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"I Am a Breast Cancer Champion"

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I vividly remember the day this young vivacious Ms Shilpa (name changed to conceal the identity of the patient) walked in to my OPD in the month of June 2017. This bright eyed, petite, 25-year-old engineer came to me holding the hand of her fiancé. She had been supporting her parents and younger siblings with her income. She belonged to a small town in one of the North-East states of India and he to Gujarat. They met each other while working in a start-up company in Delhi. They were planning to get engaged soon. She had noticed a small lump in left breast and wanted to get it removed before her engagement. During the conversation she mentioned that her maternal grandmother and one of her maternal aunts died of breast cancer at young age and for this reason the lump which she noticed was bothering her.

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She had previously shown herself to someone else and had undergone an ultrasound scan of the breasts done before coming to me. It was reported as a fibroadenoma, BIRADS 3 on left side. During clinical examination, a small 1 cm firm lump could be felt in the upper outer quadrant of her left breast. No other abnormality was found in clinical examination. Clinically as well it could have easily been dismissed as a fibroadenoma. She insisted that she wanted to get the lump removed. However, considering her family history, she was advised a repeat ultrasound scan and a core needle biopsy of the lump. As the luck would have it, it tuned out to be a triple negative breast cancer. With this report, her entire future planning had to be put on immediate hold. Although axillary nodes were not enlarged, FNAC of the ipsilateral node came out as positive.

Considering her young age at the onset of the disease, triple negative histology and family history, she was advised genetic counselling and testing and was referred to the Medical Oncology team for consideration of neoadjuvant chemotherapy. Her parents and her would be in laws came down to Delhi. Her parents had not received any formal education and were reluctant for any further tests. She refused to undergo genetic testing because her parents felt that her siblings will be stigmatised if she tests positive.

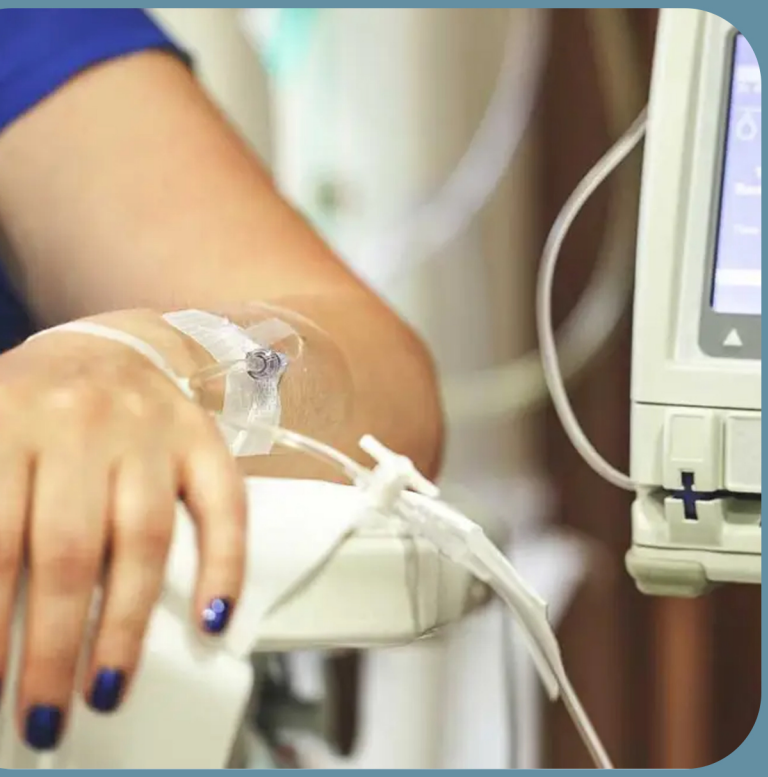
They wanted to start her treatment urgently. They were counselled regarding the impact of chemotherapy on ovarian function and fertility preservation options. Her fiancé's parents were very much concerned about her prognosis and advised him to forget her. But this young man had his head firmly on his shoulders. He expressed his determination to hold her hand all throughout. From here, during her entire forward journey, her fiancé was constantly present by her side. He

She received 4 DD AC + 4 T regimen of NACT with GNRH analogue injection. There was excellent clinical as well as metabolic response after completion of chemotherapy. She underwent oncoplastic breast conservation surgery with perforator flap based partial breast reconstruction. There was partial pathological response. At that time results of OlympiA trial were not published. She received oral capecitabine for 8 cycles (2 weeks on- one week off) after completion of adjuvant radiation. All throughout her treatment she continued to work because she had to provide funds for her treatment.

I used to see her with laptop on in chemotherapy day care. She had been so full of life and was looking forward to a bright future after completing her treatment. Her parents could not support her financially but between her fiancé and her savings they managed. Her friends and seniors at her work place became her family and took turns to be with her during each hospitalization episodes. After completion of treatment, she was very regular with follow up. She joined our breast cancer support group and was always there to hand hold all newly diagnosed patients. Things had started looking all rosy for her now. She requested to get her venous port out. In 2019, two years later she got married. She invited all the hospital staff who cared for her during her treatment. She was now a team leader in her software company and was happily settling in matrimony.

Few months after the wedding she called me on a Sunday morning and insisted on seeing me that day itself. Sensing the urgency in her tone, I agreed to see her at my home itself. As fate would have it, she had developed a suspicious lump in the other breast. After investigations, this time

she looked devastated. Thankfully it was again a localised disease. She agreed to get genetic testing done. We were not surprised to learn the result. She was a carrier of pathogenic BRCA 1 mutation.



She was advised to start the treatment with chemotherapy again. This time she received Paclitaxel + Carboplatin. By now she had resigned to her fate. She would joke around saying that now I am the Angelina Jolie of my family, but during this part of her treatment, she would lapse into severe bouts of depression and needed multiple sessions of counselling. Time and again she would cry out and ask “why me”. Her parents were away in her native place looking after her siblings. They were not in a position to support her financially and were worried about their future. This time again her loving husband stood as a pillar of strength for her. He along with his colleagues organized funds for her treatment by crowd-funding. Gradually she perked up despite suffering from significant treatment related aftereffects. After completing chemotherapy again, she was advised surgery. Shilpa and her husband opted for bilateral mastectomy. She kept on insisting for bilateral salpingo-oophorectomy. But since she was too young, she was advised to wait for few more years. Surgery was followed by radiation once again. They somehow managed to raise funds for adjuvant Olaparib.

By the age of 28, she had seen it all, lost both breasts, dealt with multiple chemotherapy sessions, capecitabine, radiation to both sides of chest wall and Olaparib. She was completely drained physically, emotionally and financially, too. However, despite dealing with two cancers at such a young age, her spirit was indomitable. She bounced back and resumed her work. With aches and pains here and there, hot flashes, mood swings, neuropathy related issues, she has gallantly moved on in her life. She is married and has a loving partner but the joys of married life have been taken away from the couple by the disease. She attends her follow up visits regularly. Most of the times she is successful in hiding her inner turmoil behind the façade of her bubbly demeanour.

In the most recent visit, what she said really caught me off guard. She said “Ma’am your Angelina Jolie is looking at death every day. I go to bed every night with a fear that the next day will bring something worse in my body. I am thankful for each day god grants me but I can not plan anything for future. I wish to be a mother; I wish to adopt but what if I am not there for that child tomorrow?

I have no answers to this.

6 May 2023 DBOG CME Gurugram

On Saturday the 6th of May, nearly 35 oncologists- medical, surgical and radiation oncologist along with nuclear medicine specialists, pain and palliative specialists and pathologists attended the DBOG event - " Less is more " - Nuances of newer Breast Cancer treatments, organized by Dr Mansi Chowhan at Doubletree Hilton, Gurgaon.

The event started with a welcome note by Dr Vinay Samuel Gaikwad, Director-surgical oncology, who greeted the specialists from various departments working for a common goal of precision oncology for our Breast Cancer patients. This was followed by an academic feast of talks and panel discussions. Dr Amal Roy Choudhary/Dr Sakshi presented an elaborate talk on the evolution of hypo-fractionation and the rationale of latest fast forward trial. Following this, Dr Bhuvan Chugh presented the evidences of neo-adjuvant endocrine therapy and shared his valuable experience about the subject. Dr Mansi Chowhan then presented the challenges of breast oncoplasty, covering tricky aspects of planning to impact of adjuvant RT on oncoplastic reconstruction and extreme oncoplasty. Panel discussion on concerns of treating Triple negative breast cancer was moderated by Dr Vikas Choudhary, emphasizing on real-life scenarios in clinical practice. Vote of thanks, on behalf of DBOG was given by Dr Kuldeep Sharma. The event focused on how more conservative approach towards this disease is actually helping us to deliver more to the patient, was well-attended by senior dignitaries and residents of oncology.

Positive trial: Hope for young breast cancer survivors!

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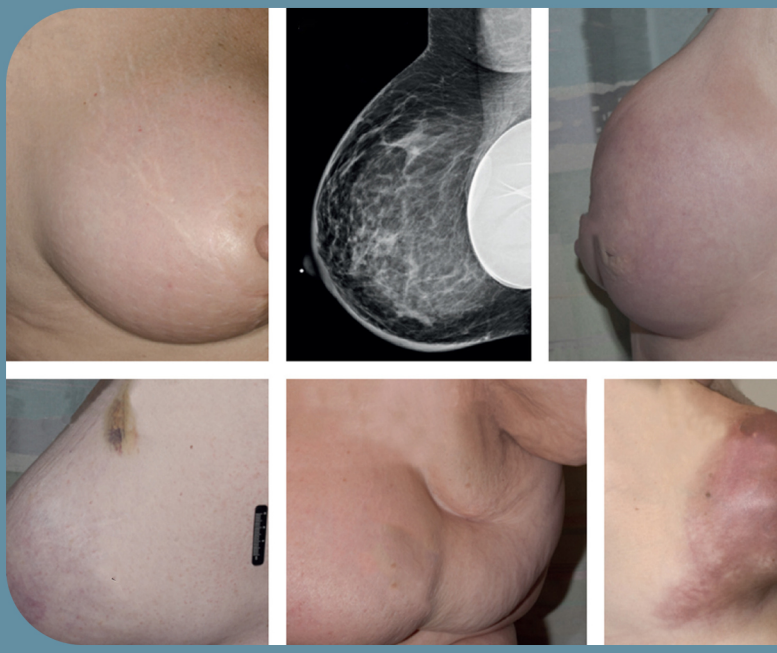
Breast cancer accounts for 30% of all the cancers among young women (15-39 years), making it the most common cancer in this age group. Many of these younger patients have not completed their family at the time of diagnosis and the therapeutic interventions of breast cancer might have an unfavourable impact on the fertility potential. These hormone positive young patients are candidates of 5-10 years of endocrine therapy (ET) during which pregnancy is contraindicated and the reproductive function will further decline with age. However, a selected group of young women with early stage, hormone receptor positive tumors have excellent long-term outcomes and an attempt has been made to allow these women to conceive by interrupting the endocrine therapy.

One such trial is POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer) trial which is a prospective single arm study evaluating the risk of recurrence associated with temporary interruption of endocrine therapy to attempt conception. This study enrolled >500 patients who were ≤ 42 years, stage I-III, HR +ve breast cancer, who have completed 18-30 months of endocrine therapy and desired to temporarily discontinue therapy to attempt pregnancy. This study allowed up to 2 years interruption of ET to attempt pregnancy after a 3 months of ET washout period. After that, endocrine therapy was restarted to complete 5-10 years of treatment. The primary end point of this study was breast cancer free interval. 517 patients from 20 different countries were enrolled from Dec 2014- Dec 2019. Median age of the patients was 37 years, 74.9% of the women had no children at the time of enrolment and 51.5% of the women underwent fertility preservation strategies.

A data safety monitoring committee conducted three interim safety analyses allowing early stoppage of the trial if incidence of breast cancer was higher than anticipated (46). At a median follow-up of 41 months, 44 patients had a recurrence of breast cancer. The 3 years recurrent rates (8.9%) were similar to external control cohort (9.2%). Of the 497 patients followed for pregnancy status, 74% (368) had at least one pregnancy and 63.8% (317) had at least one live birth. The authors found that the fertility rates were comparable to general public. The participants were strongly recommended to resume their ET following the pregnancy attempts.

This study concluded that young breast cancer patients who interrupted endocrine therapy to pursue pregnancy did not have inferior oncological outcomes and most had successful pregnancy related outcomes.

This study provides a hope to a favourable subset of young breast cancer survivors who have not completed their families and are desirous of future fertility. Further follow up of the study participants is essential to assess the long-term outcomes in these patients as hormone receptor positive cancers are known to have late recurrences. Although, the results of this trial are encouraging, it is important to have a case-based risk assessment and a multidisciplinary tumour board discussion before subjecting any patient for this approach. Is it the right time for a hormone receptor patient to become UPT positive? Only time will be able to answer.



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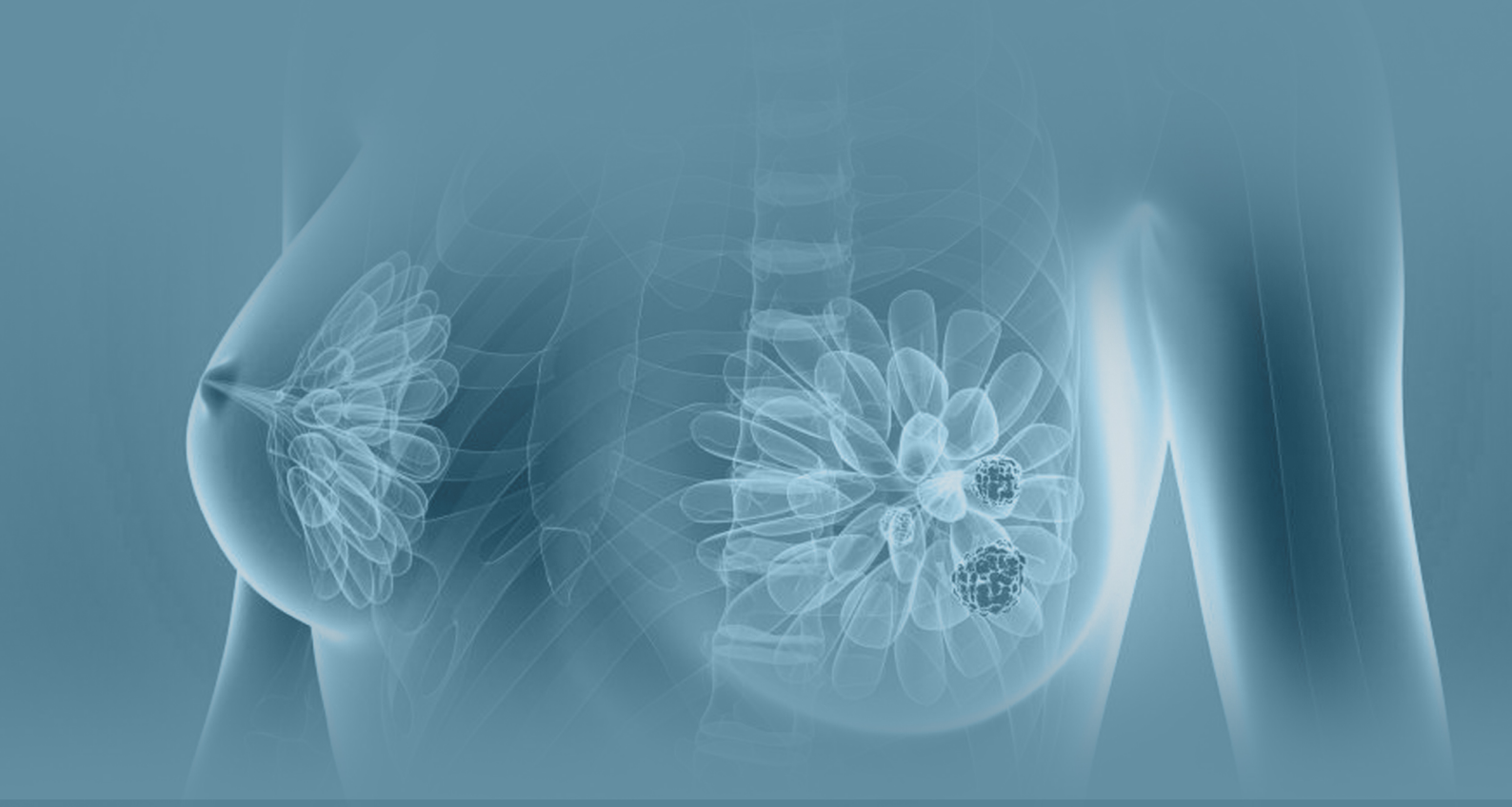

Unusual case of urogenital malignancy with metastases to breast

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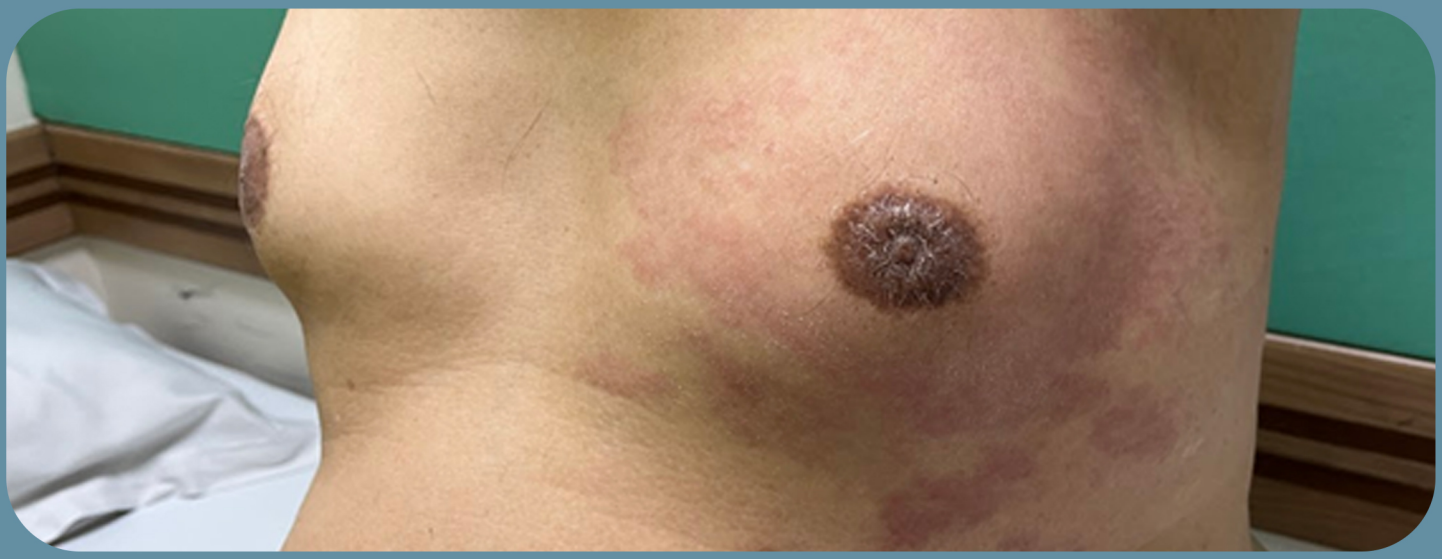
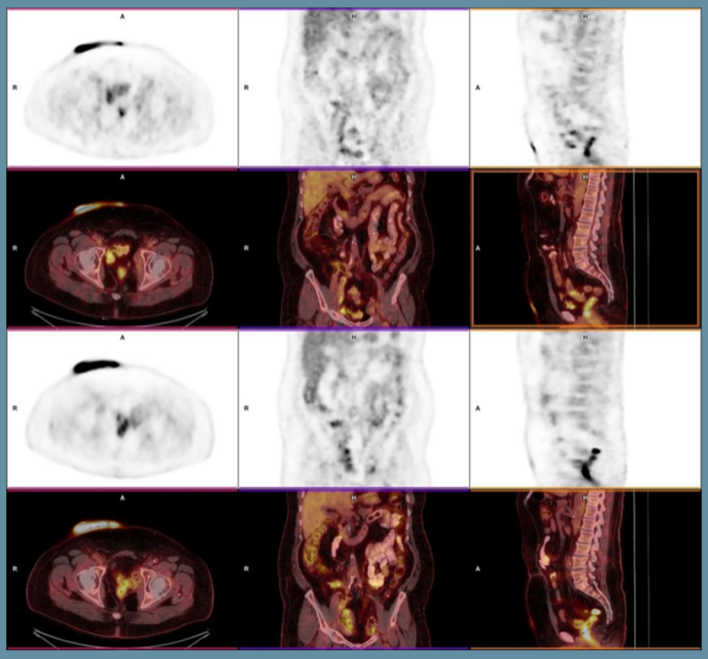
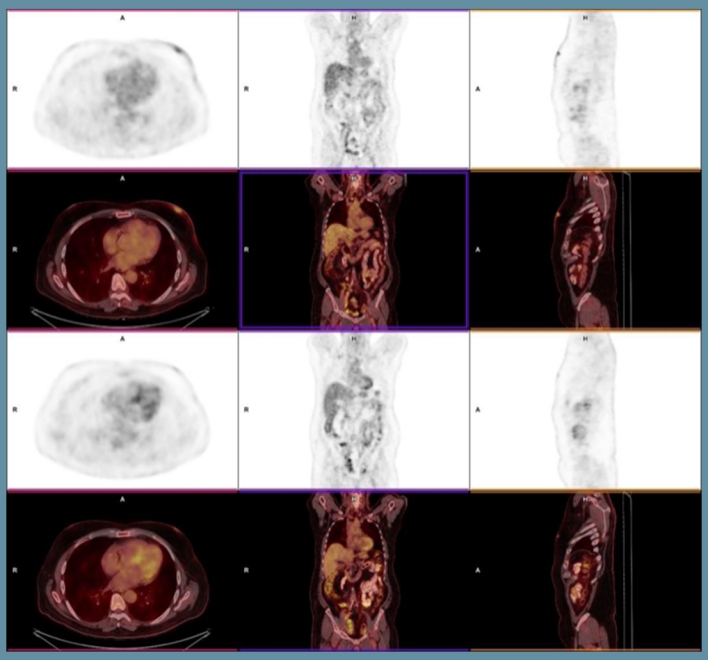
This 63 years gentleman, presented with a single episode of haematuria in 2017. He underwent cystoscopy and TURBT at that time. The pathological report suggested it to be low grade papillary urothelial carcinoma. He was followed up with periodic cystoscopies till July 2020 when he had recurrence of haematuria symptoms. Cystoscopy confirmed recurrent bladder tumour. TURBT biopsy this time came out as a high grade urothelial carcinoma with muscle invasive disease. FDG PET CT scan at this time showed presence of FDG avid urinary bladder lesion & bilateral axillary, mediastinal, abdomino-pelvic nodes and few tiny bilateral lung nodules. EBUS TBNA biopsy was however reported as inadequate. He received Gemcitabine + Cisplatin based chemotherapy. After that he underwent robotic radical cystoprostatectomy + ileal conduit and bilateral pelvic nodal dissection in September 2020. The pathological stage was ypT2N2, high grade urothelial carcinoma. He received further disease of Gemcitabine + Cisplatin based chemotherapy till May 2021. He was again followed up and two PET CT scans afterwards were reported no evidence of FDG avid disease anywhere in the body. In April 2023, he noticed firmness in left breast with thickening of left nipple areola complex and later he developed erythematous lesions on left breast skin and in pre-sternal region. FDG PET CT scan revealed a FDG avid lesion in left breast with thickened FDG avid skin overlying left breast. There was no



evidence of any FDG avid lesion elsewhere. He was referred to breast surgical OPD at this stage. Clinically a firm to hard nodular lump was palpable in left retro-areolar region with thickened skin of left nipple areola complex. The skin lesions were erythematous and elevated maculo-papular in nature. There was no axillary lymphadenopathy and right breast did not reveal any palpable abnormality. His paternal aunt had been treated for breast cancer at the age of 50 years and his father had prostatic cancer. With this background, clinical possibilities of a new primary malignancy of the left breast or metastases from urinary bladder were considered and an USG guided core needle biopsy of the breast lesion was carried out. It confirmed that it was indeed metastases of urothelial carcinoma to the breast. The immunohistochemistry work up showed it to be positive for CK, GATA3 and focally positive for CK 20.



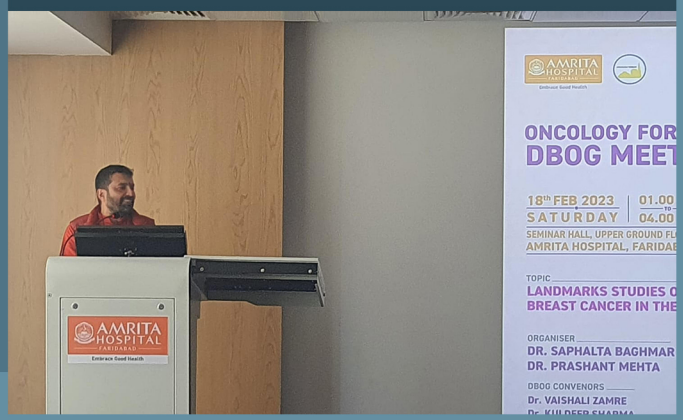


It is quite rare for urinary bladder cancer to metastasize to the breast. Common cancers which metastasize to the breast are melanomas. Neuroendocrine tumours, rectal, gastric and ovarian carcinomas. There have been only 8 reported cases of urinary bladder cancers metastasising to the breast. Clinical history and immunohistochemistry helped in diagnosis. The prognosis is not very well understood because of the rarity of the clinical situation.

The case was discussed in our Institutional MDT and he is now scheduled for Gemcitabine + Carboplatin based palliative chemotherapy. He will be followed closely.

Delhi Breast Oncology Group Academic Meeting

Dr. Saphalta Baghmer



After a long gap during and after Covid pandemic, periodical Delhi Breast Oncology Group academic meetings resumed with an event organized by Amrita Hospital, Faridabad on 25th February 2023. Dr. Saphalta Baghmar, Associate Professor, Medical Oncology successfully organized a CME in Breast Oncology under aegis Delhi Breast Oncology Forum. The theme was “Landmark Studies in Breast Cancer in the year 2022”. It was well attended by trainees and practising oncologists. The speakers (Dr. Sundeep Malla, Dr. Shiveta Razdan, Dr. Devajyoti, Dr. Rishabh Kumar and Dr. Abhishek Raj) discussed recent advances in the Breast Radiology, Surgery, Oncoplasty, Radiation and Medical Oncology. This was followed by a case based Panel discussion, moderated by Dr. Bhuvan Chugh and the panellists included Dr. Ekta Dhamija, Dr. Rohan Khandelwal, Dr. Ramanna, Dr. Gaurav Khanna and Dr. Anil.

Neo-adjuvant systemic treatment: Clinical challenges

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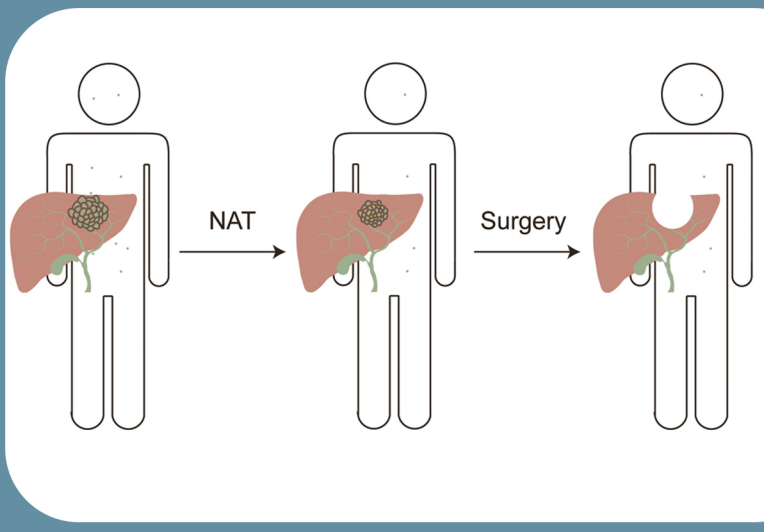
Dr. Vaishali Zamre (RGCIRC, Delhi), Dr, Shefali Sardana (Max hospital, Saket) and Dr. Kuldeep Sharma (Venkateshwar hospital, Dwarka) have recently been appointed as conveners of Delhi Breast Oncology Group. For the year 2022, we propose to organize a breast cancer CME every 3 months. We plan to discuss treatment controversies, recent updates, practice changing trials and local solutions to local issues in such events. We also plan to organize expert opinion/MDT discussions on tricky clinical scenarios. First such CME of this year was organized and hosted by Rajiv Gandhi Cancer Institute & Research Centre, Delhi on February 23, 2022. Owing to the ongoing Corona pandemic, this event was held on virtual platform. All aspects of neoadjuvant systemic therapy in breast cancer were discussed in the form of four stimulating talks followed by an interesting case-based panel discussion. The event was anchored by Dr. Sujata (Attending consultant, Surgical Oncology, RGCIRC). Various stalwarts in the field of breast oncology participated in the panel discussion and offered their valuable guidance.

Breast cancer is treated with multimodality approach which includes surgery, systemic therapy, radiotherapy, targeted therapy, endocrine therapy and immunotherapy. Neoadjuvant systemic treatment is widely used these days in locally advanced as well as in certain subsets (Triple negative and Her 2 positive subgroups) of early breast cancer also. While the goals of NAST are to downstage the disease, to make it operable, to offer breast conservation, to plan response adapted surgery as well as to plan adjuvant treatment based on response. Dr. Srujana (Consultant, Medical Oncology, RGCIRC) discussed the role of PDL1 inhibitors in the neoadjuvant setting. She discussed the evidence in favor of PDL1 inhibitors from the results of the various concluded and some ongoing trials. Addition of these novel therapeutic agents has not only increased the pathological complete response rates but has shown promising results towards the disease outcome.



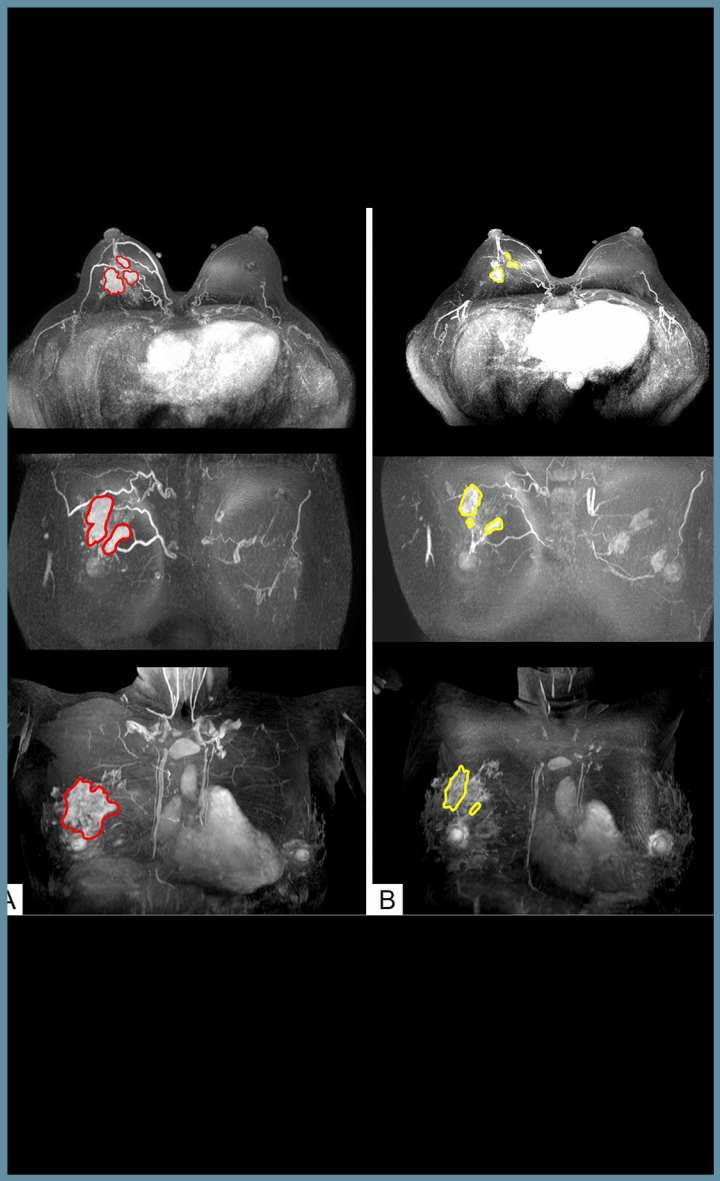
Triple negative breast cancer (TNBC) accounts for 10-15% of all breast cancers. They are highly aggressive tumours, have propensity for distant metastases & relatively a worse prognosis with 5-year survival rates in stage 2 and stage 3 being 91% and 65% respectively. Neoadjuvant Chemotherapy is the current standard of treatment for TNBC. With the use of standard chemotherapy regimens, a large percent of TNBC patients achieve pathological complete response rates (pCR) which is both a prognostic (⊠EFS, ⊠ DFS) and a predictive biomarker (in those with residual disease -Adjuvant Capecitabine or Adjuvant Olaparib in germline BRCA mutant). But still there is high unmet need for novel therapies to augment the effectiveness of chemotherapy.

A phase 3 randomized control Keynote 522 trial K randomised 1174 patients in 2: 1 ratio to Pembrolizumab+ chemotherapy (Paclitaxel/ Carboplatin) and chemotherapy+ placebo in the neoadjuvant setting of early TNBC. In the experimental arm, 9 more cycles of Pembrolizumab were administered as adjuvant therapy. Neoadjuvant pembrolizumab plus chemotherapy resulted in a significant increase in pathologic complete response rate-pCR (ypT0/Tis ypN0): 64.8% vs 51.2%, an absolute 13.6% improvement (P = .00055). The benefit in pCR was seen irrespective of stage, nodal status and PD-L1 status. Patients with residual disease have been found to have a substantially higher event-free survival if treated with Pembrolizumab. Although the chemotherapy regimen used (3 weekly chemotherapy) is not the standard practice presently, moreover, the use of platinum is still controversial in TNBC or BRCA mutant patients, this is a milestone trial for TNBC. We still have a long way to go in the quest of an ideal neoadjuvant treatment regimen based on the biological profile of the disease. Results of ongoing trials are likely to provide much needed evidence in this aspect.

Dr. Srujana's talk was followed by Dr. Vaishali Zamre's (Senior consultant & unit head, RGCIRC) talk. She spoke about the surgical challenges in patients undergoing NAST. In her talk she highlighted the importance of multidisciplinary approach for all patients who are planned for NAST, accurate clinical and radiological assessment, documentation of clinical findings, marking of the breast lump and axillary nodes, clinical photographs, response monitoring and clear communication between the clinicians and the patient. In our clinical practice, patients often seek opinion about surgery after having undergone NAST elsewhere. Sometimes the residual disease cannot be assessed clinically in such a situation. In the absence of adequate documentation about the disease extent before NAST, absence of a marker to guide the original tumour bed, offering breast conservation can be a challenge. Hence, Dr. Vaishali emphasized on the need of a multi-disciplinary approach to the management of all patients who are planned for NAST.

Her talk also elaborated on the concept of response adapted surgery, selection of patient for such an approach so that the objectives of oncological safety and reduction of surgical morbidity are achieved. She also emphasized the significance of regular clinical monitoring during NAST to identify non responders and to make appropriate modifications in the management approach for such patients. With the addition of newer targeted drugs to NAST, over 50-60% patients are found to have pCR. However, surgery is the only way to identify those patients

accurately. Clinical assessment and currently available imaging tools have not shown acceptable accuracy and false negative rates to avoid surgery altogether. Presently many prospective trials are underway to assess whether addition of vacuum assisted breast biopsy (VAB)/ CNB of the residual tumour bed can accurately predict pCR so that surgery can be avoided. Till we get level I evidence about the safety of this approach; surgery will be an integral part of curative approach to patients undergoing NAST.



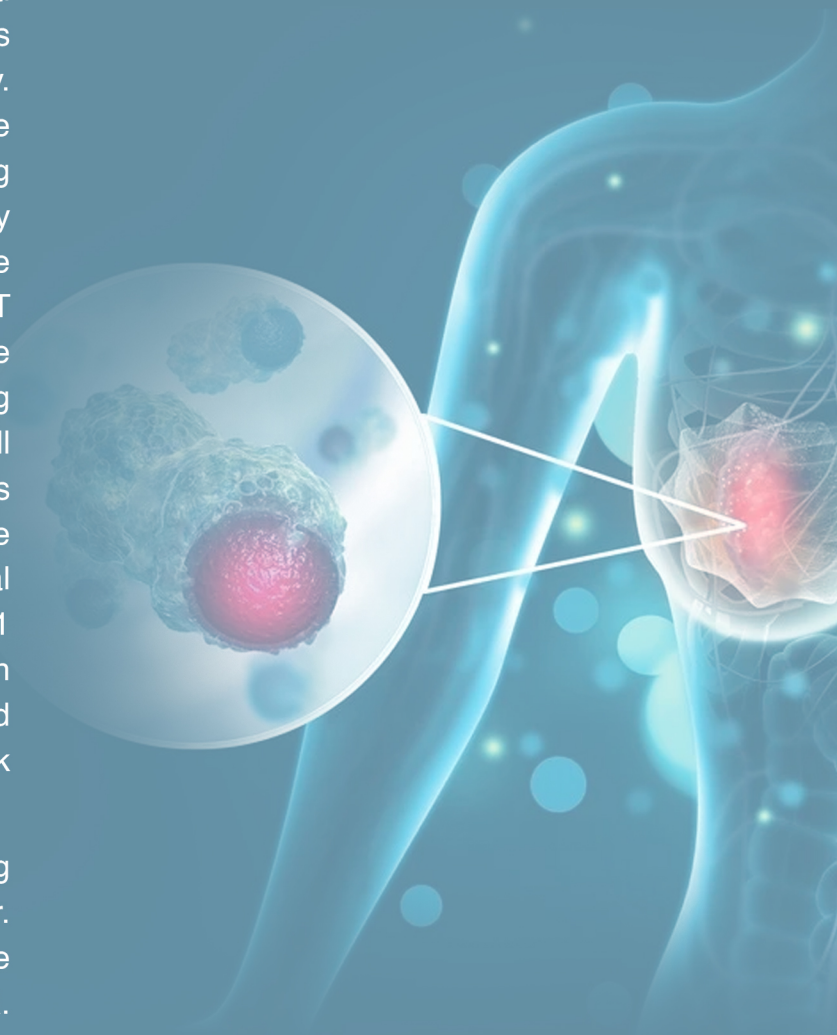
Dr. Anila Sharma (Senior consultant, Pathology, RGCIRC) discussed at length about the nitty-gritty of specimen handling, grossing, sectioning and reporting after neoadjuvant systemic treatment. She elaborated on the significance and prognostic implications of residual cancer burden. She also discussed about the need to providing complete clinical information, stage at presentation, type of systemic treatment administered, clinical response, information about tumour markers, etc. at the time of sending the specimen to the pathology lab. Her talk also focused on the recent advances in the field of pathological reporting and need of uniformity in the reporting protocols across the country.

Dr. Anila's talk was followed by Dr. Kundan Singh Chufal's (Senior consultant, Radiation Oncology, RGCIRC) talk on indications of adjuvant radiotherapy after NAST. Increasing use of neoadjuvant systemic therapy (NAST) has thrown challenges for Radiation Oncologist also. Current approach to adjuvant radiotherapy after NAST is based on the radiotherapy guidelines in primary surgery setting and none of them recommend adjusting RT as per the response to NST. On reviewing the literature, it has been found that most patients, particularly with aggressive molecular variants (Hormone receptor-negative and HER2Neu positive or Triple negative), show excellent response to NST with high rates of complete pathological response (pCR) in the range of 50-70%. Patients with clinical T1-2N1 disease achieving pCR or micrometastatic pathological residual nodal disease show very low locoregional recurrence rates (less than 10%). If the same patients are HER2Neu positive, then adding dual antibody blockade further has been

shown to have a very durable response. These patients may probably benefit from de-escalation radiotherapy strategies. Oncological safety of de-escalation approach is being studied in three ongoing phase III trials. NSABP-51 is studying the omission of locoregional RT post sentinel lymph node biopsy (SNB) or axillary lymph node dissection (ALND) in patients with clinical T1-3N1 disease who achieve pathological N0 status. The same clinical stage with residual pathological nodal disease is considered for RT only versus ALND plus RT in the Alliance-11202 study. ATNEC is a UK based trial with almost the same inclusion criteria as NSABP-51 and is studying omission of Axillary treatment versus Axillary treatment (RT or ALND). Till the time we have results from these trials, our RT recommendations should be based on the pre-NAST clinical stage and thus, ascertaining axillary status prior to NAST becomes vital. All patients showing suspicious axillary lymph nodes should undergo FNAC/biopsy to determine the status of the axilla. Outside of clinical trial settings, omission of RT in patients with cT1-2N1 stage achieving pCR should be discussed in multispecialty clinics on a case-to-case basis and only be offered after considering all the risk factors.

The talks were followed by an interesting case-based panel discussion, moderated by Dr. Garima Daga. A scintillating panel of experts like Dr. Rajeev Agarwal, Dr. Geeta Kadayaprath, DR. Kanika Sharma Sood, Dr. Rishu Singla, Dr. Shyam Bisht, Dr. Chaturbhuj Agarwal, Dr. Waseem Abbas, Dr. Kavita Jain discussed various aspects of diagnostic work up and individualised management strategies for the two challenging clinical scenarios discussed during the panel discussion.

The CME was well attended. The next DBOG meeting will be held in the month of May, 2022 and will be hosted by Asian Institute of Medical Sciences, Faridabad. We look forward to welcome you for the next meeting.



Triple Negative Breast Cancer: Exploring different treatment strategy for a different biology

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Introduction

Triple-negative breast cancer (TNBC) represents 10–20% of all invasive breast cancers (1). With its aggressive features and dismal prognosis, optimizing treatment strategies for this cohort remains a challenge. In the absence of specific treatment strategies, this tumor subgroup is currently managed with conventional therapeutic recommendations which seems highly deficient. There is a pressing need to better understand the biology of this phenotype and accordingly modify our future treatment strategies.

How TNBC biology affects its natural history

There are certain inherent biological and natural characteristics of TNBC that make it an aggressive disease. These characteristics need to be explored to optimize its treatment.

1. TNBC patients tend to have a higher risk of distant recurrence and death compared to non-TNBC patients within 5 years of diagnosis (1,2,3,4). Dent et al. reported a higher proportion of distant recurrence in patients with TNBC compared with non-TNBC (33.9% versus 20.4%, respectively; P<0.0001) (1). Wu et al. also showed that distant metastasis was the highest in the TNBC patients (27.4%) (2).

2. Recurrences in TNBC occur early after diagnosis, with a median time-to-recurrence ranging between 1.6 to 3 years (1,5,6). In a study, the risk of distant recurrence peaked at 3 years for TNBC patients then declined rapidly while it was constant for non-TNBC patients. Mean time to local recurrence was shorter for TNBC (2.8 years) than for non-TNBC (4.2 years) (1).

3. The site of locoregional failure vary between TNBC and Non-TNBC patients. Nodal relapse (particularly supraclavicular) as opposed to breast/chest wall relapse is more commonly reported in TNBC patients compared to non-TNBC patients (2,3,7). Wu et al. showed that 20% and 50% recurrences were nodal (out of total loco-regional recurrences) in non-TNBC and TNBC patients respectively (2). Noh et al. also reported similar findings (7).

4. The sites of distant failures also vary according to the phenotype where TNBC patients tend to have more visceral than bone metastases (5,2,8). They peak at 2–3 years mainly in the brain and the lung. Afterwards, that risk of recurrence fades while bone recurrence continues to occur even after 5 years.

5. TNBC patients show poor response to NACT

(neoadjuvant chemotherapy). Approximately half of the patients do not achieve pathological complete response (pCR) and are at risk of recurrence (9).

How different biology can be exploited to improve treatment results

Management of TNBC requires different approach due to its different biology and molecular characteristics as discussed in previous section.

1. To tackle higher risk of distant recurrence and death, novel strategies are needed to be explored. While exploring newer chemotherapy / immunotherapy agents is one strategy, combing them with RT (radiotherapy) to exploit the immunogenic potential of RT may be another one. This is based on the hypothesis that TNBC is the most immunogenic among breast cancer subtypes (10) where use of RT to augment response to immunotherapy may be exploited. Radiation increases mutational load of tumors, optimizes antigen presentation, and decreases immune suppressors in the tumor microenvironment, priming the tumor for responding better to immunotherapy (11). This enhances tumor immunogenicity and increases the presence of effector immune cells at the tumor site. The combination of local radiation with CTLA-4 blockade and PD-1/PD-L1 blockade has shown synergistic activity in preclinical murine models (12). Apart from local site, RT can have inhibitory effects on tumor cells lying outside the irradiation field through immune mechanism (abscopal effect). A number of ongoing clinical studies are exploring the combination of RT and immunotherapy expecting synergistic effect on metastatic TNBC.

2. Since recurrences happen early there is a need to optimize the timing and sequencing of various neoadjuvant and adjuvant modalities to control tumor repopulation in a more effective way. Starting treatment early in disease course may be a basic approach.

3. In view of higher nodal recurrence rates of TNBC, use of locoregional irradiation after mastectomy should be of utmost importance. Data from early Danish Trials published by Kyndi et al. showed that PMRT (post mastectomy radiotherapy) significantly reduced loco-regional recurrences in TNBC patients ($P<0.01$), however it didn't improve OS (13). Wang et al. also showed a lower recurrence rate with the addition of PMRT (25.4% vs. 11.7%, $P=0.02$) where OS (overall survival) was also in favor of PMRT with 78.7% in the mastectomy alone group vs. 90.4% in the PMRT group ($P=0.03$) (14). On the other hand, a recent observational analysis by Haque et al. showed that the addition of PMRT for TNBC patients with node negative disease (T1-4N0) was not associated with a significant improvement in OS in the whole group (HR of 0.88 and 95% CI: 0.75–1.03) and only T3N0 patients benefited significantly from PMRT in terms of OS (15). Thus, although no firm data warrants systematic use of PMRT in early stage (T1-2N0 patients), it should be considered for selected patients with high-risk factors (such as young age or high grade). Even newer NCCN guidelines recommend to analyze high risk factors while advising PMRT in early cases. On the other hand, T3N0 patients should benefit from the addition of PMRT to standard chemotherapy. Another point is the value of adding adjuvant RT to surgery compared to surgery alone in elderly patients with early stage TNBC. National Cancer Database review of 8,526 T1-2N0M0 TNBC

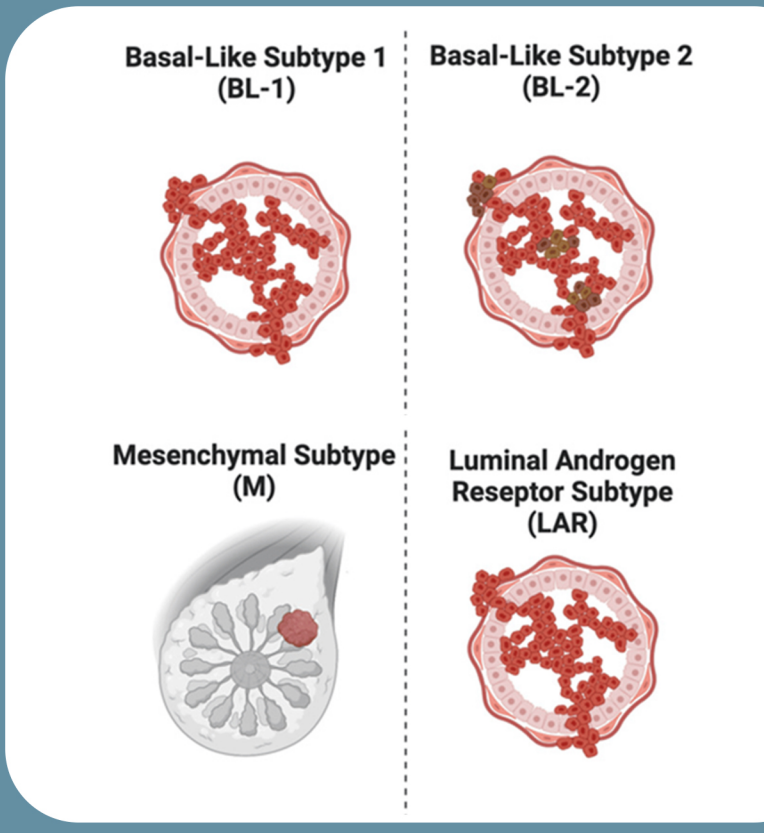
patients showed that after a median FU of 38 months, 5-year OS was higher in the group who received adjuvant radiotherapy in the order of 77.2% compared to 55.3% in the surgery alone group (P<0.001). This effect persisted after stratifying for age, stage and chemotherapy use (16). Thus, adjuvant RT should not be omitted for elderly patients with hormone positive early disease.

4. Visceral and brain metastases have high morbidity and mortality that again warrants more effective systemic treatments, better follow-up regimens and optimizing prophylactic treatments.

5. We also need better strategies to improve response rates to neoadjuvant treatments. Recently there has been an interest in revisiting pre-operative RT using modern techniques and novel RT-drug combinations (17) for breast cancer. Retrospective studies have demonstrated that NART (neo-adjuvant radiotherapy) is effective as sole modality, especially in TNBC with pCR documented in 26% patients (18). Moreover, there is a need to explore ways to enhance radiosensitivity by different means. When sensitizing NART by concomitant administration of weekly paclitaxel, a pCR was achieved in 23% of patients, reaching 54% in patients with hormonal receptor-negative subtype (19). Moreover, “rescue” chemo-RT in NACT-refractory inoperable BC allowed curative surgery in 71% of patients, in which a pCR was observed in 50% of the histological specimens (19). A phase I study tested five dose levels of stereotactic body radiation therapy (SBRT) concomitant with chemotherapy before surgery [20]. This association showed promising results with overall pCR rate of 36%, where highest pCR rate of 67% was achieved at a particular dose level (25.5 Gray in 3 fractions). The incorporation of immunotherapy agents into the preoperative RT setting opens another avenue and presents unique advantages for priming antitumor immune response and potential eradication of the disseminated micrometastatic disease. Results are awaited of other ongoing trials implementing modern concepts of NART in the management TNBC.

Conclusion

Management of TNBC requires different The available evidence and knowledge shows that TNBC has an aggressive and distinct nature. We need to have a lower threshold while considering neo-adjuvant and adjuvant treatments with surgery for these patients. Till we come up with a final management plan, patients with TNBC should be encouraged to participate in clinical trials to find answers for managing this aggressive subtype of breast cancer.



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An overview of systemic therapy in breast cancer

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Breast cancer remains a major global health concern, and systemic therapy plays a crucial role in improving patient outcomes. The three main modalities of systemic therapy for breast cancer are chemotherapy, hormone therapy, and targeted therapy. In recent years, immunotherapy has also emerged as a promising modality for breast cancer treatment.

Chemotherapy

Chemotherapy has been a mainstay of breast cancer treatment for many years. Anthracyclines and taxanes have improved response rates and progression-free survival (PFS) in both the adjuvant and metastatic settings. In the neoadjuvant setting, combination chemotherapy has been shown to improve pathologic complete response (pCR) rates compared to single-agent chemotherapy. For example, a phase II trial of neoadjuvant carboplatin and paclitaxel in patients with triple-negative breast cancer (TNBC) showed a pCR rate of 56.3%, compared to 36.9% with paclitaxel alone (p=0.03) (1).

Hormone therapy

Hormone therapy is the standard treatment for hormone receptor-positive (HR+) breast cancer. Tamoxifen, a selective estrogen receptor modulator (SERM), has been the standard treatment for HR+ breast cancer for over three decades. A meta-analysis of 20 randomized trials showed that tamoxifen reduced the risk of recurrence by 40% and breast cancer mortality by 31% (2). The introduction of aromatase inhibitors (AIs) such as anastrozole and letrozole has improved disease-free survival (DFS) and PFS in postmenopausal women with HR+ breast cancer. In the adjuvant setting, AIs have been shown to be superior to tamoxifen in reducing the risk of recurrence. The BIG 1-98 trial compared letrozole alone, tamoxifen alone, and a sequential regimen of tamoxifen followed by letrozole. The 10-year DFS rate was 82.3% with letrozole alone, 77.6% with the sequential regimen, and 77.3% with tamoxifen alone (3).

Targeted therapy

Targeted therapy has revolutionized the treatment of HER2-positive breast cancer. Trastuzumab, a monoclonal antibody that targets the HER2 protein, has significantly improved outcomes for patients with HER2-positive breast cancer. In the adjuvant setting, trastuzumab has been shown to reduce the risk of recurrence by 37% and improve overall survival by 33% (4). Other HER2-targeted therapies such as Pertuzumab and ado-trastuzumab emtansine (T-DM1) have also shown promising results in the

treatment of HER2-positive breast cancer.

CDK4/6 inhibitors such as Palbociclib and Ribociclib have also emerged as promising targeted therapies in HR+ breast cancer. These drugs inhibit the activity of CDK4 and CDK6, which are involved in the progression of the cell cycle. In the metastatic setting, the addition of Palbociclib to letrozole or Fulvestrant has been shown to improve PFS compared to endocrine therapy alone. In the PALOMA-3 trial, Palbociclib plus Fulvestrant resulted in a median PFS of 9.5 months compared to 4.6 months with Fulvestrant alone (5).

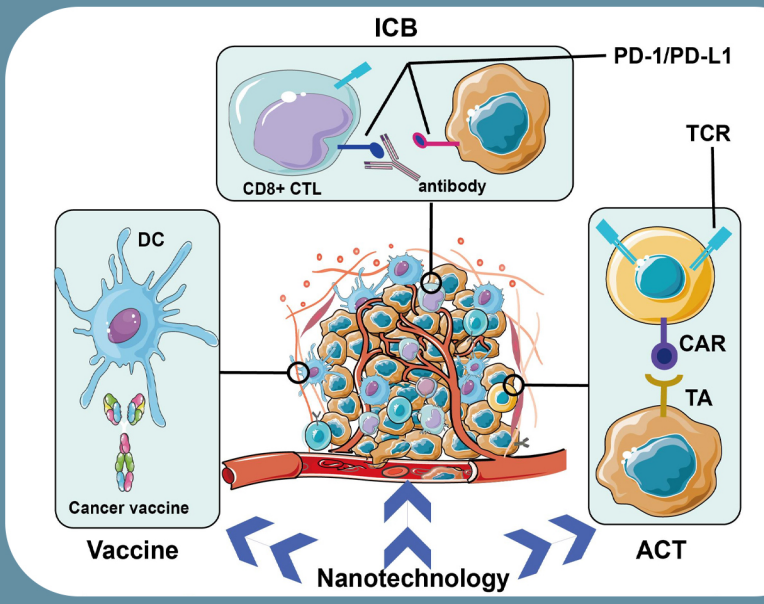
Immunotherapy

Immunotherapy is an emerging modality for breast cancer treatment. While initial studies of single-agent checkpoint inhibitors in breast cancer showed modest response rates, combination therapies are showing more promising results. In the IMpassion130 trial, atezolizumab plus nab-paclitaxel improved PFS in patients with metastatic TNBC compared to nab-paclitaxel.

In the IMpassion130 trial, atezolizumab plus nab-paclitaxel improved PFS in patients with metastatic TNBC compared to nab-paclitaxel alone (6). The median PFS was 7.2 months in the atezolizumab group and 5.5 months in the placebo group (HR=0.80, p=0.002). However, the overall survival (OS) benefit was seen only in patients with

PD-L1-positive tumors. The median OS was 25.0 months in the atezolizumab group and 15.5 months in the placebo group among PD-L1-positive patients (HR=0.62, p=0.002).

In the KEYNOTE-522 trial, pembrolizumab plus neoadjuvant chemotherapy improved pCR rates



in patients with TNBC compared to neoadjuvant chemotherapy alone. The pCR rate was 64.8% in the pembrolizumab group and 51.2% in the placebo group (p=0.00055) (7).

In India, breast cancer is the most common cancer among women, accounting for 27% of all cancer cases (8). The incidence of breast cancer is increasing in India due to changes in lifestyle, reproductive factors, and aging. A retrospective analysis of 1,483 patients with early-stage breast cancer from a tertiary care center in India showed that the most common subtype was HR+/HER2- (61%), followed by HER2+ (22%) and TNBC (17%) (9).

In conclusion, systemic therapy plays a crucial role in improving outcomes for patients with breast cancer. Chemotherapy, hormone therapy, and targeted therapy have all shown significant benefits in various subtypes of breast cancer. Immunotherapy is an emerging modality that has shown promising results in combination with chemotherapy for TNBC. Clinicians should carefully consider the molecular subtype of the tumor when selecting systemic therapy for breast cancer patients.

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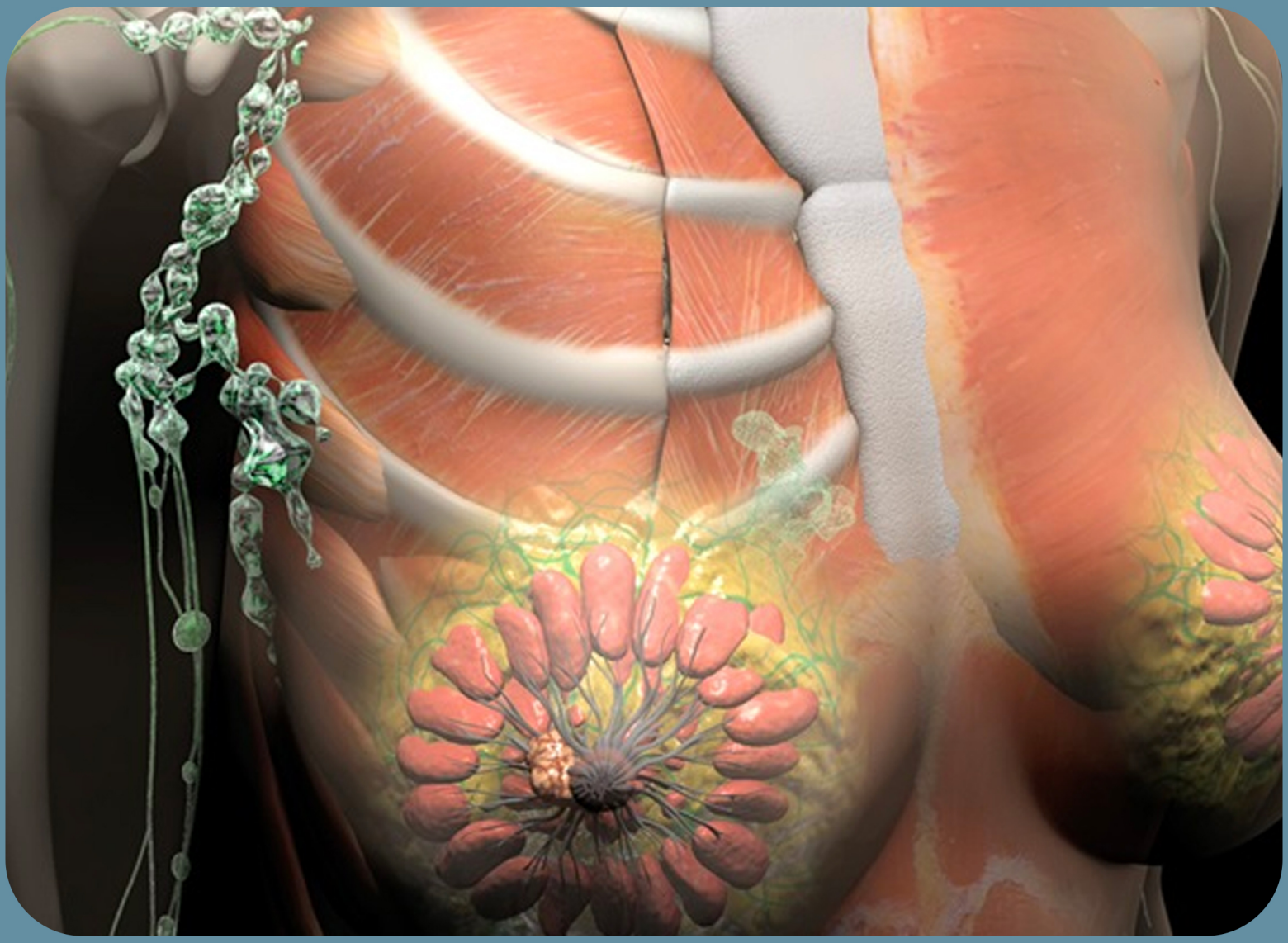

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Management of Axilla in Breast Cancer: Past, Present & Future

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Breast cancer has been a common cancer of women. With the rising incidence, it has become the leading cancer globally among both men and women. With widespread use of screening globally, progressively earlier presentation and diagnosis in rest of the world and improved outcomes due to multimodality management, integration of new drugs and biology driven therapy, the outcome of breast cancer is progressively improving, and focus has shifted to quality-of-life issues among breast cancer survivors.

Surgical management of breast cancer has been one of the most dynamic fields in solid cancer management. The journey that began with Halstead's radical mastectomy has only accelerated in recent years. Management of the primary tumor was the primary focus area in the twentieth century. However, last quarter century has been association with a revolution in the management of axilla.

One of the major controversies has been the objective of axillary surgery. In the Halstedian scheme of things, en bloc removal of axillary nodes was considered crucial for disease control. The limitations of radical mastectomy in long term disease control and survival were soon realized and a journey of de-escalation of surgical treatment started in the second half of the last century. Dr. Bernard Fisher's research and the series of multicentric clinical trials conducted subsequently pushed into limelight the idea that axillary surgery had no role in disease control and survival. The NSABP B-04 trial showed that the axillary failure rate was much lower than the incidence of axillary disease and there was no significant impairment of survival. The study also showed that axillary radiation was fairly effective in reducing axillary recurrences.

Systematic reviews and meta-analyses have now shown that axillary disease control is important for long term survival. Prevention of four recurrences saves one life in the long term. Axillary lymph node dissection (ALND) has been the standard of care for axillary management from the time of Halstead. Complete clearance of level I to level III axillary nodes with removal of interpectoral nodes and tissue is effective with very low axillary failure rates. Pathological examination of the removed axillary nodes also provides staging information and helps in decision making about systemic therapy as well as radiation therapy. However, a significant proportion of axillary dissections can be considered as unnecessary as no disease is found in the removed axillary nodes. The proportion of patients without axillary involvement has increased gradually with earlier presentation

and diagnosis of breast cancer due to multitude of reasons including population-based breast cancer screening. Further, the long-term quality of life issues related to axillary dissection i.e., lymphedema, shoulder dysfunction etc. have come into increasing focus with progressively increasing long term survival.

An acute need was felt for a method that can accurately stage the axilla without doing complete axillary dissection and allow targeting of axillary surgery to those who are going to benefit from it. Studies in the field of melanoma validated the procedure of sentinel lymph node biopsy. Similar studies were initiated in the field of breast cancer. Initial pilot studies followed by large, randomized studies confirmed the safety and accuracy of sentinel lymph node biopsy procedure in early breast cancer with uninvolved axilla (no palpable axillary nodes). There were studies about the procedural details related to SLNBx. After multiple studies, it is agreed that dual tracer technique using a blue dye and radioisotope gives the best results. However, if radioisotope facility is not available, single tracer technique with blue dye can be used. Subareolar injection is as effective as peritumoral injection but does not identify internal mammary sentinel nodes. With radioisotope based SLNBx, there is no benefit of doing lymphoscintigraphy. Alternative techniques have been explored using indocyanine green, superparamagnetic iron oxide etc. and have been shown to be effective.

One of the major changes after this was integration of axillary ultrasound and US guided FNAC/biopsy for assessment of axillary status in patient with breast cancer. Patients with negative axillary nodes (either no suspicious nodes on US or FNAC/biopsy negative nodes) undergo SLNBx while those with involved nodes (FNAC/Biopsy positive) are offered axillary lymph node dissection if primary surgery is planned. This approach reduces the need for sentinel lymph node biopsy in many cases and also allows for SLNBx in some patients with palpable axillary nodes.

The next issue that was studies was the need for axillary dissection in patients with involved sentinel nodes. Part of the issue arose from the practice of detailed pathological examination of the sentinel nodes which identified micrometastases and isolated tumor cells. Initially, all patients with micrometastatic involvement of axilla were taken up for axillary dissection. Later, the practice of ALND in all patients with positive sentinel nodes was questioned as the incidence of pathological involvement of non-sentinel nodes was low and correlated with the burden of disease in sentinel nodes.

A series of studies were planned and carried out to address the issue of completion axillary dissection. ACOSOG Z 0011 was the first study to come out with the results. It showed that breast cancer patients with favourable biology, limited sentinel node involvement (micrometastases or 1-2 macrometastases) having breast conservation and receiving chemotherapy and whole breast adjuvant therapy had no benefit from completion axillary dissection and could be spared the procedure. IBCSG and AMAROS studies also showed similar results, IBCSG study in patients with micrometastatic disease and AMAROS study comparing completion surgery with axillary radiation. Based on these trials, patients with micrometastatic or limited macrometastatic involvement of sentinel nodes can be spared completion axillary dissection.

The next frontier in axillary surgery has been de-escalation in the setting of metastatic involvement of axilla. It has been observed that sterilization of involved axilla is possible among a significant percentage of patients undergoing neoadjuvant systemic therapy. This proportion is high in patient with triple negative breast cancer and HER2 positive breast cancer. Validation of sentinel node biopsy procedure has been done in the setting of patients undergoing neoadjuvant chemotherapy (with/without targeted therapy). Patients who have negative axilla should definitely undergo SLNBx after NACT. Patient with involved axilla (N1 disease) with absence of identifiable axillary disease after NACT (both clinically and on imaging) can be offered SLNBx if a dual tracer based technique is used and at least 3 nodes are harvested. Targeting of the involved node as part of SLNBx after NACT has been suggested as a means of improving the accuracy of the procedure. Overall, there is an early acceptance that SLNBx can be safe in selected patients with involved axillary nodes after NACT.

Another procedure that has been identified to be useful in axillary surgery is primary lympho-venous anastomosis at the time of axillary dissection. This procedure has been shown to be effective in reducing the incidence of lymphedema after complete axillary dissection.

Conclusion

Sentinel lymph node biopsy is the standard of care among early breast cancer patients undergoing primary surgery if there is no involvement of axillary nodes on clinical assessment including imaging. Selected patients with involved nodes can be considered for SLNBx after NACT if there is negative axilla after NACT.