Treatment Recommendations and Prioritization Planning for Breast Cancer Patients During COVID-19 Pandemic.

Part 1: High Risk Lesions, DCIS And Hormonal Positive Breast Cancer. A Caribbean Breast Surgeon's Perspective.

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ABSTRACT

The ongoing COVID-19 pandemic has presented a challenging approach to breast surgical oncology both internationally and locally. Triage and prioritization are the cornerstones of international recommendations for cancer management during this pandemic. This formidable and unique set of challenges influences the delivery of oncological and supportive care to breast cancer patients. Preservation of hospital resources, reduction in patients' hospital visits and health care provider exposure to infection, result in non-urgent cases being deferred or cancelled. Delay of treatment, both medical or surgical, may influence patients' outcome if not strategically planned and discussed with a multidisciplinary approach.

As physicians, we need to weigh the risk-to-benefit ratio on a case-by-case scenario. Several expert oncology bodies have collaboration in the triaging, prioritizing and treatment processes of breast cancer management. The adaptation and utilization of neoadjuvant therapy is one bridging and mitigating technique heavily implemented during the pandemic.

The existing recommendations will be presented in two articles for ease of interpretation. In this article, the current recommendations for the pandemic response to high-risk lesions, Ductal Carcinoma In-Situ (DCIS) and Hormone Receptor Positive Breast Cancer management are highlighted. Suggestions for regional and national implementation of these guidelines in accordance with local resources and conditions will be outlined.

INTRODUCTION

The World Health Organization declared the COVID-19 infection a pandemic in March 2020. This infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has consigned a tremendous burden on health systems worldwide. Several challenges are identified in the management of breast cancer during the pandemic. Loss of operating theatre time, decreased clinical consultations, reduced patient traffic, increased risk of COVID-19 exposure to staff, reduction in breast cancer screening and imaging,

marked delay in test results are some of the identifiable issues.

Delay of breast cancer management is a main consequence of this pandemic. Prioritization and triaging of breast cancer patients are the general consensus and recommendation from the various international societies—American Society of Breast Surgeons (ASBrS)[1], European Society Medical Oncology (ESMO)[2] and the COVID-19 pandemic breast cancer consortium[3].

Prioritization from the aforementioned international societies generated three (3) categories: A, B and C. "A" category involves the management of urgent and life-threatening scenarios. Surgically, this would involve patients with expanding hematomas and breast abscess drainage in septic patients. Patients with oncological emergencies such as febrile neutropenia, symptomatic pleural effusions, brain metastases and hypercalcemia are all classified as category A and considered the same for medical oncology. Bleeding and painful inoperable local regional disease, progression of disease during Neoadjuvant Chemotherapy (NACT) and symptomatic stage 4 disease are also indications for a category A radiation oncology management.

"B" category involves patients who are not life-threatening cases, but whose delay of treatment should not be deferred until the end of the pandemic. Priority B patients can be delayed for a specified period of time during the pandemic. The decision for sub-classification of category B into B1 (High Priority), B2 (Mid-level Priority) and B3 (Lower Priority) involves a multidisciplinary approach. Patients are discussed with respect to breast pathological factors, comorbidities and management options.

"C" category patients' treatment can be delayed post COVID-19 pandemic, indefinitely, without affecting long-term outcomes. Sub-classification of this category C into C1 (High Priority), C2 (Mid-level Priority) and C3 (Lower Priority) would also be applicable. Benign breast disease and breast reconstruction would also be classified as category C.

The treatment for each breast cancer scenario will also be discussed with regards to Medical Oncology, Surgical Oncology and Radiation Oncology management and prioritization. Availability of services and resources nationally/regionally must be important considerations.

High Risk Lesions/Atypical Lesions/Discordant Biopsies/ Pleomorphic Lobular Carcinoma In Situ

Excision of benign lesions such as fibroadenomas and discordant biopsies that are likely benign would be prioritized as category C. High risk lesions such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia, complex sclerosing lesion, papilloma with atypia and flat epithelial atypia may harbor an invasive component and may upgrade to malignancy. These lesions may be classified as C1 or ultimately upgraded to B3 following a multidisciplinary discussion. Therefore, the pathological findings and imaging should be thoroughly reviewed by the pathologist, surgeon and radiologist.

Core needle biopsy revealing pleomorphic lobular carcinoma in situ may be managed with endocrine therapy during the COVID-19 pandemic. Chemoprevention in ADH and Lobular Carcinoma In-Situ (LCIS) was supported by the National Surgical Adjuvant Breast Project (NSABP) P-1 Trial.[4] 75% reduction in breast cancer development in ADH patients as well as LCIS patients experienced 46% risk reduction after tamoxifen treatment.

Local Breast Surgeon's Opinion

The evaluation and management of new breast lesions would still be considered urgent. However, benign images corroborated with benign clinical features may render an overall benign diagnosis and subsequently a category C classification.

Patients with previously diagnosed benign lesions, locally, would be delayed until after the pandemic. The urgency may be altered or upstaged to category B if suspicious features are clinically reported.

One of the possible negative outcomes of delayed or deferred management is loss to follow-up. This may be circumvented thorough documentation of the appropriate management post-pandemic, as well as telecommunication follow-up consults.

Ductal Carcinoma In Situ (DCIS)

The utilization of neoadjuvant therapy will be significantly implemented in this subgroup of patients. ER+DCIS would be considered C1 and bridged with Neoadjuvant Endocrine Therapy (NAET) for 3 to 6 months. However, if this lesion is associated with a mass that is increasing in size and/or is ER-DCIS, B3 prioritization label for surgical intervention would be considered. This concept of 'De-escalating' treatment of DCIS has always been highly debatable.

Hwang et al, performed a phase 2 single-arm trial of neoadjuvant endocrine therapy in postmenopausal ER+ DCIS women with Letrozole.[5] They reported a significant radiological and histological change post 6 months of therapy; 85% had persistent DCIS, 10% had invasive disease and 15% had complete pathological response after surgical intervention. Several important concepts were derived from this study. There was a possible downgrading of the invasive component since the normal upgrade rate for synchronous invasive carcinoma in resected specimens can be up to 26%.[6] The rate of complete pathological response was also significantly thought-provoking into the benefits of NAET. Letrozole is generally given to postmenopausal patients and tamoxifen to premenopausal patients.

Patients who have completed breast conservation surgical intervention for DCIS, would be considered for omission or delay of radiation Therapy (RT) during the COVID-19 pandemic. Radiation therapy in DCIS has revealed a 50% reduction in Ipsilateral Breast Cancer Recurrence (IBTR). Wapnir et al reviewed the long-term outcomes of NSABP B-17 and B-24 trials and surmised the following: Lumpectomy only Local Recurrence (LR) 19.4% versus Lumpectomy and Radiation LR 8.9% at 15 years of follow -up.[7]

Delay of RT should be no longer than 12 weeks. Several studies have shown that this is associated with an increased risk of IBTR. Shurell et al published an article reviewing the delay of adjuvant radiotherapy for 8weeks, 8-12 weeks and greater than 12 weeks.[8] The risk of IBTR was greatest in the more than 12 weeks groups at 26%.

The omission of RT in DCIS patients was also evaluated in the randomized prospective Radiation Therapy Oncology Group (RTOG) 9804 trial.[9] Low risk DCIS patients were defined as unicentric, low and intermediate histological grade, margins >3mm and size <2.5cm. The IBTR was 0.9% in the RT group and 6.7% in the no RT group. The 12-year follow up study of the RTOG 9804 trial by McCormick et al, revealed the 12-year cumulative incidence of LR was 11.4% for no RT versus 2.8% with RT.[9,10] Therefore, these results support the individualization of DCIS care based on patients classified as low risk on clinical and pathological features.

Local Breast Surgeon's Opinion

The aforementioned recommendations for DCIS can be easily adapted to our breast surgical oncology practice locally and regionally. These tenets of hormonal therapy may be readily available in the public health care system. However, this mindset and approach to neoadjuvant therapy would require routine pathological request of Immunohistochemistry (IHC) on DCIS needle core specimens. This is standard practice for invasive disease but not common for in situ disease.

IHC would categorize DCIS into ER positive or negative. Such classification would facilitate the urgency of management during the COVID-19 Pandemic. DCIS ER positive patients will be candidates for neoadjuvant hormonal therapy, permitting delay of surgical intervention during this pandemic. On the other hand, DCIS ER negative would not benefit from NAET and this translates into a more urgent scenario. Such patients would be classified as category B (3) versus DCIS ER positive category C classification. Therefore, the current scenario would necessitate a subsequent guideline change to offer hormonal therapy for DCIS ER positive and earlier surgery for DCIS ER negative patients.

Hormonal Receptor (HR) Positive Breast Cancer

HR positive breast cancers, otherwise known as the luminal cancers, generally are referred for upfront surgery. However, in the present scenario of COVID-19, the decision-making for neoadjuvant therapy adds an intriguing digression from the commonly utilized standards. The unavailability of operating time means the application of neoadjuvant therapy principles should be

applied to this sub-group of favourable breast cancers.

Patients' Biological risk of tumour response or benefit from NACT would be the 'decision' guide for the therapeutic agent used in the neoadjuvant regimen. High risk biological features suggest a significant response and/or benefit from NACT whilst low risk means the contrary. Operative candidates, patients with low-risk features and T_1-T_3 N_0 HR+, are generally offered surgery. In the present scenario of COVID-19 and limited availability of operative interventions, Neoadjuvant Endocrine Therapy (NAET) is utilized and permits the surgical delay for 6–12 months.

Low risk biological features are early breast cancers, low grade tumours, possible low genomic score, favourable tumours (pure Tubular, papillary, mucinous carcinoma), high ER expression, lobular and Luminal A subtype.

High-risk biological features are locally advanced breast cancer, low ER expression, high grade tumor, high genomic score, unfavourable tumours (metaplastic carcinoma) and premenopausal. These patients are generally considered for NACT.

However, genomic testing can be performed on the needle core specimen to differentiate the low-risk genomic patient from the intermediate and high risk genomic biological group.[11] Low genomic patients are defined by a Recurrence Score (RS) of less than 16 and high genomic patients greater than 26. However, the intermediate group of RS 16 to 26, further subclassified based on the patient's age less than 50 years.[12]

Patients with low and intermediate genomic scores (>50 years) would be treated with NAET for 6-12 months. Conversely, patients with intermediate (<50 years) and high genomic scores would be offered NACT + ET.

This is another consequence and approach that is fully integrated during the Covid-19 pandemic as a necessity. Previously, genomic testing was only performed on the resected specimen. However, in the circumstance of the pandemic, decisions to render treatment without the surgical specimen led to the validation of genomic testing on the core biopsy-yet another pearl unveiled during the current pandemic constraints.

Surgical intervention can be safely delayed with neoadjuvant endocrine therapy for up to 6-12 months. Patients need to be closely monitored and surgical intervention rendered to the high-risk group as soon as it is technically feasible within the COVID-19 challenges. Hormonal therapy is only continued up to two weeks prior to surgical extirpation of the tumour due to the associated increased risk of thromboembolic events.

HR+ breast cancer patients are referred to the radiation oncologist for adjuvant radiotherapy. Deferral of radiation can be performed for several months in the low-risk group. Several trials, such as the *PRIME II Trial* and the CALGB 9343 *Trial*, have identified a subgroup of patients that are low risk and may be considered for avoidance of radiation therapy. The CALGB 9343 trial enrolled patients over the age of 70 years, T_1N_0, ER+, randomized to adjuvant ET (Tamoxifen) with or without RT.[13] The risk of local recurrence was at 2% and 9% for with and without radiation therapy respectively after 12 years of follow-up.

Results from the more recent PRIME II trial also demonstrated similar findings. Patients in this study were 65 years or older with a tumour less than or equal to 3 cm, node negative with clear surgical margins.[14] ET was administered to all patients and patients were randomized to adjuvant radiotherapy or observation. The patients that underwent adjuvant RT demonstrated LR risk of 1.3% versus 4.1% in no RT group, after 5 years. However, both randomized trials did not reveal any difference in the survival rates between both groups.

Local breast Surgeon's Opinion

Early surgery should be offered to patients who are not candidates for NAET or NACT. However, this factor would be dependent on the pandemic's present condition, such patients will be considered Category B. Therefore, surgery cannot be withheld until after the pandemic.

NAET concept may be applicable to Trinidad's population. However, the stratification of HR positive patients into High risk and Low risk via Genomic testing would be unavailable at least in the public sector. This approach has the potential to filter those patients that are not candidates for chemotherapy and those only requiring

NAET. The de-escalation of neoadjuvant therapy NAET versus NACT has several benefits to the Ministry of Health and the patient. Reduction in adjuvant chemotherapy cost per patient found to be low risk, can potentially save the Ministry of Health the financial burden allocated for neoadjuvant or adjuvant chemotherapy. More importantly, patients avoid the toxic side effects of chemotherapy.

Locally, clinicopathological factors determine the need for adjuvant chemotherapy. Ki-67 is another adjunct implemented into this decision-making process. If there is a necessity for adjuvant therapy, the patient should be considered for neoadjuvant therapy. Hence, most HER2 or TNBC patients would be more inclined for neoadjuvant therapy.

High risk clinicopathological featured patients can be offered NACT in our public and private sectors. Low risk clinicopathological features may be conversely offered NAET. Therefore, institutionalisation of this concept can be achieved despite our unavailability of genomic testing.

Identification of the low-risk patients that can avoid adjuvant radiotherapy would have a positive impact on our overburdened radiation service in the public sector. Strict application of the defined low risk features would be required. These decisions would be thoroughly analysed in the breast surgical oncology MDT.

Figure 1: Pre-pandemic breast cancer subtype management.

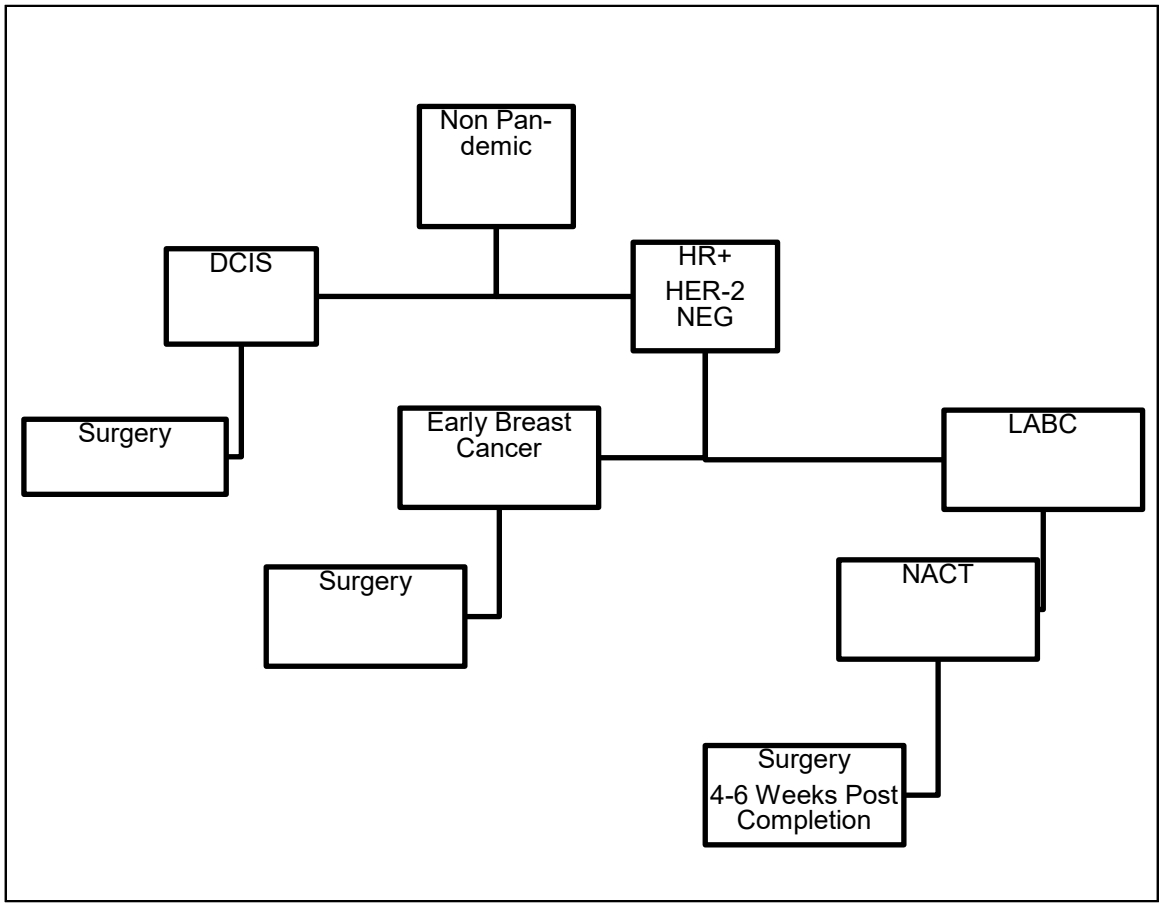
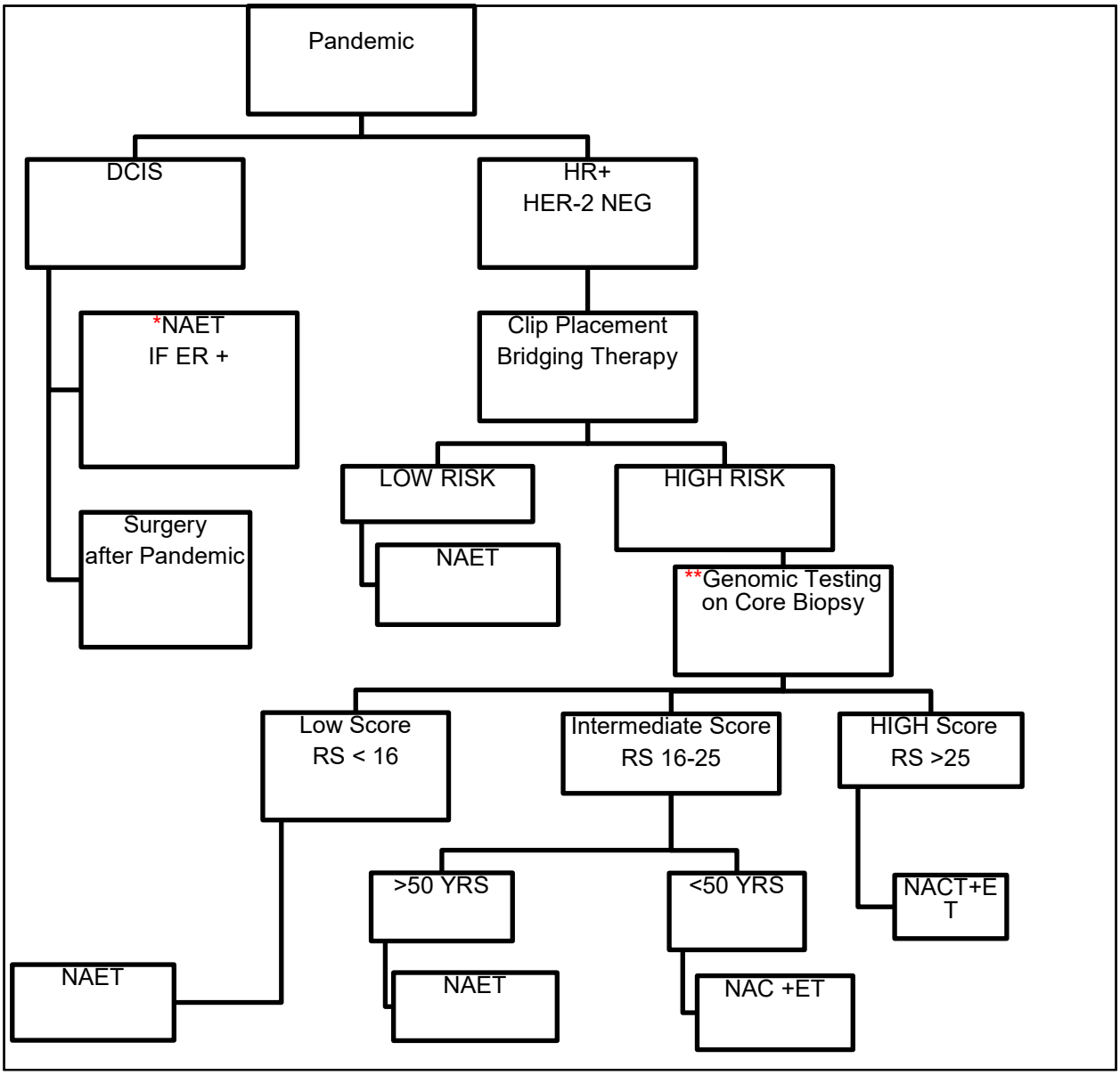


Figure 2: Changes in the management of the various breast cancer subtypes during the COVID-19 pandemic.



**Utilization of Neoadjuvant Endocrine Therapy*

***Utilization of Needle Core Sample for Genomic Testing*

CONCLUSION

The above-mentioned Part 1 recommendations represent the current approaches for high risk lesions, DCIS and Hormonal receptor positive breast cancer. This rational approach would facilitate a clear continuum of ideal breast cancer management without negatively impacting patients' outcomes. The miasma of this pandemic requires a thorough evaluation of current guidelines as the present predicament of COVID-19 continuously evolves.

Part 2 recommendations for breast cancer care during the COVID-19 pandemic would be a sequenced prolongation for Triple Negative, HER-2 positive and Metastatic breast cancer management. General considerations and implementation along with implications will be discussed in the subsequent article.

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