Archives of Surgical Research | Critical Review

Emerging Trends in Managing Central Breast DCIS in Era of Oncoplastic Surgery: Where Do We Stand?

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IMPORTANCE The management of DCIS in today's era of rapid surgical advances is improving dramatically with time. Mastectomy rates have rapidly declined as breast diseases are being diagnosed at an earlier stage through screening procedures like mammograms and increased awareness regarding breast cancer. Oncoplastic surgical techniques have revolutionized this field by providing numerous options to deal with breast cancer while preserving the breast. Advances in the field of radiation and endocrine therapy have also translated into improved treatment algorithms with acceptable morbidity and recurrence rates. This analysis, thus, provides an overview of recent advances in the management of DCIS in light of a typical central DCIS lesion scenario and envisages evolving role of oncoplastic breast surgery in this regard.

KEYWORDS Oncoplastic Breast Surgery; Breast Reconstruction; DCIS

HOW TO CITE: Ahmed AS, Ahmed SZ, Ahmed M, Waseem T. Emerging Trends in Managing Central Breast DCIS in Era of Oncoplastic Surgery: Where Do We Stand? *Archives of Surgical Research*. 2020;1(1):44-51.https://doi.org/10.48111/2020.01.07

Critical Review

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https://doi.org/10.48111/2020.01.07

Management of Ductal Carcinoma in Situ (DCIS) is consistently evolving with our improving understanding in cancer biology[1, 2]. More management options are now available for breast conservation as plastic surgery intrudes into the field of breast surgery. These options range from wide local excision to bilateral mastectomies with or without breast reconstruction[3]. Endocrine therapy, however, remains instrumental for reducing recurrence and chemo-prophylaxis. Newer radiation therapy techniques are being tested to de-escalate the use of radiation depending upon the character of the tumor. Various oncoplastic techniques are currently available which have considerably better aesthetic outcome and are replacing treatment options for cases where, in the past, radical treatment was the only choice available. In this writing, we would be summarizing these advances in the management of DCIS, where oncoplastic breast surgery is done and would come up with a treatment plan for the scenario shown along[1].

DUCTAL CARCINOMA IN SITU (DCIS)

In US alone, 60,000 women are diagnosed with DCIS annually by screening mammogram[1]. It is recommended for the women to have annual mammogram starting from the age of 45 up to 55 with an option to start screening at the age of 40[1].

CASE SCENARIO

A 52-year-old factory worker is recalled following routine breast screening. She has well-controlled type 2 diabetes but has gained significant amount of weight since she had quit smoking. She has pain at the back of chest which she attributes to her increased breast size. There is no family history of breast cancer. Mammogram showed micro-calcification in the central right breast covering an area of 35mm, and extending to area within 5mm of the NAC. Ultrasound of the breast and axilla appeared normal. 14g core biopsies showed intermediate grade DCIS. The lady is keen to preserve her breast and NAC and achieve immediate symmetry. Please provide a comprehensive management plan for this case, including a discussion of the following issues. Management options including surgery, clinical trials, endocrine therapy, most appropriate surgical option, consent process, surveillance and follow-up, PROMS and medico-legal factors. Your plan should refer and critique relevant evidences and guidelines. You are encouraged to cite relevant examples from your own clinical practice to support your response.

The above mentioned is a typical case of DCIS which has been diagnosed on a screening mammogram. Mammogram is the most common investigation to diagnose a case of DCIS. It is an important investigation especially for cases of impalpable DCIS. Pleomorphic calcification is the pathognomonic feature for diagnosis of DCIS. It can also show multicentric and multifocal lesions. Recently, however, it has been recommended to have an MRI, as it is considered to be a more sensitive investigation to pick DCIS than mammogram[4, 5].

DCIS is a complex disease for which management needs collaboration among all available specialties; namely surgery, oncology, radiology, pathology and plastic surgery[6]. To balance the risks of disease and to avoid overtreatment, it remains imperative to head for a personalized treatment approach in a multidisciplinary setting[1]. This case again shows the value of multidisciplinary meeting.

Management Options for Breast & Axilla

36% of the patients with DCIS develop invasive disease at a later stage, hence no treatment is not an option[1]. Most of the centers argue in favor of surgical resection. Recently, LORIS, LORD and COMET trials have started with the intent to offer observation alone for the patients who have small low-grade DCIS[2]. The results would follow after few years. Since our patient has intermediate grade DCIS with size 3.5 cm, it would be inappropriate to enroll her into this trial and surgical resection would remain the mainstay of the treatment in this particular case.

For the cases of diffuse and multifocal DCIS, bilateral mastectomy has been advocated as it has low recurrence rates[7, 8]. Patients have an option of choosing mastectomy over the breast conservation surgery either for the fear of cancer or to avoid radiation. Traditionally, 10-year survival associated with mastectomies is 98% vs 81% for the breast conservation surgeries[1]. With the developing techniques, skin-sparing and nipple-sparing mastectomies are also available for the patients with 5.6% recurrence rate over a period of 5 years[9, 10]. Similarly, preservation of nipple also adds to recurrence rate making it 11.6% over a period of 5 years. However, it must be explained to the patients that skin-sparing and nipple-sparing mastectomies are associated with higher complication rate in up to 29% cases. In addition, the preserved nipple may be lost due to de-vascularization in 7.8% cases[11, 12].

25% of mastectomies done for DCIS show foci of invasive disease, demonstrating the reliability of mastectomy in terms of disease clearance[13]. For all mastectomies done for DCIS, SLNB should be performed because SLNB at a later time following mastectomy is not possible due to changes in lymphatic architecture.

Clinical Reasoning for Scenario

It would be especially important to have MRI done for this particular case to rule out multifocality and multicentricity where we have a plan to conserve the breast. Stereotactic biopsy and wire localization remain important when we have to perform the oncoplastic surgery. Other modality would be the use of radio-seeds which has shown to be associated with operative ease at the time of resection. It would be important to know the exact location of the micro-calcifications and distance and depth of the lesion from the NAC. By looking at the mammogram alone, it appears to be located in the lower deep central location. It is important to do MRI of both breasts as well as to exclude multifocality and multicentricity when we have planned for conservation of breast.

Trucut biopsy apart from diagnosing a case of DCIS preferably should include information regarding type of DCIS, Ki Index and status of the immunostaining with ER, PR and HER-2/neu receptors.

Large breast size by looking at pictures is likely in line with Grade III ptosis which would also be important part of the oncoplastic technique to be used for breast reconstruction.

Genetic counseling is recommended for the patients who have strong family history of the breast, ovarian or prostate cancer. The genetic screening should include many potential mutations including BRCA1/2. Since there is no strong family history in this particular case, there is no need to perform genetic screening per se.

It would be important to find the cause of the backache for which MRI of the spine and Bone Scan is appropriate initial investigations along with DEXA Scan. It would rule out spinal metastasis, osteoporosis or any impending spinal fracture. She might require an Orthopedics consultation at this stage too.

Planned weight reduction and control of diabetes should be ensured pre-operatively.

Since this patient does not have a strong family history and patient has opted for a breast conserving surgery, bilateral mastectomy is ruled out.

ONCOPLASTIC SURGERY OPTIONS

Therapeutic mammoplasty has extended the role of breast conserving surgeries by incorporating the principles of reduction mammoplasty and radiation therapy. The long-term oncological safety of oncoplastic techniques has been

accepted and are henceforth rapidly replacing the traditional treatment algorithms. There are number of mammoplasty techniques available in the armamentarium of an oncoplastic surgeon, which can be adapted according to the location and size of the tumor. For the larger breasts volume displacement techniques are used and for the smaller breasts volume replacements in the form of flaps has been advocated. These techniques not only improve the oncological safety but also improve the psychological and aesthetic well-being of the patients[14, 15].

Nottingham approach as described by Steve McCulley is considered a widely utilized methodology for catering the oncoplastic resection, although many other techniques can also be used as described by Clough et al[16, 17]. It is also widely accepted that Wise pattern incisions provide the best cosmetic outcome. Therapeutic mammoplasty hinges on the notion that patient has large breasts and the lesion usually lies within the Wise-pattern incision line (Scenario A as described by McCulley et al[16]. Although the lesions outside the Wise pattern incision can also be entertained with medial or lateral pedicles (Scenario B as described by McCulley et al) [16]. Patients with large volume breasts preferably C, D and E cup size with grade III and IV ptosis would be ideal candidates.

Like reduction mammoplasty, there are certain risk factors associated with failure or poor cosmetic outcome which include high BMI, smoking and very large breasts with grade IV & V ptosis. These factors need to be considered carefully and preferably need to be optimized prior to any surgical intervention. The complications, however, are less as compared to implant-based or flap based autologous reconstruction. Pre-operatively it remains imperative to rule out multifocality and multicentricity of the disease by mammogram or preferably MRI[14].

When the margins are in doubt, it would be appropriate to perform a WLE followed by an oncoplastic procedure at a later date when the patient is disease free.

For descriptive purposes, McCulley et al divided the breast into nine zones (Fig. 1)[16]. Mammoplasty incisions are the basis of the markings of these nine zones. Infra-mammary fold (IMF) is considered an important landmark to provide the markings for the future nipple areolar complex (NAC) area. Please refer to the markings in the figure 1 for Wise pattern markings. Zone II, III and IV are easily handled by the wise pattern technique. Zone I can either be handled separately if lesion is quite superficial and adherent to NAC or within the same above markings as Zones II, III and IV. Zones V and VI can be handled by lateral and medial pedicles. Zone VII, VIII and IX are the most difficult to be managed by Wise pattern incisions. Batwing, round block excisions, lateral and medial mammoplasty may instead be used for these difficult locations.

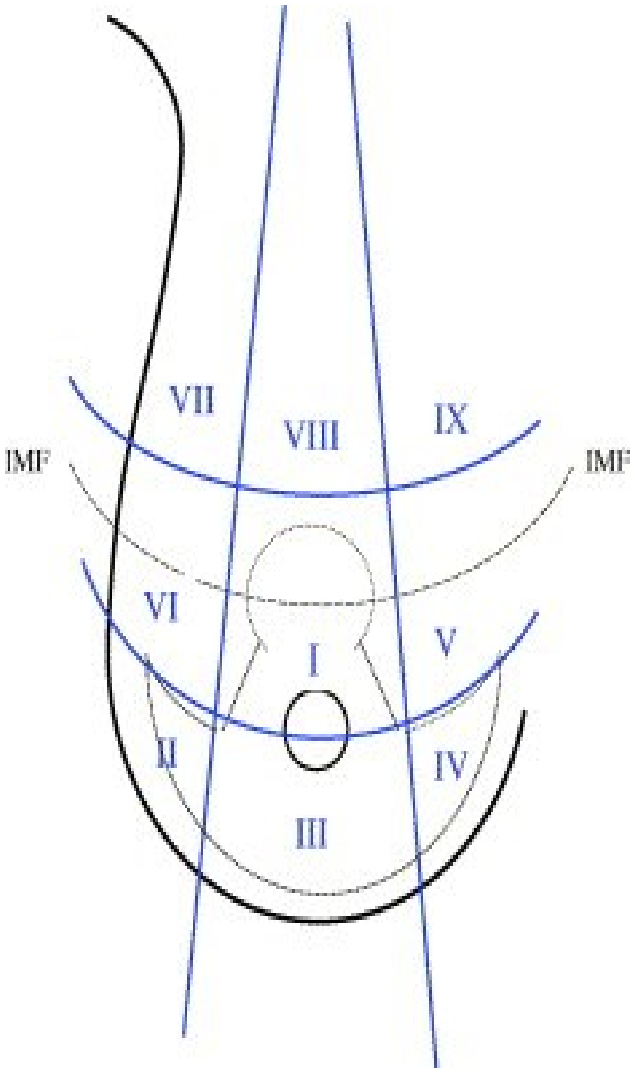


Figure 1
Zones of the breast for oncoplastic resection as proposed by McCulley et al[16].

McCulley has provided us with the table shown below to choose the location of the lesion and their respective incisions and pedicles. (Table 1)[16].

It is very important to differentially and accurately localize the exact position, size and dimensions of the lesion and its relationship with NAC. For this very purpose, mammogram and MRI are the best modalities. If the NAC is not involved then the patient would typically fit into Scenario A described by McCulley[16]. If the NAC is involved then it would be likely to scarify the NAC and follow the Scenario 3 for Zone I.

Table 1: Common options for planning therapeutic mammoplasty (adopted from McCulley et al) [16]

Common options for planning therapeutic mammoplasty							
	Scenario	**Common pedicle**	**Alternative pedicle**	**Common skin pattern**	**Alternative skin pattern**	**Ease to fill defect by extending pedicle**	**Ease to fill defect by secondary pedicle**
Zone I	A or B	Inferior	Medial	Wise	N/A	N/A	
Lateral	Vertical						
Zone II	A	Superior	Medial	Wise	Vertical	N/A	N/A
Sup/medial	Lateral						
Zone III	A	Superior	Medial	Wise	N/A	N/A	
Sup/medial	Lateral	Vertical					
Zone IV	A	Superior	Medial	Wise	Vertical	N/A	N/A
Sup/medial	Lateral						
Zone V	B	Sup/lateral	Inferior	Wise	Vertical	Fair	Fair
Lateral	Superior						
Zone VI	B	Sup/medial	Inferior	Wise	Vertical	Excellent	Good
Medial	Superior						
Zone VII	B	Sup/medial	Inferior	Wise	Vertical	Good	Fair
Medial	Superior						
Zone VIII	B	Inferior	Medial	Wise	Excellent	Fair	
Lateral	Vertical						
Zone IX	B	Sup/lateral	Inferior	Wise	Vertical	Fair	Fair
Lateral	Superior						

Scenario A—tumor lies within Wise pattern incision

The tumors within level I to IV can be easily handled with Scenario A provided they do not involve the NAC. Typically, this is the most feasible and cosmetically acceptable scenario for the lower tumors. Figure 2 describes the incisions and the resection pattern for the lesions involving the lower breast.

Pedicle orientation is decided by the position of tumor. Most of the Zone II-IV tumors are dealt with superior or superomedial pedicle. For the Zone 1 tumors, the pedicle can be drawn from anywhere depending on the location of tumor to avoid positive margins. The choice of Wise Pattern Incision depends both on the location of tumor and the size of the breast. For example, the central breast tumors and inferior Zone III tumors not involving NAC can be easily adapted in vertical Wise pattern incision. For larger breasts with grade III ptosis, it would be more appropriate to take the formal Wise pattern with excision of the lower zones as done in reduction mammoplasty.

As suggested previously, size and site of the tumor is of prime importance in deciding the markings of the incision. The tumor which are lying within Zone I-IV are easily dealt through the traditional markings, however the Scenario B cases can be dealt by carefully dissecting the tumors ensuring clear and negative margins through palpation of the normal and abnormal tissue. Undermining of the skin is also required in cases where the tumor lies outside the resection markings. In those cases, markers can be placed to predict the future recurrence. Specimen radiology can also be used to accurately document if excision is complete or incomplete. Superior, superomedial or superolateral pedicles can be used for the scenario A cases.

Central tumors (zone I) requiring removal of NAC

There are two important approaches to deal with such lesions but each depends on requirements or availability of the zones I-IV for excision. To give an example, if the tumor is involving the central zone and the patient has large breasts and can afford excision of the lower zones; then simple inverted T incision as in Wise pattern or Goldilocks' mastectomy can be used. As such an incision is suitable for tumors where NAC has to be sacrificed[16].

On the other hand, if the breast size is small and lower zones are not available for the resection, Grissoti's flap may be the right choice as it not only avoids the excision of the lower zones but also only targets the central zone and displacement of the inferior portion of the breast into the central zone[14].

Alternative to therapeutic mammoplasty is mastectomy with immediate or delayed reconstruction[10]. This approach is more likely to avoid radiotherapy and is likely to be associated with either implant based or autologous reconstruction[18]. The cosmetic outcome and complications of therapeutic mammoplasty are similar to reduction mammoplasty and are superior to complete reconstruction in terms of lower morbidity and nipple-related complications[19, 20].

The patient needs WLE/ Oncoplastic Resection depending on the location of the tumor with at least 2mm healthy margin as suggested by ASCO and ASTRO[21, 22].

The radial distance and depth of the area of calcification to the NAC and its size would dictate about the possible survival of the NAC. Considering the large breast and grade III ptosis, the tumor resection may be incorporated within the Wise Pattern or Nottingham approaches. Consequently,

if the nipple is not definitely involved by NAC, it may be used as a flap or a free graft depending on the location.

As it appears from the provided mammogram that DCIS lay quite deep in central lower portion, it may be feasible to save NAC in medial or lateral pedicle. If per-operatively NAC is found quite close to tumor, it would be wise to go for either NAC construction through free nipple grafting immediately or at a later stage. However, SLNB is not recommended in cases of low or intermediate grade DCIS with normal axillary ultrasound.

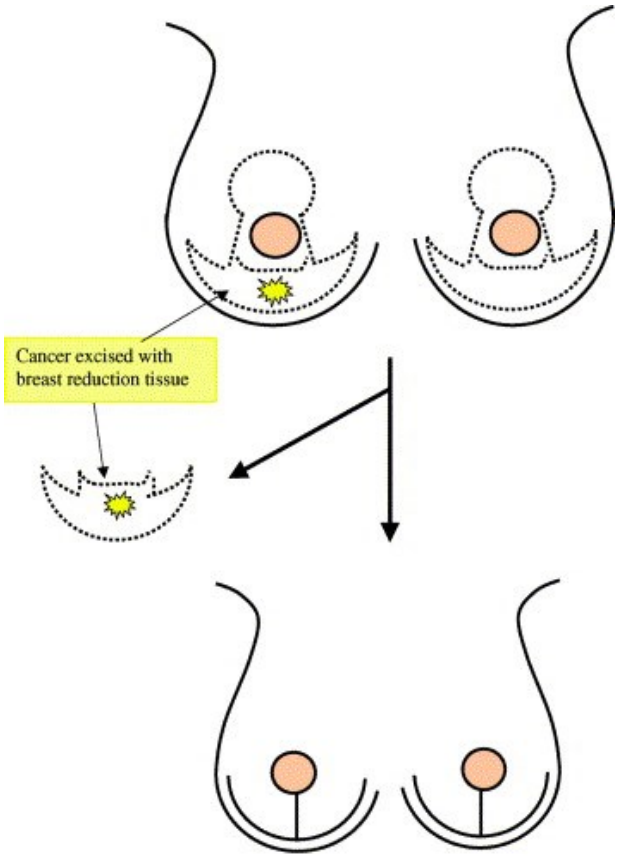


Figure 2
Incisions and the resection pattern for the lesions involving the lower breast[16]. (Courtesy: McCulley et al)

The figures below show two possible surgical options for this particular patient [16]:

Consent Process

The process of taking consent should include the information regarding the failure of flap, repeating the surgery if required, take-backs and the possible complications associated with the flaps. The modalities that would result in case of failure should especially be explained like thrombosis, infection and loss rates[20, 1].

Adjuvant Therapy

Adjuvant therapy can influence the outcomes of the reconstruction and overall treatment. The need to pre-operatively assess if adjuvant radiation therapy is needed or not is extremely significant, so that the reconstructed breast suffers the least[1].

Radiation therapy has traditionally been an essential component of the breast conserving surgery or oncoplastic resection even in cases of the DCIS in adjuvant setting, in the past. Whole Breast Radiation Therapy (WBRT) is the standard of care in most centers all over the world. At least five randomized trials have proven the efficacy of external beam radiation therapy in reducing recurrence rates following lumpectomy[23, 24, 25, 26, 27]. In a meta-analysis, addition of WBRT reduced the recurrence rates from 28.1% to 12.9% in 10 years without effecting the overall survival[28]. The most common dose of radiation used is 5000cGy delivered Monday through Friday with daily fractions of 200cGy spread over the 5 weeks. In a Canadian study however, hypo-fractionation has been postulated with 4250cGy in 16 fractions spread over 3 weeks with similar results[22]. Thus, 2018 ASTRO guidelines recommend hypo-fractionation. The role of external beam boost in lumpectomy bed is strongly considered for the positive and ER negative high grade tumors[29]. Recent advances in Intensity Modulated Radiation Therapy (IMRT) and Deep Inspiratory Breath Hold can dramatically reduce the toxicity of radiation to the surrounding structures[30, 31, 32, 33]. ASTRO also recommends Partial Breast Radiation Therapy (PBRT) for low grade unifocal up to 2.5 cm lesions of DCIS but is still not a standard practice. Radiation may be omitted in low grade small unifocal tumors as described in ECOG 5194 trial[34]. This forms the basis of LORIS and COMET Trials. Based on Oncotype Dx and gene analysis, low grade tumors may be identified and stratified for radiation regimen likely to be effective[35].

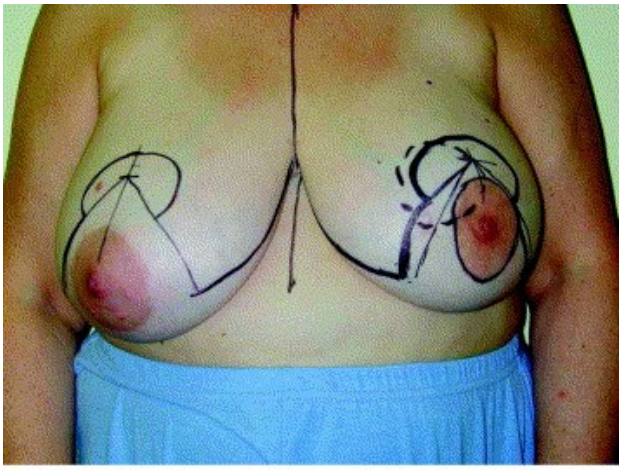
Endocrine therapy remains standard for the ER positive tumors. The NSABP B-24 trial randomized patients to 5 years of Tamoxifen, 20 mg daily, or placebo following lumpectomy and radiation and reduced the ipsilateral breast cancer by 32% which equates to the 7.3% risk of cancer in normal contralateral breast over a period of 15 years[36, 37]. This trial showed that tamoxifen reduced the incidence of invasive cancers in the ipsilateral breast by 32% compared to those who had lumpectomy and radiation alone. At 15 years, the rate for ipsilateral invasive recurrences for those who received tamoxifen was only 8.5%. This was very similar to the rate for a contralateral breast cancer event i.e 7.3%. NSABP-35 also shows aromatase inhibitors to be effective for such patients under the age of 60 years[38]. Targeting of HER2/neu is currently under investigation in NSABP-43 trial[39].

In this particular case, whole breast radiation WBRT or IMRT is recommended. Hypo-fractionation based on the Canadian study is also recommended. IOBRT may be considered in case of threatened margins. Partial Breast Radiation Therapy (PBRT) does not appear to be appropriate for a 3.5 cm lesion[22].

If ER positive should have Tamoxifen vs. Aromatase inhibitor for 5 years with Her 2 neu being positive, patient should be considered for enrolment in any trial like NSABP-43 if available. Lesion does not appear to be appropriate for enrolment in LORIS, LORD or COMET trial[1].

Surveillance and Follow-up

National guidelines argue for follow up to be 6-12 monthly for 5 years if patient undergoes oncoplastic resection and then yearly by mammogram till 65 years of age. New lesions have to be biopsied and treated appropriately if found to have DCIS or invasive breast cancer. For patients who commence the aromatase inhibitors should have baseline DEXA scan. Supplemental calcium and Vitamin D apart from the weight bearing exercises remain an appropriate part of the management. Bisphosphonate therapy may be the answer to the developing osteopenia. Risk of stroke and DVT should be communicated to the patient taking Tamoxifen. If



the patients taking Tamoxifen develop vaginal bleed then U/S and adjuvant pelvic work up may be required.

PROMS

Breast-Q has importance in familiarizing the outcomes of the breast undergoing oncoplastic resection and they should be incorporated into surgical practice[40]. Recently, BCCT.core has also emerged as a tool for the assessment of aesthetic value of these techniques.

Medico-legal Factors

Patient education remains pivotal about the breast conservation, radiotherapy, endocrine therapy and complications associated with oncoplastic resection. Future recurrence, need for surgery, mastectomy, failure of the oncoplastic resection, loss of nipple and sensation around the nipple, seroma formation, and hemorrhage should all be clearly communicated.

Future Directions of Treatment for DCIS

There are many options available for the patients with DCIS now, which conform to our modern understanding of tumor

pathology. Now breast conservation coupled with oncoplastic techniques and radiation therapy is producing almost equivalent outcomes in terms of oncological control and aesthetic outcome. Mastectomy with immediate reconstruction is the alternative option for the patients with high risk, multifocal, diffused disease associated with significant family history. Oncotype DX can provide an additional molecular insight into the aggression of the tumor to help in individualizing the treatment options[41]. For low grade tumors, observation alone is being tested in LORIS, LORD and COMET trials. Efficacy of Trastuzumab is being tested for HER2/neu positive DCIS through NSABP-43 trial[39].

ARTICLE INFORMATION

Accepted for Publication: February 21, 2020 Published Online: March 30, 2020.
https://doi.org/10.48111/2020.01.07

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Financial Support and Sponsorship: Nil.

Conflicts of Interest: There are no conflicts of interest

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