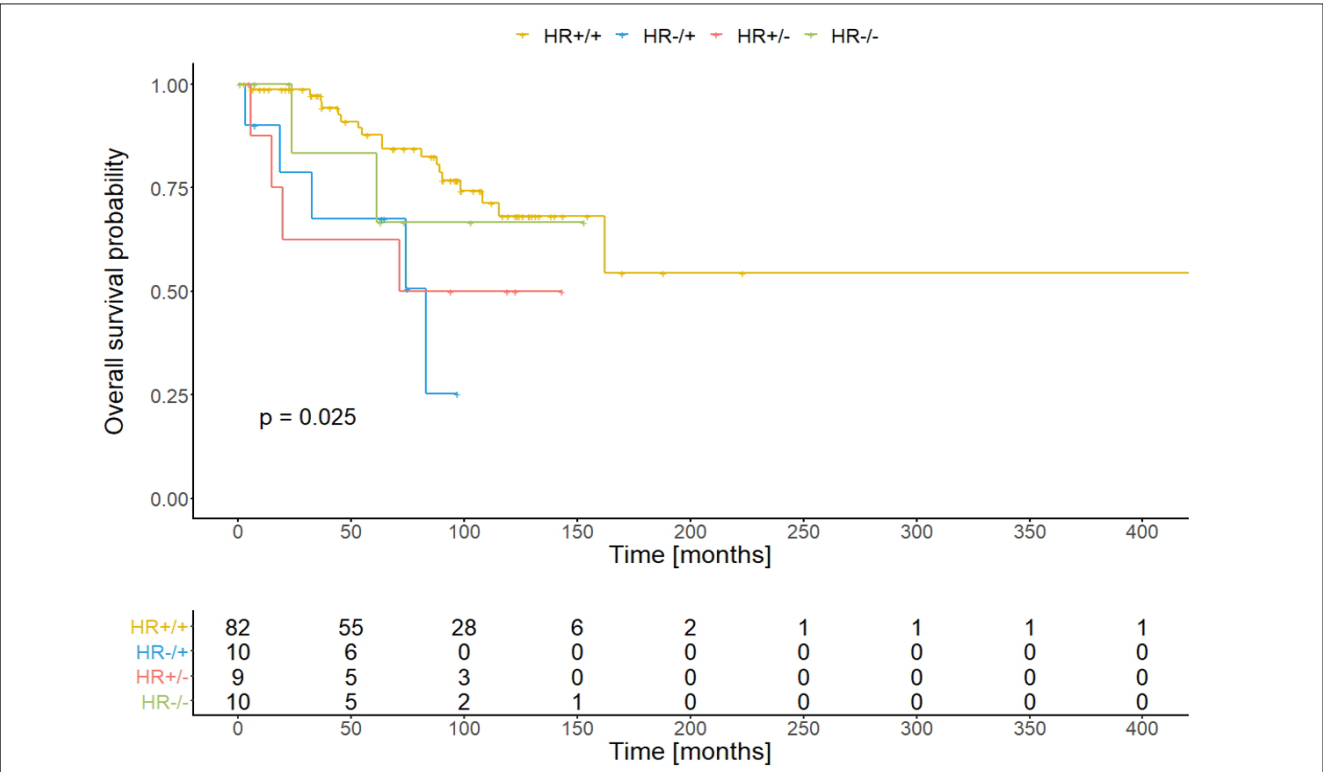


Figure S2. Survival analysis of the whole population by HR status of both tumors (HR status index tumor/2nd tumor)

The Composite Planning Technique in Left Sided Breast Cancer Radiotherapy: A Dosimetric Study

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ABSTRACT

Objective: The aim of this retrospective study is to reduce the dose of heart, both lung and opposite breast and left anterior descending artery (LAD) and avoid long term complication and radiation induced secondary malignancies in radiotherapy left breast/chest wall without losing homogeneity and conformity of the Planning Target Volume (PTV), contoured using Radiotherapy Oncology Group (RTOG 1005) guideline.

Materials and Methods: The treatment plans were generated retrospectively by TFIF, VMAT and Composite techniques for 30 patients. Dose-Volume Histograms (DVHs) were evaluated for PTV and organs at risk (OAR's) and analyzed in two groups BCS and MRM using Wilcoxon signed rank test.

Results: The homogeneity index (HI) was improved in Composite technique by 32.72% and 21.81% of VMAT, 50.66% and 49.41% of TFIF in BCS and MRM group respectively. The Conformity Index (CI) for composite plan was statistically same as VMAT and superior by 27.94% and 41.37% of TFIF in BCS and MRM group respectively. The low dose volume V_{5Gy} and V_{10Gy} of the heart were improved in Composite plan by 47.9% and 26.1% of VMAT respectively in BCS group and in MRM group, improved by 21.2% and 45.6% of VMAT. The V_{5Gy} and V_{10Gy} of ipsilateral lung were improved in Composite plan by 16% and 13.7% of VMAT respectively in BCS and 8.4% and 3% of VMAT respectively in MRM group.

Conclusion: The Composite plan consisting of VMAT and TFIF plan with an optimum selection of fractions can achieve lower low dose exposure to the OAR's without compromising coverage compared to VMAT.

Keywords: BCS, composite plan, breast, dosimetric comparison, MRM

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Introduction

Breast cancer or carcinoma of the breast (Ca-Breast) is the most common malignancy among women and the second most commonly occurring cancer overall in the world (1). In breast cancer, the most common treatment is conservative surgery or mastectomy followed by adjuvant chemotherapy and radiotherapy with or without hormonal therapy (2). Several prospective studies have shown that radiotherapy in Ca-Breast improved the disease free survival by almost 15% at 10 years and reduced the 15-year risk of Ca-Breast death by 4% (3). Thus making the chronic sequelae of the breast cancer radiotherapy more important (4). But it has been shown that patients treated with radiation to chest wall or breast alone developed pneumonitis in 1% cases which increased to 4% in patients treated with loco-regional irradiation including draining lymph node (5).

Oie et al. (6) reported that radiation pneumonitis (RP) mostly developed in ipsilateral lung and arose next to the rapidly decreasing dose area. Previous reports have shown that irradiation of the breast/chest wall with supraclavicular field led to an increased incidence of symptomatic radiation pneumonitis (7, 8) (SRP). Wen et al. (9) have suggested that the volume receiving 20Gy and 30Gy (V_{20Gy} , V_{30Gy}) were

the main predictors for SRP and also suggested that with new technologies such as IMRT and hypo-fractionated RT additional studies of corresponding dose-volume parameters should be performed for better guidance in practice. Shaikh et al. (10) studied radiation pneumonitis in patients receiving taxane-based trimodality therapy for locally advanced esophageal cancer. In their study the authors concluded that the volumes covered by 5Gy (V_{5Gy}), 10Gy (V_{10Gy}), 20Gy (V_{20Gy}) and 30Gy (V_{30Gy}) were associated with risk of RP grade 2 plus and $V5_{Gy} \leq 65\%$ was the optimal threshold to prevent it. Other studies have also supported that the low dose volume of lung was associated with an increase in risk of RP (11, 12).

In the 1930's, the heart was considered as a radio-resistant organ below a dose of 30Gy (13), but current studies have shown that the cardiovascular disease could occur with mean doses as low as 3 to 17 Gy (14). However, at low doses the typical latent period for cardiac related problems is often long. The risk of myocardial infarction after post lumpectomy radiation treatment for left sided breast cancer (15) is more than right sided breast cancer and it has also been found that increase in radiation dose to heart leads to increased cardiac related mortality (16, 17). Darby et al. (18) reported that 1 Gy added to the mean heart dose could increase the rate of ischemic heart disease by 7.4%, regardless of the threshold dose. Also, there is a relationship reported between low-radiation doses (~5 Gy) and cardiac mortality (19). Data published by authors such as Hortobagyi et al. (20) on anthracycline and trastuzumab in Ca-breast showed that patients who had received anthracycline based chemotherapy were at a higher risk for developing cardiac toxicity.

In long-term survivors, second malignancy is also a cause of non-breast cancer mortality. Stovall et al. (21) found that women who were less than 40 years of age and received a radiation dose more than 10 Gy to the contralateral breast had a 2.5 times higher long-term risk of developing a second primary in contralateral breast.

Radiotherapy planning of the breast cancer has challenges in balancing delivery of adequate radiation dose to the breast and internal mammary chain (IMC) nodes with sparing of heart, lungs and contra lateral breast mainly due to large tissue in-homogeneity (22). There are several guidelines available for breast contouring like Radiotherapy Oncology Group (23) (RTOG), European Society for Radiotherapy and Oncology (24) (ESTRO) and Project on Cancer of the Breast (25) (PROCAB) guidelines. The planning target volume (PTV) with RTOG-1005 guidelines for intact breast or post modified radical mastectomy (MRM) chest wall is very irregular and with conventional 3 dimensional (3D) planning, it is not possible to conform the dose distribution to this shape. The Tangential Field in Field (TFIF) technique is often not able to achieve the desired coverage of the PTV, and ipsilateral lung and heart dose volume constraints are also violated. But Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) planning techniques are able to conform the dose to concave/irregularly shaped PTV's in the breast or chest wall with lower dose to ipsilateral lung and heart. In IMRT planning, generally an odd number of fields and inverse optimization are used to improve the dose homogeneity, conformity and avoidance of normal tissues such as heart and lung (26) and contra-lateral breast. The VMAT is a novel form of IMRT, in which generally partial arc fields are used to improve dose homogeneity and conformity in the PTV, reduce dose to normal tissues, and also reduce Monitor Units (MU's) as well as total treatment time (22).

In breast cancer radiation planning, VMAT results in an increased low dose radiation spillage to lung, heart and contralateral breast as compared to conventional plans (27). TFIF plans on the other hand have shown to reduce the number of MUs and treatment time but with inferior PTV coverage as compared to VMAT. Also, lung volume receiving 20 Gy or above is slightly higher in TFIF as compared to VMAT.

In this retrospective study we have attempted composite treatment planning to reduce the dose to heart, both the lungs, and opposite breast in radiotherapy to left breast or left chest wall without compromising on dose homogeneity and conformity of the PTV. As a result, we expect a decrease in the incidences of long term complications and radiation induced secondary malignancies with the composite treatment technique.

Materials and Methods

Patients

A total of 30 patients with left Ca-breast were selected for this retrospective study having equal number of patients in two groups namely post breast conserving surgery (BCS) and post modified radical mastectomy (MRM). The planning computed tomography (CT) data were taken in the head first supine position with 5 mm thick contiguous slices from the level of mandible to 3 cm inferior to the last rib with the CT simulator (Somtom Definition AS20 Siemens, Munich, Germany).

Target delineation

The Clinical Target Volume (CTV) for breast or chest wall and supraclavicular nodes were delineated according to RTOG (23) (1005) guideline. The PTV was cropped 5 mm and 3 mm in the body contoured for BCS and MRM groups, respectively. The organs at risk (OARs) such as ipsilateral lung, contra-lateral lung, heart, opposite breast, esophagus, left anterior descending artery (LAD) and spinal cord were contoured (Figure 1). The PTVs and OARs were contoured by the same oncologist for all the patients.

Treatment planning

All treatment plans were generated on Eclipse (Varian Medical System, Palo Alto, California, United States) Treatment Planning System version 10.0 for hypo fractionation of 42.5 Gy in 16 fractions. The most common site for recurrence is chest wall in breast malignancy (28), so for MRM cases, a combined plan comprising 10 fractions with 5mm thick bolus and remaining 6 fractions without bolus was generated. The selection of bolus and no-bolus sub-plans was in such way to increase the skin to 80-85% of the prescribed dose (29) for treating microscopic disease due to skin violation by malignant cells during surgery. All plans used 6MV photon beam and 2.5 mm dose calculation grid. For evaluation purposes the boost treatment plan was not included. Our aim was, the 95% of PTV should be covered with 95% of the prescribed dose with minimal dose to OARs.

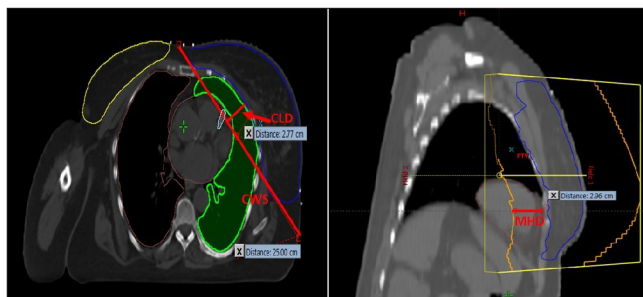


Figure 1. An axial and Sagittal slice showing contour of PTV and OAR's

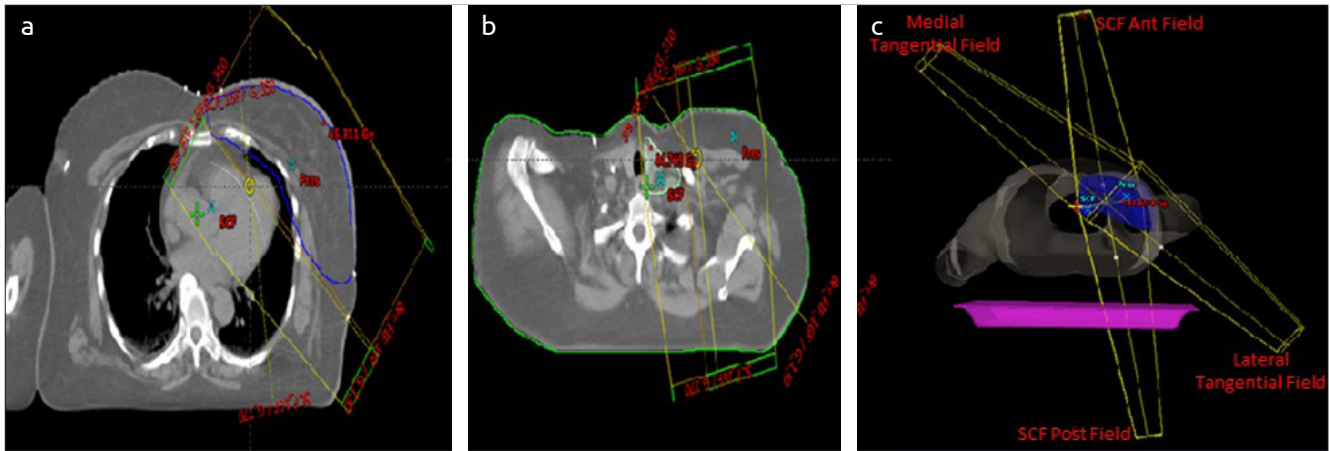


Figure 2. a-c. TFIF planning fields (a) Axial slice with medial and lateral tangential fields (b) Axial slice with anterior and posterior SCF fields (c) Beam's eye view

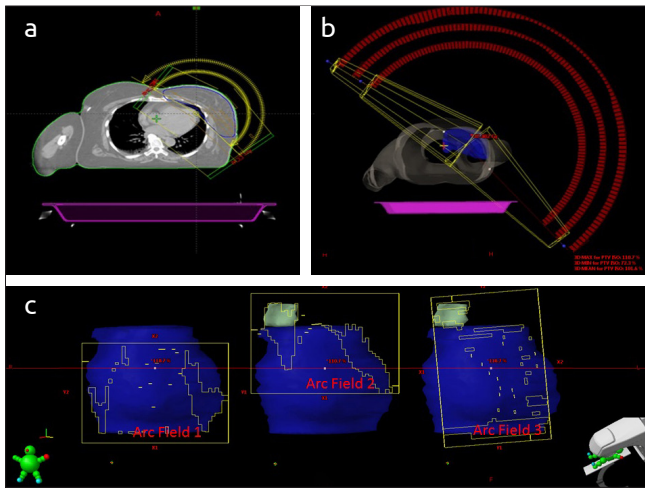


Figure 3. a-c. VMAT planning Fields (a) Axial slice with three partial arc fields (b) Beam's eye view

Detailed treatment planning procedure

The TFIF plan was the combination of two mono-isocentric plans. In the first plan for the chest wall/breast two main tangential fields namely medial tangential and lateral tangential fields with subfields were placed with gantry angle ranging between 305-315° and 125-135°, respectively. In the second plan for supraclavicular (SC) nodes, one anterior field was placed with gantry angle ranging between 350-0° and an additional posterior field was placed as 170-180° gantry angle, to avoid the high dose to the skin (Figure 2). For calculations, two normalization points were used; one for chest region and the other for SC region. Gantry angles, collimator angles, beam weights and MLC shapes were optimized to get the best plan.

In VMAT technique, 3 partial coplanar arc beams with arc angle ranging between 300-310° to 135-155° (Figure 3) were used with a single isocenter in such a way that no direct beam entered through the contralateral lung or breast. The maximum MLC leaf travel distance (distance between the most extended leaf and the most retracted leaf on the same side) for a Varian linear accelerator (Palo Alto, California, U.S.) is 15 cm. If the field width is more than 15 cm then the plan optimization was compromised due to MLC reach. Therefore, for better optimization the X-Jaw was opened asymmetrically with a collimator angle 90° to cover the chest wall/ breast PTV and the SC nodes in cranial-caudal

direction for two arc fields. The Y-jaw was opened according to PTV width and the remaining arc field was placed with symmetric X-Jaw and a collimator angle between 5-10° (Figure 3). The plan was optimized with progressive resolution optimizer (PRO). The tissue in-homogeneity correction was considered during optimization and anisotropic analytical algorithm (AAA, version 10.0.28) was used for dose calculation.

The Composite plans were a combination VMAT (8-10 fractions) and TFIF (remaining fractions) to ensure minimal doses to OARs without compromising the coverage of the PTV in such a way that 95% of the prescribed dose covered at least 95% of the PTV. Also, not more than 15% of the volume of PTV exceeded 105% of the prescribed dose.

Dosimetric evaluation

Dose Volume Histograms (DVH) were used to evaluate the PTV and the OARs. A combined PTV of breast/ chest wall and SCF nodes was used for the evaluation purposes. The following parameters were used to evaluate the plan quality: dose to 95% volume of PTV ($D_{95\%}$), dose to 5% volume of PTV ($D_{5\%}$), volume of PTV covered by 95% of prescribed dose ($V_{95\%}$), volume of PTV (V_{PTV}), irradiated volume of the body covered with 95% of prescribed dose ($TIV_{95\%}$), volume of PTV covered with more than 105% of the prescribed dose ($V_{105\%}$), irradiated volume of the body outside the PTV covered with 100% of the prescribed (hot spot) in cm^3 , and integral dose in $Gy \cdot cm^3$. Additionally, Homogeneity Index (HI), Conformity Index (CI) and Integral Dose (ID) were also estimated. The HI was calculated by the following formula (30).

$$HI = \frac{D_{5\%} - D_{95\%}}{D_{Pres}} \quad (1)$$

Where D_{pres} is the prescribed dose. The lower HI value meant better homogeneity. The CI was calculated with by following formula (31).

$$CI = \frac{V_{95\%}}{V_{PTV}} \times \frac{V_{95\%}}{TIV_{95\%}} \quad (2)$$

The ideal value of CI is 1. The ID was estimated to indicate the dose deposited in healthy tissues of body outside the PTV and given by following formula (32).

$$ID = \text{Total Body Volume} \times D_{mean PTV out} \quad (3)$$

Where Dmean PTV out is mean dose deposition in healthy tissues of body outside PTV.

Also, the dosimetric data such as percentage volume covered with 5 Gy (V5Gy), 10 Gy (V10Gy), 20 Gy (V20Gy), mean dose (Dmean) for lung and heart were estimated, and Dmean for LAD and opposite breast were estimated.

Statistical analysis

All computational statistics were performed with statistical analysis in social science software (SPSS) Statistics package (IBM SPSS Corp.; Armonk, New York, USA), version 24. The Wilcoxon signed rank test was used to analyze the difference in dosimetric parameters and p value <0.05 was considered statistically significant.

Table 1. PTV, lung and heart characteristic for BCS and MRM patients (n=15, arithmetic mean and standard deviation)

Parameters		Mean±SD
Volume of PTV (cc)	BCS	1511.03±450.32
	MRM	1037.13±243.58
CWS of BCS (cm)	BCS	25.2±2.9
	MRM	25.01±2.2
CLD (cm)	BCS	2.9±0.43
	MRM	3.16±0.5
MHD (cm)	BCS	2.91±0.85
	MRM	2.73±0.45

cc: centimeter cube; CWS: Chest Wall Separation; CLD: Central Lung Distance; MHL: Maximum heart Length.

Results

The data set was divided into two groups for analyses: Group 1 comprised of patients who had undergone BCS and group 2 comprised of patients who had undergone MRM. The average PTV volumes, chest wall separation (CWS), central lung distance (CLD) and maximum heart distance (MHD) for both the groups are summarized in Table 1. The CLD was defined as the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall, and the MHD was measured on the CT slice with the thickest section of heart contained within the field defined as the distance between the anterior cardiac contour crossing over the posterior edge of the tangential fields. The CWS was defined as the distance between the most posterior field edges of the non-divergent tangential beams measured at the centre of the cranio-caudal axis (33).

The plan selection criteria were: D_{95%} of the PTV should be at least 95% of the prescription dose (42.5 Gy), and maximum point dose within the PTV should be kept below 110% (V_{110%} = 0) of the prescription dose. These criteria were not met with TFIF plans.

Target coverage

The composite planning technique generated the best results in terms of PTV coverage and dose homogeneity in both the groups. The D_{95%}, V_{95%}, V_{105%}, mean CI, HI and ID values are shown in tables Table 2 and 3 for the BCS and MRM groups, respectively. Figure 4 shows the dose distribution for all the techniques.

OAR sparing

The comparison of the average dosimetric parameters of the OAR is listed in Table 4 and Table 5 for BCS and MRM groups, respectively.

Planning time and monitor units

The planning time for VMAT was about 3 to 4 hours and higher than TFIF about 1 hour because of beam modeling and inverse planning. The mean values of MU for total treatment (16 fractions) in BCS group were

Table 2. The comparable target Dosimetric parameters for three techniques for BCS group (n=15, arithmetic mean and standard deviation)

Parameters	Composite Plan Mean±SD	VMAT Mean±SD	TFIF Mean±SD	Estimated p values		
				TFIF vs VMAT	TFIF vs Composite	Composite vs VMAT
Hotspot (cc)	37.36±24.41	33.43±19.78	242.45±117.64	0 ^a	0 ^b	0.11
D _{95%} (Gy)	40.41±1.1	40.43±0.57	38.6±1.19	0 ^a	0 ^b	0.21
V _{95%} (%)	94.99±1.7	95.01±1.78	92.85±3.95	0.02 ^a	0 ^b	0.45
V _{105%} (%)	5.56±5.05	11.82±6.39	11.8±9.6	0.89	0 ^b	0b
D _{5%} (Gy)	43.59±0.41	44.97±0.43	45.16±0.73	0.31	0 ^b	0b
Dmean (Gy)	42.95±0.32	43.24±0.36	42.58±0.45	0 ^a	0 ^b	0.12
Conformity Index	0.87±0.02	0.88±0.02	0.68±0.05	0 ^a	0 ^b	0.18
Homogeneity Index	0.074±0.03	0.11±0.01	0.15±0.04	0.01 ^a	0 ^b	0.015 ^b
Integral Dose (Gy.cc)	100902.45±30757.51	118711.9±32284.66	82882.62±32648.73	0 ^c	0.01 ^c	0

Hotspot: The volume outside of PTV covered by more than prescribed dose (cc); D_{95%}: Dose received by 95% of the volume (Gy); V_{95%}: volume covered by at least 95% of the prescribed dose (%); V_{105%}: Volume covered by more than 105% of the prescribed dose (%); D_{5%}: Dose received by 5% of the volume (Gy); p value^a <0.05 for VMAT plan; p value^b <0.05 for Composite plan; p value^c <0.05 for TFIF plan

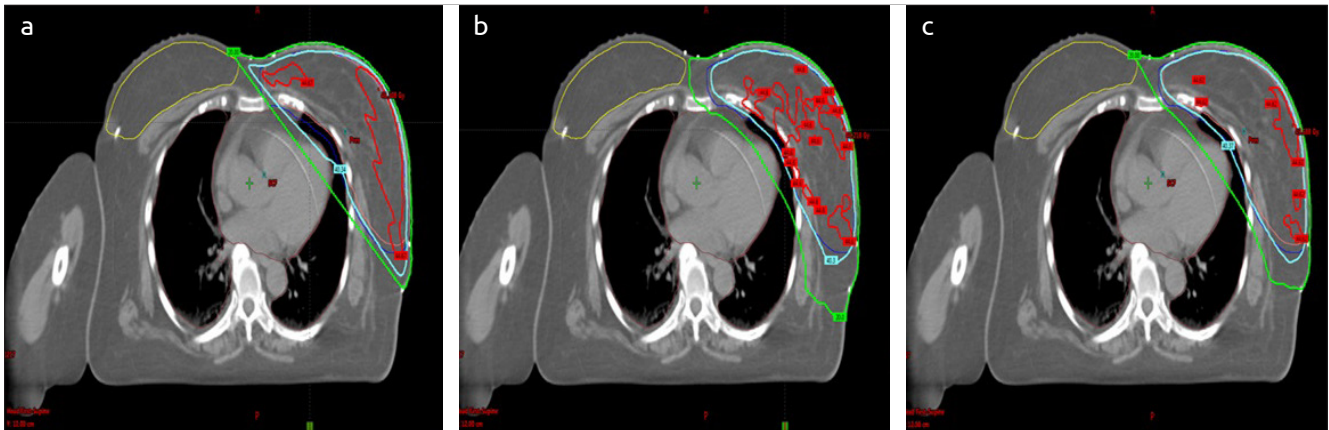


Figure 4. a-c. Dose Distribution axial view red line indicates for 105%, cyan for 95% and green for 20% of the prescribed dose for (a) TFIF (b) VMAT (c) Composite Plan

Table 3. The comparable target Dosimetric parameters for three techniques for MRM group (n=15, arithmetic mean and standard deviation)

Parameters	Composite Plan Mean±SD	VMAT Mean±SD	TFIF Mean±SD	Estimated p values		
				TFIF vs VMAT	TFIF vs Composite	Composite vs VMAT
Hotspot (cc)	51.13±19.18	46.41±20.83	311.99±131.19	0.00 ^a	0.00 ^b	0.16
D _{95%} (Gy)	40.33±0.64	40.18±0.58	38.5±1.16	0.00 ^a	0.01 ^b	0.33
V _{95%} (%)	95.37±1.73	94.57±1.94	92.99±2.29	0.02 ^a	0.00 ^b	0.13
V _{105%} (%)	10.75±4.22	14.37±4.41	20.26±8.9	0.89	0.00 ^b	0.02 ^b
D _{5%} (Gy)	43.99±0.23	45.01±0.56	45.65±0.9	0.31	0.00 ^b	0.034 ^b
Dmean (Gy)	43.23±0.2	43.37±0.2	43.09±0.44	0.00 ^a	0.15	0.01 ^b
Conformity Index	0.82±0.06	0.78±0.2	0.58±0.07	0.00 ^a	0.00 ^b	0.09
Homogeneity Index	0.086±0.02	0.11±0.02	0.17±0.03	0.01 ^a	0.00 ^b	0.035 ^b
Integral Dose (Gy.cc)	111666.4± 23440.47	125945.68± 23180.06	83526.36± 17842.6	0.00 ^c	0.00 ^c	0.01 ^b

Hotspot: The volume outside of PTV covered by more than prescribed dose (cc); D_{95%}: Dose received by 95% of the volume (Gy); V_{95%}: volume covered by at least 95% of the prescribed dose (%); V_{105%}: Volume covered by more than 105% of the prescribed dose (%); D_{5%}: Dose received by 5% of the volume (Gy); p value^a <0.05 for VMAT plan; p value^b <0.05 for Composite plan; p value^c <0.05 for TFIF plan

7720, 13519, 11344 and in MRM group were 10582, 15122 and 13420 for TFIF, VMAT and composite planning techniques respectively.

Discussion and Conclusion

Many studies have shown that in BCS or in MRM cases the VMAT planning technique gave better target coverage and lower doses to OARs as compared to 3-dimensional conformal radiotherapy (3DCRT) or conventional IMRT (,). Viren et al. () showed that there was no significant difference in OAR doses between 3CDRT and tangent IMRT (t-IMRT), although in t-IMRT, the MU's were higher. In this study, the authors compared these planning techniques to VMAT. They concluded that using FIF technique, the planning and treatment time could be reduced.

Al-Rahbi et al. (37) reported that the forward plan IMRT technique (FP-IMRT) was a simple and efficient planning technique in breast cancer treatment. In their study, 20 left side breast cancer patients were

included. The homogeneity and conformity indices were similar for inverse IMRT (IP-IMRT), FP-IMRT and 3D-CRT techniques. The V5Gy for heart in IP-IMRT technique was 72.9%, whereas in our composite technique, it was 38.35% and 35.1% for BCS and MRM group respectively. Zhang et al. (38) reported that the VMAT technique was better than the IMRT to achieve target coverage and normal organ sparing. In their study, the V5Gy for ipsilateral lung and heart were 61%, 77% for IMRT and 66%, 78% for VMAT respectively. The contra- lateral lung and breast mean doses were lower in VMAT (4.49 Gy and 1.7 Gy) than IMRT (4.67 Gy and 2.3 Gy). In our composite technique V5Gy for ipsilateral lung value was 57.62% and 62.49% for BCS and MRM group respectively. The V5Gy for heart was 38.35% and 35.1% for BCS and MRM group respectively. The contra-lateral lung and opposite breast mean dose were also lower in our composite technique than the above quoted study.

A similar study was done by Shaffer et al. (39) In this study VMAT technique improved the plan quality and achieved better normal organ

Table 4. The comparable OAR's Dosimetric parameters for three techniques for BCS group (n=15, arithmetic mean and standard deviation)

Parameters	Composite Plan Mean±SD	VMAT Mean±SD	TFIF Mean±SD	Estimated p values		
				TFIF vs VMAT	TFIF vs Composite	Composite vs VMAT
Heart V _{5Gy} (%)	38.35±10.63	73.71±89.99	21.44±6.12	0 ^c	0 ^c	0 ^b
Heart V _{10Gy} (%)	18.43±5.88	24.93±6.59	14.53±4.67	0 ^c	0 ^c	0 ^b
Heart V _{20Gy} (%)	8.17±3.23	8.02±2.47	11.63±4.65	0 ^a	0.01 ^b	0.25
Heart D _{mean} (Gy)	6.3±1.42	7.97±1.25	6.03±1.35	0.23	0 ^c	0 ^b
LAD Dmean (Gy)	11.22±6.53	13.37±4.86	20.31±9.41	0.02 ^a	0.01 ^b	0.23
Ipsilateral Lung V _{5Gy} (%)	57.62±10.98	68.59±10.73	43.3±11.69	0 ^c	0.23	0 ^b
Ipsilateral Lung V _{10Gy} (%)	37.88±9.82	43.89±8.17	32.19±10.03	0 ^c	0 ^c	0 ^b
Ipsilateral Lung V _{20Gy} (%)	25.23±7.6	23.65±5.68	26.42±9.03	0.05 ^a	0.04 ^b	0.07
Ipsilateral Lung D _{mean} (Gy)	10.3±2.28	12.85±2.34	13.28±2.31	0.12	0.16	0.07
Contralateral Lung V _{5Gy} (%)	6.03±6.66	15.58±10.38	0.01±0.04	0 ^c	0 ^c	0 ^b
Contralateral Lung V _{10Gy} (%)	0.18±0.38	2.37±2.85	0±0	0 ^c	0.07	0 ^b
Contralateral Lung D _{mean} (Gy)	1.93±0.71	3.08±0.85	0.38±0.21	0 ^c	0 ^c	0 ^b
Total Lung V _{5Gy} (%)	28.71±8.42	39.64±9.22	19.67±5.46	0 ^c	0 ^c	0 ^b
Total Lung V _{10Gy} (%)	17.35±4.69	21.28±4.79	14.59±4.58	0 ^c	0 ^c	0 ^b
Total Lung V _{20Gy} (%)	10.84±5.5	10.75±2.68	11.99±4.15	0.06	0.21	0.26
Total Lung D _{mean} (Gy)	6.8±1.55	7.67±1.33	5.75±1.67	0 ^c	0 ^c	0 ^b
Opposite Breast D _{mean} (Gy)	2.55±2.92	2.83±0.49	0.38±0.42	0 ^c	0 ^c	0.01 ^b

D_{2%}: Dose received by 2% of the volume (Gy); V_{5Gy}: Volume received at least 5Gy (%); V_{10Gy}: Volume received at least 10Gy (%); V_{20Gy}: Volume received at least 20Gy (%); V_{25Gy}: Volume received at least 25Gy (%); D_{mean}: Mean Dose (Gy); D_{max}: Dose received by 0.03cc of the volume (Gy); p value^a <0.05 for VMAT plan; p value^b <0.05 for Composite plan; p value^c <0.05 for TFIF plan

sparing than the conventional IMRT (c-IMRT) and 3D-CRT techniques. Also, the V5Gy of heart and lung were 83% and 70.1% for VMAT and 100% and 91.9% for c-IMRT, respectively. Berrington de Gonzalez et al. (40) published a study on dose to the contra-lateral breast and risk of second primary breast cancer and showed that the risk was dose dependent and inversely related to age. Women under 40 years of age had an elevated risk of second breast cancer. Based on this study, younger patients should benefit from a technique in which lesser dose to contra-lateral breast is achieved. Yorke et al. (41) showed the effect of low doses (less than 20Gy) on the development of RP. A complication rate of 20% was expected if more than 50% of the lung volume received 10Gy thus highlighting the need to minimize the dose to heart and lung.

Our results show that the HI and CI indices for TFIF were poorer than the other two techniques and also did not achieve the acceptable criteria. Further, high dose volumes such as V_{20Gy} for lungs and heart were also higher for TFIF. The low dose exposure with VMAT was significantly higher that could translate into increased probability of radiation-induced carcinomas (42).

The V105% is significantly correlated with higher probability of developing skin toxicity (43). The V_{105%} of the whole breast PTV should be less than 10% to keep grade 3 dermatitis rates below 2%. In our study the volume V_{105%} was lowest at 5.56% in composite planning technique

and significantly lower than both VMAT (11.82%, p=0.001) and TFIF (11.8%, p=0.0006) for BCS and for MRM groups, it was 10.75% in composite plan and statistically lower than VMAT as 14.37% (p=0.003) and TFIF as 20.26% (p=0.023).

In our study, the composite plan showed significantly better results for low dose volume irradiation as compared to VMAT plans for both the groups of patients. The ipsilateral lung dose V_{5Gy} in the composite plan was reduced by 15.99% and 8.42% of VMAT for BCS and MRM groups, respectively without compromising the homogeneity and conformity indices. The ipsilateral lung V_{10Gy} of was also reduced by 13.69% and 3.03% of VMAT for BCS and MRM group, respectively. The contra-lateral lung V_{5Gy} and V_{10Gy} values in the composite plan were significantly reduced by 61.29% and 92.4% of VMAT for BCS and 50.14% and 38.02% for MRM groups. The mean dose of contra-lateral lung was also reduced by 37.33% and 33.53% of VMAT value in the composite plan for BCS and MRM groups, respectively.

Similarly, the V_{5Gy} of heart was significantly reduced in the composite plan by 47.97% and 21.22% of the VMAT values for BCS and MRM groups, respectively. The V_{10Gy} of heart was also reduced by 26.07% and 45.67% of VMAT values for BCS and MRM groups in the composite planning technique. The mean dose to heart in the composite plan was reduced by 20.95% and 18.52% of VMAT value for the BCS and MRM groups, respectively. The contra-lateral breast mean doses

Table 5. The comparable OAR's Dosimetric parameters for three techniques for MRM group (n=15, arithmetic mean and standard deviation)

Parameters	Composite Plan Mean±SD	VMAT Mean±SD	TFIF Mean±SD	Estimated p values		
				TFIF vs VMAT	TFIF vs Composite	Composite vs VMAT
Heart V _{5Gy} (%)	35.1±8.81	44.56±11.09	20.55±5.95	0.00 ^c	0.00 ^c	0.00 ^b
Heart V _{10Gy} (%)	18.09±5.37	33.3±43.27	15.25±5.14	0.00 ^c	0.00 ^c	0.00 ^b
Heart V _{20Gy} (%)	8.71±3.49	8.53±2.73	11.93±4.1	0.00 ^a	0.00 ^b	0.09
Heart D _{mean} (Gy)	6.29±0.97	7.72±1.25	6.33±1.56	0.42	0.00 ^c	0.00 ^b
LAD D _{mean} (Gy)	11.45±6.13	12.87±4.22	16.09±9.01	0.02 ^a	0.02 ^b	0.17
Ipsilateral Lung V _{5Gy} (%)	62.49±6.01	68.24±7.65	50.73±8.97	0.00 ^c	0.00 ^c	0.00 ^b
Ipsilateral Lung V _{10Gy} (%)	44.14±4.72	45.52±5.11	39.19±8.05	0.00 ^c	0.00 ^c	0.28
Ipsilateral Lung V _{20Gy} (%)	28.29±4.96	27.65±2.72	32.51±7.2	0.05 ^a	0.02 ^b	0.11
Ipsilateral Lung D _{mean} (Gy)	12.83±1.5	12.63±0.98	14.87±7.16	0.12	0.25	0.41
Contralateral Lung V _{5Gy} (%)	8.53±4.01	17.11±5.97	0.18±0.7	0.00 ^c	0.00 ^c	0.01 ^b
Contralateral Lung V _{10Gy} (%)	0.19±0.33	3.05±1.95	0.11±0.44	0.00 ^c	0.33	0.00 ^b
Contralateral Lung D _{mean} (Gy)	2.16±0.39	3.25±0.54	0.48±0.17	0.00 ^c	0.00 ^c	0.00 ^b
Total Lung V _{5Gy} (%)	32.92±4.41	41.27±5.61	23.45±5.18	0.00 ^c	0.00 ^c	0.00 ^b
Total Lung V _{10Gy} (%)	20.47±2.86	22.55±2.73	18.17±4.45	0.00 ^c	0.00 ^c	0.02 ^b
Total Lung V _{20Gy} (%)	12.96±2.55	12.63±1.44	15.09±3.73	0.06	0.01 ^b	0.2
Total Lung D _{mean} (Gy)	7.87±0.89	8.38±0.66	7.29±1.33	0.00 ^c	0.02 ^c	0.00 ^b
Opposite Breast D _{mean} (Gy)	2.13±0.6	3.16±0.62	0.54±0.58	0.00 ^c	0.00 ^c	0.00 ^b

D_{2%}: Dose received by 2% of the volume (Gy); V_{5Gy}: Volume received at least 5Gy (%); V_{10Gy}: Volume received at least 10Gy (%); V_{20Gy}: Volume received at least 20Gy (%); V_{25Gy}: Volume received at least 25Gy (%); D_{mean}: Mean Dose (Gy); D_{max}: Dose received by 0.03cc of the volume (Gy); p value^a <0.05 for VMAT plan; p value^b <0.05 for Composite plan; p value^c <0.05 for TFIF plan

were also significantly reduced by 9.89% and 32.90% of the VMAT values in the composite plans for BCS and MRM group, respectively.

Although in this study, the mean heart, LAD and ipsilateral lung dose were higher because the most of the selected patients were with locally advanced disease and RTOG guideline was followed for contouring being liberal than other guidelines like ESTRO, it leads to more MHD, CLD resulting high lung and heart dose. In that scenario we tried to reduce OAR's dose using composite planning technique. There is a scope to treat such patients with deep inspiration breath hold (DIBH) technique, which has advantage to reduce mean heart dose (44) and lung dose (45). But additional cost and challenges to patient as well as staff are also associated with this technique. In our department we have recently started DIBH technique, but the data size is small to analyze.

In the present study, the dosimetric endpoints were compared for three planning techniques in the setting of intact breast and post MRM irradiations. During this study, it was felt that the TFIF technique is easy in planning, required lesser planning time than VMAT and lesser monitor unit to delivered desired dose, but at the same time homogeneity and conformity are poorer than other techniques. The composite plan consisting of a combination of VMAT and TFIF plans resulted in lower doses to the OARs as compared to the VMAT plan, and also in better dose uniformity in the target as compared to the TFIF plan. Thus the composite plan is superior to both the VMAT and TFIF plans alone.

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Cytomorphological Spectrum of Granulomatous Mastitis: A Study of 33 Cases

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ABSTRACT

Objective: Granulomatous mastitis is an uncommon benign breast disease. Varied aetiologies such as tuberculosis, foreign body reactions, sarcoidosis, fungal and parasitic infections and autoimmunity have been suggested. Pre-operative definitive diagnosis is essential for proper treatment. In developing countries like India, fine needle aspiration is still widely used as a reliable technique for preoperative evaluation of palpable breast lumps. The objective of this study is to study the cytomorphological features of different forms of granulomatous mastitis and correlate with other clinical findings including histological features.

Materials and Methods: A total of 33 cases of granulomatous mastitis were reviewed. The patients underwent fine needle aspiration. Cytomorphological features were studied in detail and correlated with histopathological features and other clinical findings.

Results: All the 33 patients showed varied cytomorphological features which included epithelioid cells/granuloma with lymphocytes/plasma cells/ polymorphs with or without necrosis/caseous necrosis and with or without giant cells. Ziehl Nelson stain showed acid fast bacilli in 13 smears. Out of 17 cases, the eight cases showed positive acid fast bacilli culture. Fungal stain such as Grocott- Gommeri Methane amine did not show fungi. Based on cytomorphological features in aspiration smears, they were grouped into 4 Groups. A total of 27 breast lesions were diagnosed as tuberculous mastitis, the four lesions were diagnosed as idiopathic granulomatous lobular mastitis and two lesions were diagnosed as foreign body granulomatous mastitis. Grocott- Gommeri Methane amine did not showed fungi. Based on cytomorphological features in aspiration smears, they were grouped into 4 Groups. A total of 27 breast lesions were diagnosed as tuberculous mastitis, the four lesions were diagnosed as idiopathic granulomatous lobular mastitis and two lesions were diagnosed as foreign body granulomatous mastitis.

Conclusion: Epithelioid granulomas with caseous necrosis with or without acid fast bacilli in cytology smears are diagnostic of tuberculosis. Cytology smears showing epithelioid granulomas with predominant polymorphs without necrosis and acid fast bacilli, a diagnosis of idiopathic granulomatous lobular mastitis must be considered. Histopathological examination is essential for definitive diagnosis in these cases.

Keywords: Epithelioid cells, lobular mastitis, mastitis, needle aspiration, tuberculosis

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Introduction

Granulomatous mastitis (GM) is an uncommon benign breast disease. Two defined forms of GM have been identified. 1) Idiopathic granulomatous lobular mastitis (IGLM), 2) GM with specific aetiology. Many aetiologies such as tuberculosis, foreign body reactions, sarcoidosis, mycotic and parasitic infection and autoimmunity have been suggested (1, 2). Some of the forms clinically simulate carcinoma. Extra-pulmonary tuberculosis is on the rise world over. Tuberculous mastitis is relatively a rare disease with reported incidence varying from 3-4.5 % in developing countries like India. The radiological features are non-specific. IGLM is a rare chronic inflammatory disease of unknown aetiology. It has high rate of recurrence and develop complications such as sinus formation and skin ulceration. To avoid unnecessary surgery definitive diagnosis of various forms of GM is warranted (2-4). In developing countries, fine needle aspiration (FNA) is widely accepted as a reliable technique for preoperative evaluation of palpable breast lumps (5, 6). The aim of this study is to evaluate the cytomorphological features of different forms of granulomatous mastitis and correlate with other clinical findings including histological features.

Materials and Methods

This is a retrospective study over the period of five years. A total of 33 cases of mastitis were included in the study. Inclusion criteria: Benign breast lesions showing epithelioid cells in FNA smears. Exclusion criteria: Known cases of tuberculous mastitis on treatment. The

study included 33 cases of GM diagnosed on FNA. Medical records of these cases were retrieved and all the clinical details were noted. Cytomorphological, histological features and other clinical findings were reviewed and analysed. All the patients underwent FNA after prior written consent. Aspiration was done with aseptic precautions using 22-gauge needle connected to a 10ml syringe with FNA gun. Smears were stained using Leishman and Haematoxylin and Eosin (H and E) stains. Remaining smears were stained with Ziehl and Nelson (Z.N.) and Grocott-Gomori methanamine (GMS) stains for the presence of acid fast bacilli (AFB) and fungi, respectively. Cases in which aspirate was available or pus, was sent for AFB culture.

FNA smears and histopathology slides were studied independently by two pathologists. FNA smears were looked for epithelioid cells/granulomas, lymphocytes, polymorphonuclear leukocytes, plasma cells, eosinophils, giant cells, necrosis/caseous necrosis, AFB, fungal hyphae, and other cytological findings. Detailed clinical presentation including age, sex, marital status, number of pregnancies and last pregnancy, history of lactation, use of contraceptives, nicotine abuse, presence of systemic disease, cough, fever, weight loss and any family history of tuberculosis were noted. Ultrasonography and mammography finding were noted in all cases.

Cases in which surgical/biopsy specimens were received for histopathological examination, were formalin fixed and paraffin processed. 3-4 microns thick sections were stained with routine H and E, Z N and GMS stains. FNA features were correlated with clinical findings, radiological findings and histopathological findings. Culture for AFB was done in 17 cases by using Lowenstein Jensen (LJ) media. Subsequently findings of additional investigations such as tuberculin test, X ray and computed tomography (CT) of the chest were available in all patients. Statistical data was analysed and tabulated.

Results

In the series of 33 cases of GM, 32 were females and one was male. The patients age ranged from 19 to 75 years with mean age of 44 years. Maximum patients (n=12) were in the age group of 31-40 years. Table 1 show detailed age and sex distribution of 33 patients. Right breast (n=23) was commonly involved than left breast (n=10).

The diagnosis of GM was made by presence of epithelioid granulomas or scattered epithelioid cells along with other inflammatory cells with or without giant cells in FNA smears. Based on clinical findings and morphology of granuloma with other inflammatory cells, giant cells and presence or absence of AFB in FNA smears, AFB culture examination and histomorphological features, aetiology of GM was specified. Out of 33 cases of, maximum (n=27) cases were diagnosed as tuberculous mastitis (TM), followed by IGLM (n=4) and foreign body granulomatous mastitis (n=2). Right breast was involved in 23 cases and left breast was involved in 10 cases. Out of 27 patients of TB mastitis, maximum (n=21) patients presented with nodular pattern of growth. Table 2 show detailed age sex group and clinical findings in various forms of granulomatous mastitis.

Ultrasonography and mammography were done in all cases. Commonest ultrasonography finding (n=25) was heterogeneous hypoechoic lesion. Mammography showed focal asymmetric density in 29 cases. All the patients were seronegative for human immunodeficiency virus (HIV).

Cytomorphological features were studied in detail and they were categorised into four groups (Table 3).

Table 1. Age and sex distribution of granulomatous mastitis

Age (Years)	Male	Female	Total
0-20	0	3	3
21-30	0	7	7
31-40	1	11	12
41-50	0	4	4
51-60	0	3	3
61-70	0	2	2
70 above	0	2	2
Total	1	32	33

Table 2. Age, sex and clinical features in different types of granulomatous mastitis

Age group		TB Mastitis (n=27)	Foreign body Granulomatous Mastitis (n=2)	IGLM (n=4)
0-20		3	0	0
21-30		3	0	4
31-40		12	0	0
41-50		2	2	0
51-60		3	0	0
61-70		2	0	0
>70		2	0	0
Total		27	2	4
Sex	M	1	0	0
	F	26	2	4
Clinical Findings				
Nodular Pattern		20	0	2
Sclerosing Pattern		3	2	2
Disseminated Pattern		4	0	0
Mastalgia		3	2	2
Axillary lymphadenopathy		3	0	0
H/o lactation since last 6 months		1	1	3
Family history of tuberculosis		2	0	0
IGML: Idiopathic granulomatous lobular mastitis				

Group 1 (n=2) showed epithelioid cells/granuloma mixed with lymphocytes and plasma cells without necrosis with or without giant cells (Figure 1a and b).

Group 2 (n=22) showed epithelioid cells/granuloma with necrosis/caseous mixed with lymphocytes and plasma cells with or without giant cells (Figure 1c and b).

Table 3. Pattern of granulomatous inflammation on FNA smears of 33 granulomatous patients

Pattern	Cytomorphology	N (number)	%
Group 1	Epithelioid granulomas mixed with lymphocytes, plasma cells without necrosis with or without giant cells	2	6.06
Group 2	Epithelioid granulomas mixed with lymphocytes, plasma cells with necrosis/ caseous with or without giant cells	22	66.66
Group 3	Suppurative necrosis with epithelioid granulomas / epithelioid cells	6	18.18
Group 4	Epithelioid granulomas mixed with predominantly neutrophils, lymphocytes with or without giant cells	3	9.09

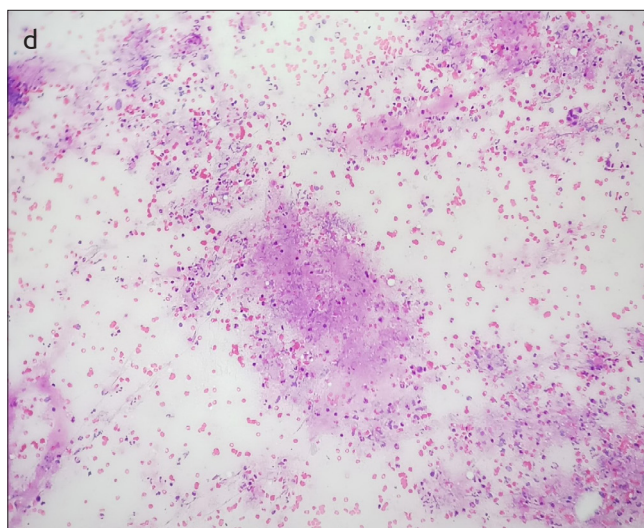
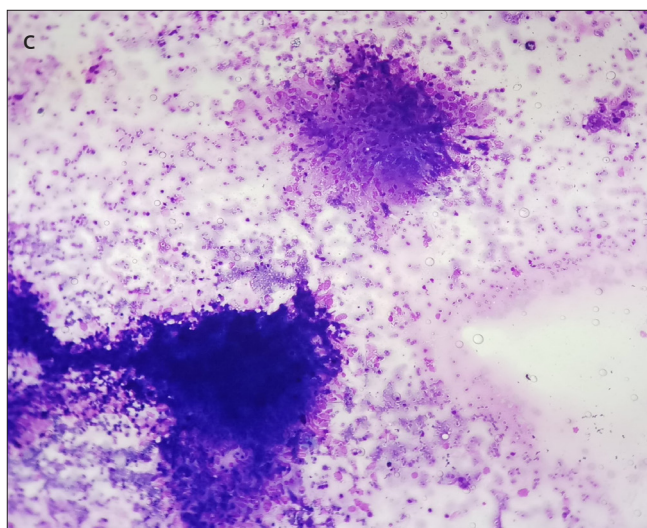
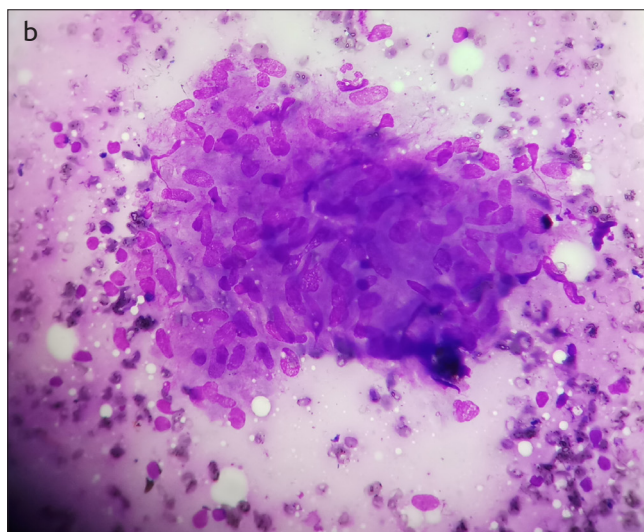
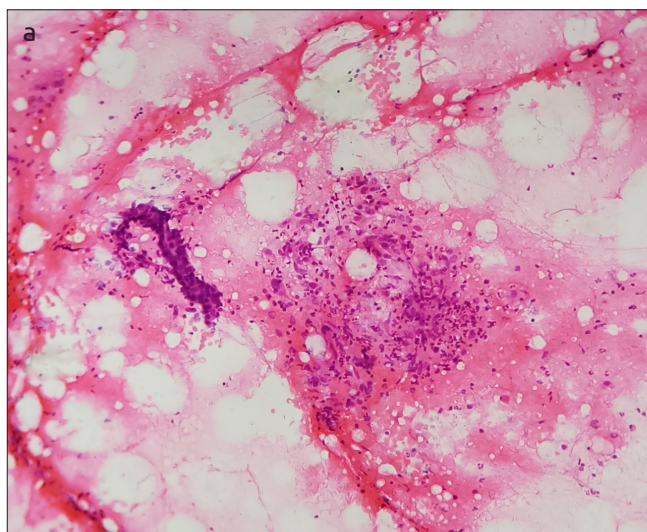


Figure 1. a-d. (a) Smear show epithelioid granuloma, and ductal epithelial cells. (a) (Haematoxylin and Eosin x100). (b): Smear show epithelioid granuloma (Leishman stain x400). (c): Smear show epithelioid granuloma with areas of necrosis (Leishman stain x100). (d): Smear show caseous necrosis (Leishman stain x100)

Group 3 (n=6) showed suppurative necrosis with epithelioid cells/granuloma (Figure 2a and b).

Group 4 (n=3) showed epithelioid cells/ granuloma mixed with polymorphonuclear leukocytes without necrosis and with or without giant cells (Figure 2 c and d).

In addition, three cases showed few scattered large atypical epithelial cells (Figure 3a).

ZN stain was done in all FNA smears and AFB were seen in 13 smears. Out of 17 cases in which AFB culture was done, 8 cases showed positive AFB culture. Fungal stain was done in 7 cases and none of the cases showed fungi.

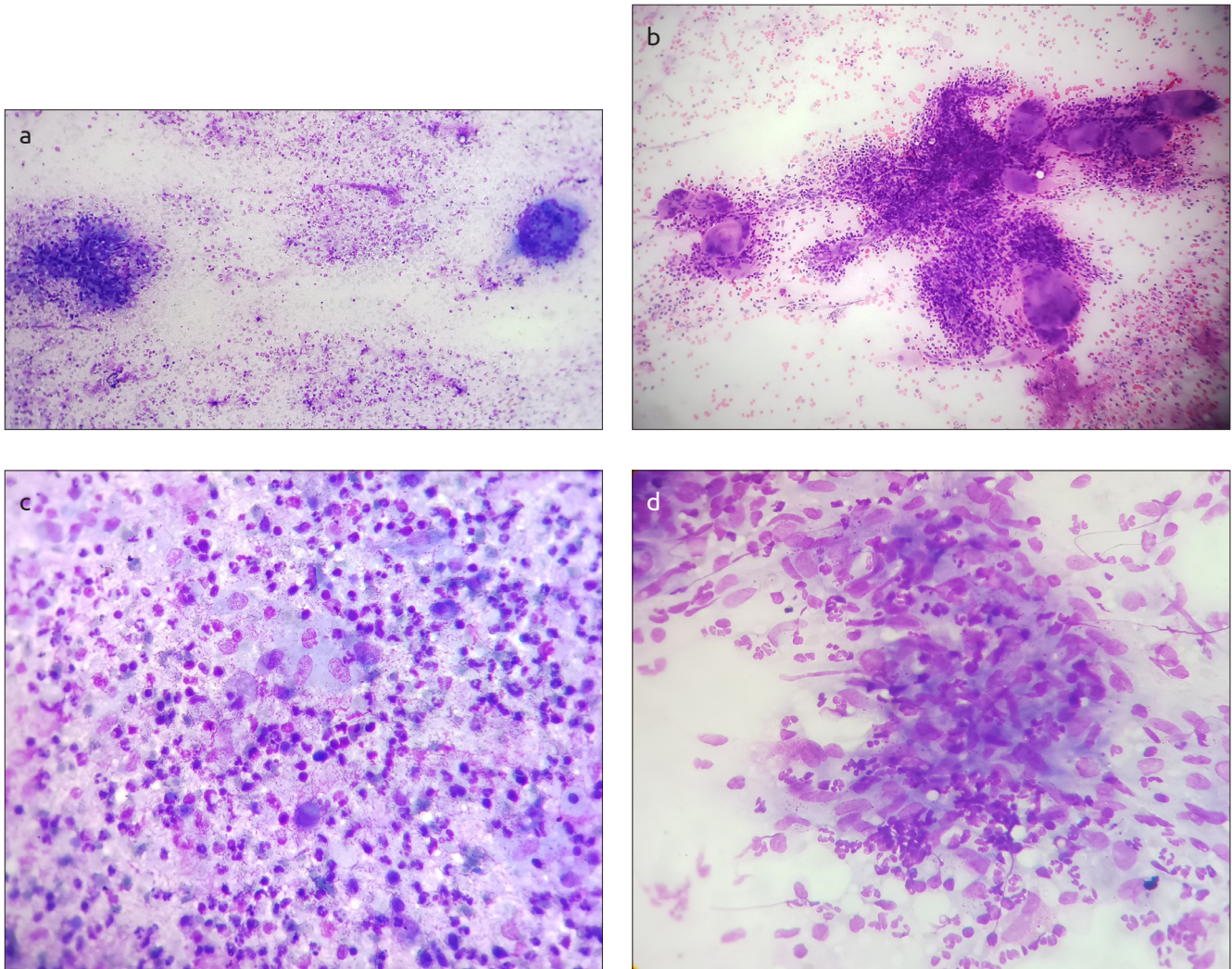


Figure 2. a-d. (a) Smear show epithelioid granuloma, giant cell and suppurative background (Leishman stain x100). (b): Smears show many epithelioid granulomas, giant cells and polymorphs (Leishman stain x400). (c): Smears show many epithelioid granulomas, giant cells, polymorphs and few lymphocytes (Leishman stain x400). (d): Smears show many epithelioid granulomas mixed with polymorphs (Leishman stain x400)

The definitive diagnosis of tuberculous mastitis was based on FNA features of epithelioid cells/granuloma with caseous necrosis with or without AFB or AFB culture positivity. The cases in which necrosis or AFB were not seen in FNA smears, the diagnosis Tb mastitis was established by AFB culture or histopathological examination.

Out of 27 cases of Tb mastitis, histopathological examination was done in six cases. out of 6 cases, two cases in which FNA smears showed Group 1 pattern, biopsy showed epithelioid granulomas mixed with lymphocytes, occasional Langhans giant cell and caseous necrosis. ZN stain in both cases showed AFB and diagnosis of Tb mastitis was established. The four cases out of which FNA smears in three cases of Group 4 pattern and one case of Group 3 pattern did not show AFB or fungi on special stains. Biopsy in these cases were received for histopathological examination showed inflammatory infiltrate of polymorphs, lymphocytes and epithelioid granulomas and giant cells confined predominantly to lobules. Stroma showed focal scanty lympho-plasmocytic inflammatory infiltrate. There was no caseous necrosis (Figure 3b). Special stains did not reveal AFB and fungi. In all these four cases, diagnosis of IGLM was made. None of the patients showed evidence of pulmonary tuberculosis on X ray and CT of the chest.

Diagnosis of foreign body granulomatous mastitis based on strong clinical history, FNA features of granulomas, giant cells without AFB in smears and negative AFB culture. The diagnosis was confirmed by histopathological examination.

Discussion and Conclusion

In 1972, Kessler and Wolloch emphasized in their study that granulomatous mastitis is a rare condition and its aetiology is not known (7). Subsequently, Jayram G from India reported cases of granulomatous mastitis of tubercular aetiology (8). Other aetiologies such as foreign body reactions, sarcoidosis, fungal and parasitic infections and auto-immunity have been suggested (1, 2). Though granulomatous mastitis can occur at any age, it is more common in women of child bearing age and commonly occur in 3rd and 4th decade (9, 10). Males are rarely affected and it has been occasionally reported in elderly patients (2). In contrast in our study, GM (n=19) more commonly occurred in 2nd 3rd decade (Table 1).

Breast is a uncommon site for tuberculosis even in countries like India, where tuberculosis is rampant. It affects commonly women in the reproductive age group of 21 to 40 years (11-13). In our study, a substan-

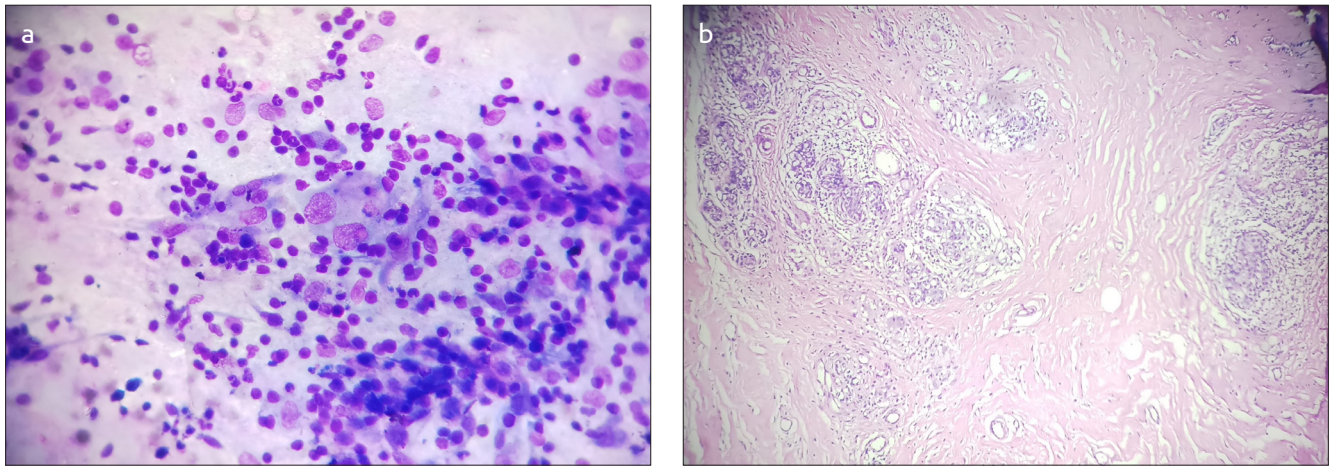


Figure 3. a, b. (a) Smears show lymphocytes on background and few atypical cells (Leishman stain x400). (b) Breast tissue show inflammatory cells and occasional epithelioid granuloma (Arrow) confined to breast lobules (Haematoxylin and Eosin x100)

tial number of cases (n=12) were evenly distributed in the remaining age groups (Table 3). Khanna et al. (14) observed TB mastitis in 15 - 58 years of age group while in our study oldest patient was of 70 years old. Though it is extremely rare in males, it is known to occur (14).

Three different clinical types such as nodular, sclerosing and disseminated have been identified in breast tuberculosis. The commonest is nodular variant (11). Similar observations were made in our study (Table 2). Ultrasonography and mammography lack specificity (11, 13). Though lactation makes the breast vulnerable to tuberculosis, only one patient in our study gave history of lactation. Similarly, other constitutional symptoms like fever, weight loss and night sweats did not aid in the definitive diagnosis of TB mastitis.

Though breast tuberculosis can be primary, it is believed that infection usually occur secondary to tubercular focus elsewhere in the body which may not be clinically or radiologically apparent. Similar observations were made in our study and other studies (22).

Out of 27 cases of TB mastitis, Group 2 cytomorphological features (Table 3) coupled with or without acid fast bacilli in FNA smears or AFB culture positivity established a definitive diagnosis of TB mastitis in 22 cases. In remaining five cases of GM, the diagnosis of TB mastitis was aided by either AFB in FNA smears or culture or by histopathology. Detection of caseous necrosis in FNA smears depend on experience of the pathologist and is diagnostic of tuberculosis in developing countries like India. It is typically seen as acellular granular material with loss of cellular details (22). Out of 22 cases (Group 2 pattern) in which necrosis was seen, 10 cases showed caseous necrosis in our study.

Overall culture positivity was only 23% in our study. Possible reason can be inadequate material for culture.

IGLM is a rare chronic inflammatory disease of unknown aetiology (19). Autoimmune pathogenesis is proposed and accepted in many studies. It commonly occurs in patients with history of recent pregnancy and lactation (20). With increasing use of FNA as an initial investigative modality for breast lesions there is a need for an increased awareness of this disease entity. Cytomorphological features have been discussed in few foreign studies (16-18, 21). Ultrasonography and mammography lack specificity (3, 16-18). Usefulness and reliability of FNA is still debated. There is no commonly accepted treatment of IGLM.

In our study, all the patients were in between 21 to 30 years with the mean age of 25 years while other studies observed higher mean age ranging from 33 to 35 years (14, 17, 21). Three patients gave history of lactation within six months (Table 2).

Out of four cases of IGLM, three FNA smears showed Group 4 pattern and one case showed Group 3 pattern (Table 3). Gangopadhyay et al. (19) observed epithelioid granuloma, variable number of epithelioid histiocytes on the background and predominant polymorphonuclear inflammatory infiltrate. The Tse GMK (17) observed background epithelioid histiocytes as a dominant cytological feature in smears followed by epithelioid granulomas. Neutrophil was the dominant inflammatory infiltrate. Lymphocytes, plasma cells and giant cells were in variable numbers. The Seo Na HR (21) studied 24 patients of IGLM and only 25% patients were diagnosed on FNA, while remaining patients showed non-specific inflammatory findings or insufficient material in FNA smears. In our series, epithelioid granuloma, polymorphonuclear infiltrate were dominant features in cytology smears (n=3). Variable number of lymphocytes, plasma cells and giant cells were seen. The remaining one case showed Group 3 pattern and she was a 25-year-old female and she complained of non-healing surgical wound and increase in size of the lesion. Possible reason for suppurative necrosis in FNA smears (Group 3) can be due to secondary bacterial infection. In all these cases, we were not able to demonstrate AFB or fungi in FNA smears and there was no clinical or radiological evidence of tuberculosis. Histological examination in all these cases showed inflammatory infiltrate confined to lobules. It mostly comprised of lymphocytes, plasma cells and occasional collection of epithelioid cells. There was no necrosis. AFB and fungal stains on tissues did not revealed AFB and fungi. Final diagnosis of IGLM was made in all four cases.

Remaining 2 cases in which FNA smears showed Group 2 pattern, both cases showed fatty necrosis on histological examination which evoked granulomatous reaction. ZN stain did not reveal AFB or fungi and the patient gave history of minor surgical intervention at the site three months back. To conclude, GM is a rare uncommon benign breast disease. There is a need to identify specific aetiology preoperatively for appropriate therapy. Tuberculosis is the most common cause of GM in developing countries like India. IGLM occur in younger age group as compared to tuberculous mastitis. Epithelioid granulomas with caseous necrosis with or without AFB in FNA smears and cul-

ture is diagnostic of Tb. Smears in which AFB or caseous necrosis is not detected histopathology provide definitive diagnosis, FNA smears showing epithelioid cells/ granulomas with predominant polymorphs without necrosis or AFB, a diagnosis of IGLM must be considered. Histopathological examination is essential for definitive diagnosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr D Y Patil Medical College and Hospital, Pimpri Pune.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.C.; Design - S.C., P.N.; Supervision - S.C., A.R.; Resources - A.S., M.S.; Materials - S.C., M.S.; Data Collection and/or Processing - A.Ab., A.R.; Analysis and/or Interpretation - S.C., P.N.; Literature Search - A.R., M.S.; Writing Manuscript - S.C., P.N.; Critical Review - S.C., A.S.; Other - A.R., M.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Bilateral Paget's Disease of the Breast in a Patient with CHEK2 Mutation

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ABSTRACT

We report a case of a 53-year-old woman with a CHEK2 mutation who was found on histology to have bilateral incidental Paget's disease of the breast following bilateral prophylactic mastectomy.

Keywords: Breast, Mammary Paget's disease, CHEK2

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Introduction

CHEK2 is a tumor suppressor gene that encodes a serine/threonine kinase involved in DNA repair, cell cycle arrest or apoptosis as a result of DNA damage. CHEK2 germline mutations have been implicated in numerous types of cancers. In women with the CHEK2 mutation and no family history of breast cancer, the risk of developing breast cancer has been estimated to be as high as 20%, but that risk can be as high as 44% in women with a family history of breast cancer (1). However, bilateral prophylactic mastectomy is generally not recommended for asymptomatic women with the CHEK 2 mutation, as it is considered a low to moderate penetrance mutation. We now report a case of a woman with CHEK2 mutation and a strong family history of breast cancer who specifically requested bilateral prophylactic mastectomy and was found to have an incidental finding of bilateral mammary Paget's disease on histology. Mammary Paget's disease (MPD) accounts for 1-3% of new cases of breast cancer diagnosed each year in the United States (1). Paget's disease is commonly unilateral; therefore, bilateral MPD is of even more interest.

Case Presentation

Clinical history

A 53-year-old postmenopausal female with a past medical history of duodenal lymphoma presented with bilateral clear nipple discharge and intermittent right nipple bloody discharge of 9 months.

Radiologic investigation

The patient had a normal screening mammogram the year prior. Upon presenting with new onset of nipple discharge, she underwent a diagnostic mammogram, reported as BIRADS 2 devoid of suspicious masses, adenopathy or of architectural distortion. A few typically benign calcifications were noted bilaterally; however, the breast tissue was noted to be heterogeneously dense, which could obscure detection of small masses. As a result, a bilateral gadolinium contrast-enhanced magnetic resonance imaging (MRI) exam was performed, which showed a 4 mm oval circumscribed mass in the right breast at 6:00 axis anterior depth, 1.9 cm from the nipple.

Histopathologic examination

She underwent an MRI-guided core needle biopsy of the mass using a 9-gauge vacuum-assisted Suros coaxial biopsy device. 9 specimens

were obtained and submitted to pathology in formalin. The pathology revealed an intraductal papilloma without any evidence of atypia or malignancy.

Genetic examination

The patient indicated that both her mother and sister, had died of breast cancer, and her sister was found to harbor the CHEK2 mutation. The patient underwent genetic testing and was found to have the same CHEK2 c.1100delC deleterious mutation as reported for her sister.

Management

The patient requested bilateral prophylactic mastectomy, and a bilateral skin-sparing mastectomy with immediate autologous reconstruction was performed, and the specimen submitted for routine histopathological examination.

Histopathologic examination

Bilateral mastectomy specimens were submitted for histopathologic examination. There were no grossly identifiable lesions in bilateral breasts and both nipple/areola complex were grossly unremarkable with no scaling, crusting or erythema. Formalin fixed paraffin embedded sections were stained with hematoxylin & eosin stain for histologic examination. Scattered large atypical cells with round to oval nuclei, vesicular chromatin, prominent nucleoli and abundant pale eosinophilic cytoplasm were noted in the nipple epidermis, predominantly in the basal layers (Figure 1). Some of these atypical cells formed glandular structures with lumen containing focal mucin droplet (Figure 2). The atypical cells were strongly positive for CK7, estrogen receptor, progesterone receptor and negative for HER2/neu by immunohistochemistry (Figure 3). Extensive sampling of the remainder of the breast tissue showed no evidence of in-situ or invasive carcinoma. A diagnosis of bilateral Paget disease of the nipple was rendered.

Discussion and Conclusion

To the best of our knowledge, this is the first report of bilateral Paget's disease in a CHEK2 mutation carrier.

Clinical Paget's disease which presents as an eczematous or ulcerated lesion on the nipple that spreads to the areola is rare; however, Paget's disease diagnosed on histology is more frequent (2). This lesion may also be associated with pain, pruritus, bloody discharge or nipple retraction. A case series of 3000 mastectomy specimens demonstrate a 0.7% incidence of clinical Paget disease while histologic evidence of Paget disease was observed in 4.9% of mastectomies (3). Given that 85-88% percent of cases of MPD have an underlying breast cancer-

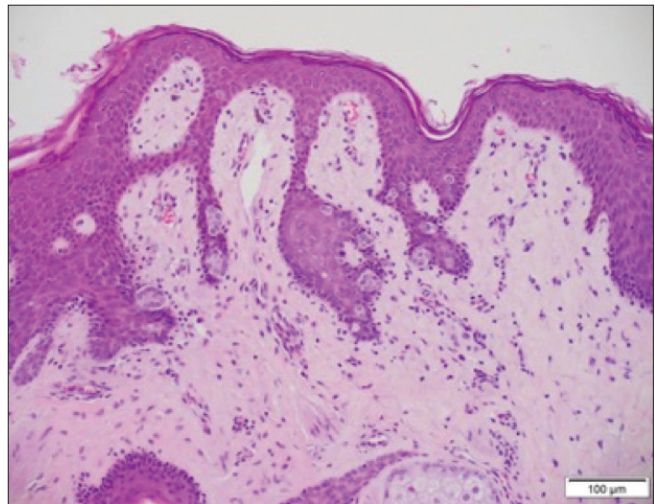


Figure 1. Histologic examination of breast biopsies, where scattered atypical cells were noted in the basal layers of the nipple epidermis

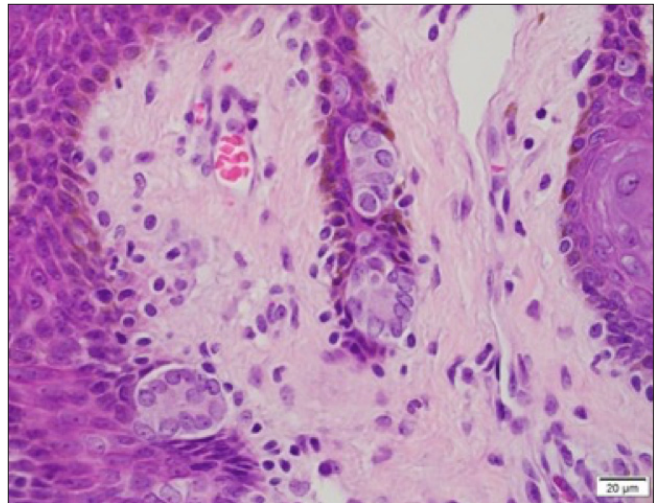


Figure 2. Histologic examination of the same tissue, where the atypical cells were observed to form glandular structures with lumen containing focal mucin droplet

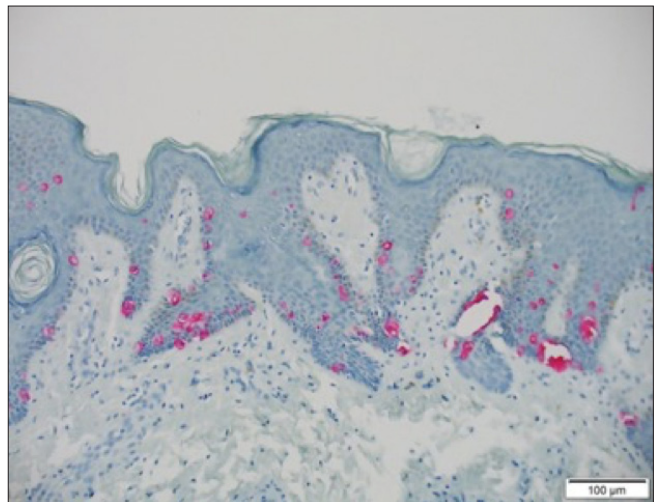


Figure 3. CK7 evaluation of the atypical cells by immunohistochemistry

Key Points

- CHEK2 germline mutations have been implicated in numerous cancers.
- Carriers of CHEK2 deleterious mutations are at increased risk of breast cancer.
- We report the first case of bilateral mammary Paget's disease in a patient with CHEK2 c.1100delC deleterious mutation.
- Further larger series studies are needed to determine the safety of nipple-preservation in CHEK2 mutation carriers.

invasive or in situ process-, the diagnostic workup of MPD with mammogram and skin or core biopsy focuses on both establishing a diagnosis based on the presence of malignant intraepithelial adenocarcinoma within the epidermis of the nipple and identifying an underlying breast cancer (4). According to the epidermotropic theory, neoplastic ductal epithelial cells migrate from the duct into the epidermis of the nipple; therefore, many cases of MPD have an underlying breast cancer lesion (5).

Whole exome sequencing of MPD has identified frequent recurrent mutations within chromatin remodeling genes such as ARID2 and KMT2C and recurrent somatic mutations such as CDCC168, CASP8AP2, FSIP2 (6). Transcriptome analyses have revealed dysregulation of glandular developmental regulator gene FOXA1; however, CHEK2 mutation has never been described in association with MPD (7). Our patient had CHEK2 c.1100delC mutation. The 1100delC protein-truncating variant has been associated with a threefold increased risk of breast cancer (8). Research has shown that this breast cancer risk is correlated with family history and the risk increases with first and second-degree relatives with breast cancer.

Standard therapy for MPD is simple mastectomy or breast-conserving therapy. Breast-conservation for MPD entails a central lumpectomy with en bloc excision of the nipple-areolar complex, axillary staging if an invasive component is identified, followed by adjuvant whole breast radiotherapy. The safety of nipple-sparing mastectomy (NSM) is CHEK2 has not yet been studied, and thus, our case report serves as a caution to breast surgeons that NSM may not been indicated in this specific patient population. Further studies (e.g. prospective larger series) are needed to determine the safety of NSM in CHEK2 patients.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.B., M.D., A.N., I.J., M.E.; Design - N.B., M.D., A.N., I.J., M.E.; Supervision - M.E., I.J., A.N.; Resources - N.B.,

M.D., A.N., I.J., M.E.; Materials - A.N., N.B.; Data Collection and/or Processing - N.B., M.D., A.N., I.J., M.E.; Analysis and/or Interpretation - N.B., M.D., A.N., I.J., M.E.; Literature Search - N.B., M.E.; Writing Manuscript - N.B., M.D., A.N., I.J., M.E.; Critical Review - N.B., M.D., A.N., I.J., M.E.; Other - N.B., M.D., A.N., I.J., M.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Prescribing for Women with Breast Cancer in Their Survivorship Phase for Menopausal Symptoms

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Dear Editor,

In developed countries breast cancer survival is improving. In the UK the rate of survival has doubled in the last 40 years. In the 1970s, four in ten women diagnosed with breast cancer survived their disease beyond ten years, now it's around eight in ten (1).

There were 55,000 new cases of invasive breast cancer diagnosed in the UK between 2014-2016. With around 8,000 new breast carcinoma in situ cases identified every year, this equates to 22 new cases being recorded every day (2). With treatment these women can be advised that they have an estimated 78% survival rate of ten or more years (2). Around two-thirds (65%) of women diagnosed with breast cancer in England and Wales survive their disease for twenty years or more (1). It is noteworthy that the age range 50-69 years is when the chances of breast cancer survival are highest (Figure 1).

Breast Cancer and Menopause Management

Women with breast cancer depending on their diagnostic stage and prognosis may be advised to undergo treatments which include chemotherapy, radiotherapy and adjuvant hormone therapy (Figure 2) (3, 4). Breast cancer treatments per se can induce the menopause, which can be accompanied by debilitating vasomotor and emotional symptoms. Generally, the climacteric, the period of life when fertility and sexual activity are in decline and which depicts the end of the reproductive phase in women, ranges from age 45 to 55. Natural menopause occurs around 51 years of age (5). Many women will go through an earlier menopause with breast cancer therapy (3) or may be at the age of natural menopause and then face additional debilitating symptoms with breast cancer treatment.

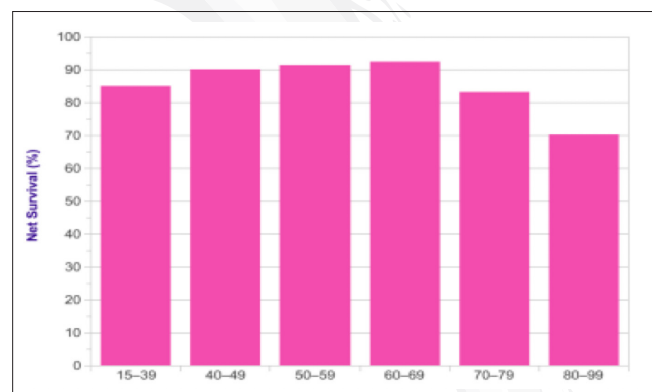


Figure 1. Breast cancer (C50): 2009-2013. Five year net survival by age, Women, England (2)

Acknowledgement Cancer Research UK

The Breast Cancer and Menopause Service (BCMS)

In this paper we present the treatment and prescribing guidance which has been compiled (Appendix 1), working in close liaison and jointly by specialist multi-disciplinary teams, within our hospital. The treatment and prescribing guidance provide the evidence base and consensus for best practice and care for patients seen within the breast cancer and menopause service.

The BCMS service was established in 2007 after identifying the need and following a pilot phase (6, 7). The service accepts referrals for women with high risk for breast cancer or those with breast cancer who have undergone treatment, who are now in their survivorship phase, and suffering with menopausal symptoms. The joint BCMS service has been established using a clinical governance approach (6-14), and operates at a general district hospital which is a university accredited health-care Trust in North West London. Patient views are important

and can assist with successful service development. In line with this, research has been undertaken with various breast cancer patient cohorts including Caucasian (14, 15), Asian (16) and women with breast cancer who have been seen within the BCMS service and those who have not (Table 1) (14). Figure 3 shows the symptom assessment chart that all patients seen within the general menopause and the BCMS service complete at each clinic visit. The symptom assessment chart is used to help with objective assessment of symptom relief in between consultations.

The approach (6-8) taken to ensure a high standard of patient care delivery has involved joint collaborative working between the Trust breast and menopause services and included input from the genetics counselling team, the development of an appropriate history taking

proforma by the BCMS service multi-disciplinary team which is also utilised to support teaching and training for junior medical staff, and audit and research activity to drive evidence based service development (7, 8, 13-15), and as stated above the writing of the BCMS prescribing guidelines. These were first drafted in 2009 after an extensive literature search, updated subsequently in 2012 and 2015 and with ratification by the Trust Drugs and Therapeutics Committee (DTC) at each stage.

These guidelines have undergone evidence-based review and have been updated using collaborative consensus methodology. We present the current updated document of the BCMS guidelines in Appendix 1 and invite comments and input from the readership to further inform safe, holistic and empathetic delivery of care to women with high risk for breast cancer or for those with breast cancer in their survivorship phase.

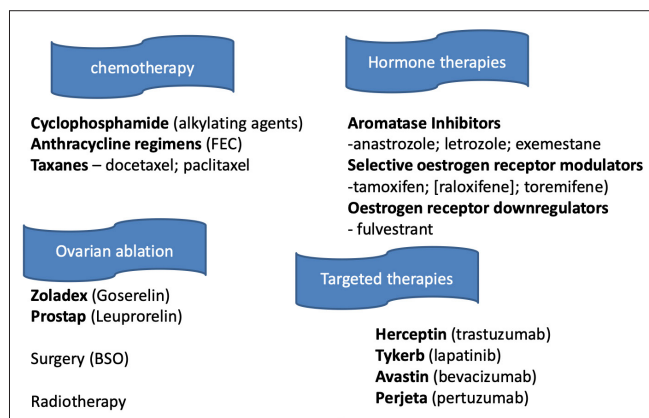


Figure 2. Treatments inducing menopause (temporary or permanent) and those causing menopausal symptoms

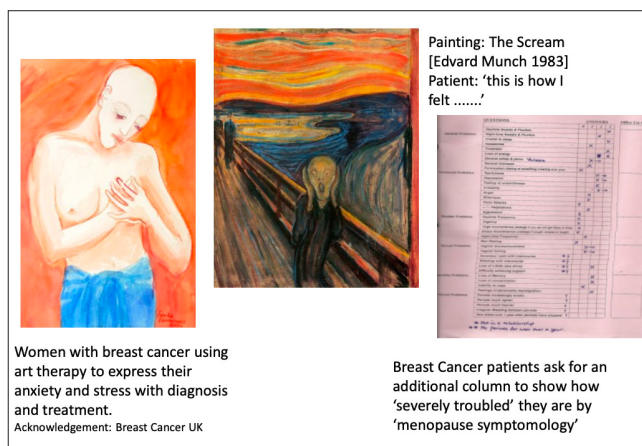


Figure 3. Breast cancer survivorship

Table 1. Demographic data for focus group participants - UK Caucasian and Asian women attending support group. Breast Cancer Patient Stories Project (15)

	Caucasian BC patient group	Asian BC patient group	Comments
No. of women taking part in focus group	13	7	All 13 of 13 Caucasian, but only 7 of 25 Asian women attending on the evening took part in the focus group
Average Age (range)	62.4 years (49-91)	55.4 (49-61)	Older Asian women who could not speak English decided not to take part.
No. with first BC/No. with BC recurrence	12/1*	7/0	Patient with BC recurrence*, recently diagnosed, felt her strong faith would help her get through this phase in life
Partner/Carer attending	2/1**	0/1**	Both carers** were sisters of BC patients
Time since first diagnosis	6 years (range 9 month-14 years)	1.9 years (range 1.2-4.3 years)	The patient with BC recurrence* had had her first BC 5 years before
Menopausal stage at time of BC diagnosis:			
Postmenopausal (last normal menstrual period 12 months before)	7	7	1. BC patients were not sure if they had menopausal symptoms or whether this was due to their BC condition/BC treatment.
Perimenopausal (still having some menstrual periods)	3	0	2. Asian women complained of erratic and heavy bleeds as the most common problem at the time of their menopause.
Premenopausal (regular menstrual periods)	3	0	3. Self medicating but safety?

BC: Breast Cancer

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.T., N.K.; Design – N.T.; Supervision – N.K., L.F.; Materials - BCMS Prescribing Guidelines, London North West University Healthcare NHS Trust, September 2019; Literature Search – N.T.; Writing Manuscript – N.T.; Critical Review – N.K., L.F.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Appendix 1. BCMS Prescribing Guidance July 2019



The Joint Breast Cancer and Menopause Symptom Clinic Women Services, London North West University Healthcare NHS Trust.

Prescribing Guidelines

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Introduction

NICE guidance NG23 (Nov 2015) suggest that women likely to go through the menopause as a result of medical or surgical treatment (including women with cancer, women at high risk of hormone sensitive cancer or having gynaecological surgery) should be offered

- ☐ support and information about menopause and fertility before their treatment
- ☐ referral to a healthcare professional with expertise in menopause.

Non hormonal prescribed options are generally not as effective for symptomatic treatment of menopause as HRT, but there may be individuals who may benefit (Drewe 2015; NICE NG23 2015; NICE NG101 2018). The evidence base or best practice for non hormonal options in breast cancer is presented below.

Menopausal women with or at high risk of breast cancer should be provided with information

- ☐ on all available treatment options
- ☐ that the SSRIs Paroxetine and Fluoxetine should not be offered to women with breast cancer who are taking Tamoxifen (anti-oestrogen) .

Treatment of Hot Flashes in Women with Breast Cancer

Prescribing notes:

1 **SSRI: Selective serotonin reuptake inhibitors / Anti-Depressants**

1. Best evidence for Paroxetine; off license use in UK (Nelson 2006)
2. Dose: 10mg daily (BNF app Jan 2019); higher doses not associated with improved control
3. Adverse affect on libido
4. Interaction with Tamoxifen (* see pg.4); do not prescribe concurrently for breast cancer patients on Tamoxifen
5. Other SSRIs evaluated in short duration trials for menopause symptom control include Fluoxetine and Citalopram with caution advised with concurrent prescribing with Tamoxifen (* see pg. 4).
6. If a decision is made to prescribe SSRI with Tamoxifen (* see pg.4), then Citalopram may be the option to consider (Drewe 2015)

2 **SNRIs: Serotonin noradrenaline reuptake inhibitors / Anti-Depressants.**

1. Venlafaxine at doses 37.5mg – 150 mg Modified Release daily, off license use in UK.
2. Dose: 37.5 mg daily for 1 week, then increase to 75mg daily (BNF app Jan 2019). 75 mg daily dose well tolerated; moderate GI or CNS symptoms in 10-20% users.
3. Counsel patients regarding nausea side effect; may be reduced by using long acting formulation as once daily dose with food, at night; the long acting formulation may also offer better control due to sustained systemic levels
4. Little or no interaction with Tamoxifen* - Note that Venlafaxine has weak potency for CYP450 2D6 genotype pathway interaction, so compared to SSRIs, is the preferred prescription for patients on Tamoxifen (Drewe 2015)



5. May have an adverse effect on libido, but potentially lesser extent than SSRIs. One study with breast cancer patients reported improved libido with SSRIs / SNRIs.
6. Caution in patients with cardiovascular risks, eg. Cardiac ventricular arrhythmia; uncontrolled blood pressure; left ventricular dysfunction; recent MI; monitor cholesterol levels with long term treatment.
7. NB: Desvenlafaxine (active metabolite of Venlafaxine) evaluated for menopause symptom control. Not licensed in the UK; did not receive EMA approval 2017.

3. **Gabapentin: Gamma Aminobutyric Acid Analogue / Anti- epileptics.**

1. Researched in breast cancer patients on Tamoxifen, although short duration 12 week trials
2. Dose: 900 mg daily, off license use (BNF app January 2019). Suggested initial regimen 300 mg day 1, 300 mg twice daily on day 2, then 300 mg 3 times daily from day 3.
3. Clinical experience suggests that slower titration of dose increase may help with improved patient compliance / concordance, eg. 300 mg daily for 2 weeks, increase to 300 mg bd for 2 weeks, then if tolerated increase to 300 mg tds. If daytime drowsiness is a major side effect, could try administration of total dose at night.
4. 2006 meta-analysis suggests Gabapentin has best evidence for vasomotor symptom control; but not well tolerated; 50% patients reported at least one adverse event.
5. Gabapentin is also used for treatment of neuropathic pain, trigeminal neuralgia (off license) and in postherpetic neuralgia where amitriptyline has failed to give adequate control
6. NB: Gabapentin (and pregabalin) classified as a class C controlled substance from April 2019, due to substance misuse concerns.

4. **Clonidine: Alpha Adrenergic Receptor Agonist / Anti - Hypertensives.**

1. Helps to reduce hot flushes, although evidence base contradictory
2. Clinical trial daily dose range: 50 micrograms – 150micrograms orally; one trial with transdermal system demonstrated better symptom control than reported with oral route
3. Clonidine 50 micrograms twice daily for 2 weeks; then increase if necessary to 75micrograms twice daily; licensed in UK for menopausal symptom control
4. Side effects, including difficulty sleeping, in up-to half of users
5. Prescription should not be stopped abruptly, as this could cause rebound hypertension



5. Progestogens: Hormones used in gynaecology

1. Unlicensed for menopause vasomotor symptom control; lower doses than those used for breast cancer treatment eg. Norethisterone 1-10 mg daily; Megestrol Acetate 20mg to 40mg daily .
2. NICE NG101 states that progestogens should not to be prescribed in breast cancer patients to help with menopausal vasomotor symptom control.
3. Progestogens for vasomotor symptom control could be considered in patients with non hormonal sensitive tumours, after a full risk benefit discussion. Caution: With tumour studies with progesterone receptor sensitivity, decision to use progestogens for vasomotor symptom control must be agreed with patient's oncologist and based on level of progestogen sensitivity (strong to weak)
4. Licensed as breast cancer treatments in high doses; role of progestogens in breast cancer has declined.
NB: Doses: Medroxyprogesterone in breast cancer 400 – 1500 mg daily; Megestrol in breast cancer 160 mg daily, in single or divided doses; Norethisterone in breast cancer, 40 mg daily increased to 60 mg daily if required

* **Tamoxifen - Interaction with SSRI and SNRIs**
The efficacy of tamoxifen therapy (a selective oestrogen receptor modulator) for the treatment of breast cancer varies widely among individuals. Selective serotonin reuptake inhibitor antidepressants are often prescribed to treat hot flashes in women who may or may not be co-prescribed tamoxifen (1).

Plasma concentrations of the active tamoxifen metabolite, endoxifen, are associated with the cytochrome P450 (CYP) 2D6 genotype. Endoxifen is thought to play a role in providing protection against breast cancer recurrence. (2,3,4)

Some SSRIs are known to inhibit cytochrome P450 (CYP) 2D6, an enzyme that is important for the metabolism of many drugs, including tamoxifen (2). Venlafaxine, an SNRI, is thought to be a less potent inhibitor as compared to the SSRIs. It has also been noted that the magnitude of decrease in endoxifen concentration was greater in women with the wild-type CYP2D6 genotype than in those with a variant genotype (P=0.03) (5)

Interactions between CYP2D6 polymorphisms and co-administered antidepressants and other drugs that are CYP2D6 inhibitors may be associated with altered tamoxifen activity. Jin Y and colleagues demonstrated that the plasma endoxifen concentration was slightly reduced in women taking venlafaxine, a weak inhibitor of CYP2D6, but reduced substantially in subjects who took paroxetine (a potent inhibitor of CYP2D6) (2).

Binkhorst L et al noted that paroxetine and fluoxetine are associated with the greatest ability to inhibit CYP2D6 activity and significant, up to 66 %, reduced endoxifen plasma concentrations were observed in tamoxifen-treated patients receiving these drugs concomitantly (6).



A quality care initiative program (7) noted that some studies raised concerns about interactions between tamoxifen and antidepressants that inhibit cytochrome P450 2D6 (CYP2D6), reducing the conversion of tamoxifen to the active metabolite endoxifen and, thereby, increasing the risks of recurrence and mortality. However, meta-analyses have suggested that the reductions in endoxifen do not translate into increased breast cancer recurrence rates or mortality rates, possibly because the therapeutic dosing of tamoxifen fully saturates the oestrogen receptor.

Existing recommendations (8) are conservative, cautioning avoidance of potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, high-dose sertraline, bupropion) with tamoxifen. Although these antidepressants are not recommended as first-line agents, clinical judgement can be exercised in their use with patients for whom safer alternatives are not an option, after discussion with the treating oncologist has occurred and informed consent been obtained. More potent CYP2D6 inhibitors may be safer to use in postmenopausal women or women with a known extensive metabolizer CYP2D6 genotype. When possible, it is prudent to prefer antidepressants with low CYP2D6 inhibition (e.g., citalopram/escitalopram, venlafaxine/desvenlafaxine, or mirtazapine) as first-line agents.

Recent critical appraisal of the literature has provided evidence for the value of comprehensive CYP2D6 genotyping panels in guiding treatment decisions for non-metastatic ER-positive breast cancer patients. Based on this information, it is recommended that alternatives to standard tamoxifen treatments are considered in CYP2D6 poor or intermediate metabolizers (9,10). NB: Currently the Trust does not have access to genotyping services

Bottom line: When prescribing an SSRI or SNRI, due consideration needs to be given to this interaction, which may result in lowered tamoxifen efficacy in breast cancer patients.

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Weaning off HRT in breast cancer patients

1. For postmenopausal patients to be prescribed Aromatase Inhibitors

1. Stop HRT, including local ERT
 - NICE NG101 2018 states that HRT may, in exceptional circumstances, be given to women with early stage cancer with severe menopausal symptoms, as long as the woman has been fully informed about the associated risks of HRT.
 - May be acceptable clinical decision for patients on Tamoxifen (anti-oestrogenic activity on breast tissue); not for patients on aromatase inhibitors.
 - Tibolone and progestogens are not recommended to treat menopausal symptoms (Drewe 2015; NICE NG101 2018)
2. Counsel patient about breakthrough vasomotor symptoms. Cross refer for ongoing counselling support (breast cancer specialist nurses, menopause unit specialist nurse; menopause unit counsellor)
3. Evidence base for alternative management strategies weak, but can include acupuncture. NICE NG101 2018 states that soy isoflavones, red clover, black cohosh, vitamin E and magnetic devices are not recommended for treatment of menopausal symptoms
4. For postmenopausal patients, the risk of osteoporosis is higher due to aging and oestrogen deficiency. This risk is further increased in breast cancer patients prescribed aromatase inhibitors. Assess patient for bone sparing therapy (eg. Bisphosphonates) and offer advice on lifestyle interventions
 - Bisphosphonates can be used in breast cancer to prevent and treat osteoporosis or skeletal events, or manage osteolytic lesions, bone pain or hypercalcaemia of malignancy. Bisphosphonates are not licensed for preventing recurrence or improving survival in people with early breast cancer, and use for this indication is off-label (NICE ES15).
5. NICE NG101 2018 / SIGN 2013 recommends that patients with early invasive breast cancer have a baseline DEXA scan if starting adjuvant Aromatase Inhibitor therapy, have treatment induced menopause or are starting ovarian ablation or suppression therapy



6. Both SIGN 2013 and NICE NG101 (2018) provide recommendations for extended endocrine therapy, ie continuation after initial treatment in women with ER positive invasive breast cancer. –see excerpt from NICE guidance below

Extended endocrine therapy (NICE 101 2018)

1.7.6 Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER- positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking Tamoxifen for 2 to 5 years.

1.7.7 Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER- positive invasive breast cancer who are at low risk of disease recurrence and who have been taking Tamoxifen for 2 to 5 years.

1.7.8 Consider extending the duration of Tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer.

2. For patients on HRT, with decision to wean off when diagnosed with breast cancer

1. If Aromatase Inhibitors are prescribed, HRT is stopped immediately
 - But if time allows, wean patient off her HRT slowly prior to starting AIs
2. If Tamoxifen is prescribed, warn patient of its side effects which include vasomotor symptoms such as hot flushes and night sweats.
 - Tamoxifen long duration / extended use is linked with increased risk for thrombosis and endometrial cancer; bone density loss in premenopausal women (NICE NG101 2018)
3. Note that Tamoxifen (SERM action) helps with protection of bone mineral density in postmenopausal women (SIGN 2013; NICE NG101 2018).
4. NICE NG101 2018 states that patients with early invasive breast cancer started on Tamoxifen, regardless of pre-treatment menopause status, do not require a baseline DEXA scan
5. Newly diagnosed breast cancer patients can wean themselves off HRT gradually; but those due to have endocrine surgery to wean themselves off at faster pace.
 - Check oestrogen and progestogen content of HRT regimen that patient is on, use half the doses for a month and then stop. Contact Pharmacist (Women's Health) on Health Professional Link-line 020 8869 2937 for advice on HRT regimens that can be used to gradually wean a patient off HRT and for other medication issues.
6. Breast cancer patients with Tamoxifen side effects, seriously affecting their quality of life, can be cross referred for oncologist reassessment, with view to considering alternatives to Tamoxifen for breast cancer recurrence risk reduction (NICE NG101 2018)



7. Use of HRT for women on Tamoxifen, or those with non hormonal sensitive tumours, could be considered after full discussion of risks and benefits with patient. HRT in these circumstances is not a complete contraindication.
8. Evidence base for alternative management strategies weak; but can include acupuncture.

3. **Use of local oestrogen replacement therapy (ERT)**

1. Vaginal oestrogen therapy can be prescribed for local urogenital symptom relief including vaginal dryness, dyspareunia and lower urinary tract infections.
2. Safe usage of vaginal ERT in breast cancer patients has not been studied within RCTs of long duration
3. Clinical consensus suggests that local ERT can be used and is considered safe as long as high levels of systemic absorption are avoided, but decision should be made in co-ordination with the woman's oncologist for women on AIs.
4. Consider switching from Aromatase Inhibitors to Tamoxifen in severe cases of vaginal atrophy, before decision re use of local oestrogen replacement therapy
5. For patients with tissue tumour studies suggesting oestrogen receptor negative status, could consider Vagifem (10microgram oestradiol vaginal tablets) or the less potent Ovestin or generic oestriol vaginal creams (0.1%, 0.01% oestriol respectively). Vagifem licensed for indefinite use, based on patient's symptoms.
6. Estring, a vaginal oestrogen ring can be used for up-to 2 years without resulting in high sustained systemic absorption warranting co-prescribed progestogen for endometrial protection (Estring SPC; but not tested in breast cancer patients)
7. Consider non hormonal vaginal lubricants or moisturisers as the first line choice, eg. Replens (a bio-adhesive vaginal moisturiser), YES, Sylk etc in patients with vaginal symptoms, especially where local ERT is not acceptable as treatment. NB: KY Jelly is a vaginal lubricant that should be avoided as not effective. Can feel gritty, irritate vaginal tissue and patients may find it to be 'messy'.
8. NB: Newer licensed treatments for symptomatic vulvar vaginal atrophy (VVA) but contra-indicated in breast cancer include
 - a. Ospemifene (SERM, with oestrogen like effect in the vagina, increasing cellular maturation and mucification of vaginal epithelium). Licensed dose 60mg tablet once daily (Senshoi SPC)
 - C/I: suspected breast cancer or active breast cancer treatment
 - Ospemifene could be used for VVA but only after treatment of breast cancer, including adjuvant therapy, has been completed (SPC July 2018]
 - Not on Trust Formulary



- b. Prasterone; this DHEA product is metabolised into oestrogenic compounds (Intrarosa 6.5mg pessary; for treatment of vulvar and vaginal atrophy) .(Intrarosa SPC)
 - C/I: known, past or suspected breast cancer (ema.europa.eu)
 - Not on Trust Formulary

Alternative strategies

- to include lifestyle and self care options

1. Lifestyle management

- Advice has not been tested within rigorous RCT study designs
- Should include weight reduction or maintenance, smoking cessation, caffeine reduction, stress management, both weight bearing and toning exercise, environmental control.

2. Counselling support

- May be dealing with younger patient struggling with sexual dysfunction and body image (Finch et al 2011)
- Important to consider holistic management plan individually tailored to patient need.
- Offer patient personalised, culturally aware, support
- Address realistic expectations
- Include options for psychotherapy and psychosexual therapy (Andersen BL et al; Stanton AL et al.)
- MENOS1 (2012) RCT (n=96) reported reductions in problem rating at 9 weeks (less depressed mood, fewer sleep problems, less anxiety) and 26 weeks (less depressed mood, fewer sleep problems, less bodily pain) comparing CBT with usual care.
- NICE NG23 2015 recommends CBT as an effective option for low mood associated with menopause

3. Alternative therapies

- Examples cited in the literature include reflexology, massage, acupuncture (weak evidence base; survivors of breast cancer who have had axillary surgery should avoid acupuncture to the particular arm), aromatherapy (some caution), hypnotherapy, homeopathy
- Anecdotal evidence but no good robust RCT research
- Advice patient to see a qualified, regulated practitioner



4. **Herbal treatments and food supplements**

- Should not be recommended for use by breast cancer patients on Aromatase Inhibitors
- Caution with use of these supplements in breast cancer patients as all have some oestrogenic activity and safety data for use in these patient groups is not available
- May be safe in breast cancer patients with Stage 1 and 2 receptor negative status
- 3 year RCT study in 401 women with family history of breast cancer, designed to study use of Novogen Red Clover isoflavones (40mg per tablet), reported neutral effect on mammographic breast density (Powles T et al. Menopause Int. 2008)
- Phytoestrogens can form a large part of dietary intake in certain ethnic groups. These patients can be advised to continue with what may be considered to be normal levels of dietary intake, but it is not known if it is safe for breast cancer patients to take supplements of higher doses.
- NICE NG101 2018 states that soy isoflavones, red clover, black cohosh, vitamin E and magnetic devices are not recommended for treatment of menopausal symptoms
- NICE NG23 2015 suggests that women are advised that the quality, purity and constituents of complementary therapies may be unknown
- NICE NG101 2015 recommends that women with a history of or at high risk of breast cancer should be advised that there is some evidence that St John's Wort may be of benefit for vasomotor symptom control, but
 - there is uncertainty about appropriate doses, persistence of effect, variation in the nature and potency of preparations
 - there are some potential serious drug – drug interactions (including tamoxifen, anticoagulants, anticonvulsants and immunosuppressants).

BRCA testing and induced menopause

With the wider use of genetic testing for BRCA1 and BRCA2 gene variants, women are increasingly seeking advice in relation to the use of hormone replacement therapy (HRT) following Risk Reducing Bilateral Salpingo-oophorectomy (RRBSO). In this group of women, RRBSO is usually performed around the age of 40 years. Some women will also undergo risk reducing bilateral mastectomy, others will opt for annual breast surveillance or medical intervention, such as Tamoxifen.

All women who undergo RRBSO will face the effects of surgical menopause, both short term which may include vasomotor symptoms, sleep disturbance and sexual dysfunction as well as potential long term risks of osteoporosis, coronary heart disease and cognitive decline associated with premature menopause (1,2). In addition, they may experience psychological issues surrounding facing the menopause at a young age (3)



Guidance from NICE covers this in two ways. Guidance NG 164 (Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer) explains that women should be given information about the effects of surgical menopause prior to surgery and strategies discussed to reduce symptoms and reduce risk of long term health effects. In the absence of contraindications, women who do not have personal history of breast cancer are advised to use HRT until the average age of menopause (CG 164, 1.71.61). Guidance NG 23 (Menopause diagnosis and management) advises that women about to undergo surgical menopause as a result of cancer or for risk reducing purposes should be referred to a health professional with expertise in menopause (1.3.6)

NB: NICE NG 101(2018) also recommends genetic testing for BRCA1 and BRCA2 variants for women under 50 years with triple-negative breast cancer, including those with no family history of breast or ovarian cancer. The Pan Thames Clinical Genetic Services offer genetic testing for BRCA1 and BRCA2 variants for women with triple negative breast cancer diagnosed under the age of 60 years, as studies have shown that there is at least a 10% chance of identifying a BRCA1 or BRCA2 variant in this patient subgroup.

LNWUHT Recommendations

For women diagnosed with BRCA1 or BRCA2 variant, there should be close multidisciplinary working with breast team, genetics team and menopause team for management of women undergoing RRBSO.

- Referral to the Menopause Clinic prior to surgery useful in order to provide women with information in advance of surgery and to enable them to make an informed decision about the use of HRT if indicated.
- Evidence base for routine recommendation for TAH and BSO is not robust.
 - TAH option may be considered on individualised patient basis, for another indication, with risk benefit evaluation.
- If appropriate, oncology team to consider endometrial sampling with discussion of Mirena option as the progestogenic component of HRT regimen, at time of RRBSO.

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