REVIEW ARTICLE

# TREATMENT OF BREAST CANCER; REVIEW AND UPDATES

**Muhammad Furrukh, Asim Qureshi***

**Department of Radiation Oncology, SHIFA International Hospital, Islamabad-Pakistan, *Department of Pathology, Sultan Qaboos University Hospital, Muscat-Sultanate of Oman**

Cancer of the breast is the leading female cancer accounting for one fourth of the malignancies. The tumour remains the most researched, read and practiced upon around the Globe. The treatment has substantially improved breast cancer related outcomes, both for early as well as late stages with substantial improvements in disease free and overall survival. Therapeutic decisions not only rest on clinical & tumour characteristics, but also with the evolution of molecular biology and tissue microarray intrinsic sub-types have been found. Attempts are being made to translate therapy from genomic architecture of individual breast cancer. This facilitates customization of treatment avoiding un-necessary toxicity, costs and inconvenience. Optimizing treatment based on individual breast biology seems logical and allows unifying treatment. The paper reviews literature, incorporate updates and also describes immunohistochemistry based molecular classification: which are found simple to adapt, record, present and subsequently manage, summarizing clinical practices in management of these patients.

**Keywords:** Breast; Cancer; Molecular biology; Triple negative; Immunohistochemistry; Receptor, erb-B2;Therapy; Antibodies, Monoclonal

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## INTRODUCTION

Breast cancer is the leading cancer amongst females around the globe with approximately 1.67 million new cases which accounts for 25% of all cancers diagnosed in 2012. It is the fifth cause of death from cancer overall (0.522 million).[1] According to American Cancer Society (ACS), Breast Cancer Facts & Figures 2013-2014: 232,340 new cases of breast cancer was expected to be diagnosed among US women and approximately 39,620 US women was expected to die from it.[2] The age standardized rates (ASR; per 100,000) are; 90 (USA), 75 (UK), 55 (Bahrain), 48 (Kuwait), 47 (Qatar), 24 (UAE), 18 (Saudi Arabia) and 13 (Oman).[3] The percentage diagnoses by stage and 5 year survival rates from diagnosis are presented in table-1 from a Omani study and compared with that from surveillance, epidemiology and end results (SEER 2013-14), USA.[4,5]

**Table-1: Diagnosis by stage and survival[4,5]**

| | | |
|---|---|---|
| **Percentage diagnosis by stage** | | |
| USA | | Oman |
| Localized | 63 | Stage I 05 |
| Regional | 29 | Stage II 39 |
| Distant | 06 | Stage III 36 |
| Un-staged | 03 | Stage IV 18.5 |
| **5 year survival rate by stage at diagnosis;** | | |
| Localized | 97% | Stage I 100% |
| Regional | 78% | Stage II 87% |
| Distant | 23% | Stage III 62% |
| Un-staged | 56% | Stage IV 38% |

It is not unusual to encounter a patient in clinical practice who harbours a small breast primary and has metastases, and another has a fungating breast mass which may still have localized disease at the initial staging. In recent times, the importance of tumour biology has been recognized for prognosis as well as for prediction of therapeutic response. Oncologist continue to treat their patients based on clinical practice guidelines and often find patients, seeking multi-disciplinary team and tumour board discussions for unmet answers. Immunohistochemistry (IHC) allows clinicians to classify breast cancer biology into molecular sub-types, and there is room to develop guidelines on systemic agents and chemotherapy protocols based on these.

## MATERIAL AND METHODS

Literature is retrieved from searches in Medscape, PubMed, Google, and from review articles published in reputable indexed medical journals (Annals of Oncology, The Oncologist, Journal of Clinical Oncology, New England Journal of Medicine, Lancet Oncology, The Lancet, Annals of Surgery, European Journal of Cancer, Journal of National Cancer Institute, Journal of Pathology, International Journal of Radiology Oncology Biology & Physics, Nature, Haematology Oncology Clinics of North America, Medical Dosimetry, Clinical Cancer Research, Breast Cancer Research and treatment, The Journal of Clinical Investigation, Critical Review Oncology

& Haematology, Journal of American Medical Association, Hereditary Cancer Clinical Practices). Information is also gathered from key groups e.g. National Comprehensive Cancer Network (NCCN), American Society of Cancer (ACS), American Society of Therapeutic Radiology (ASTRO), European Society of Therapeutic Radiology (ESTRO) and European Society of Clinical Oncology (ESMO). Data is also retrieved through electronic mail alerts from Saint Antonia Cancer Symposium 2014, ASCO post 2014, ASTRO, and Cancer Network. Only, Journals and groups in English are reviewed. Key words are verified through MeSH of the NCBI website.

## REVIEW OF LITERATURE AND UPDATES:

Patients with localized breast cancer are traditionally risk stratified (low, intermediate and high risk) for disease relapse,[6] and are treated based on final histologic sub-type, clinical features and tumor characteristics, taking prognostic and predictive biomarkers into consideration. A marker is considered prognostic if it predicts the outcome (what disease does to the patient), regardless of the treatment, and predictive if it predicts the outcome of a specific therapy (what treatment potentially does to the disease). Key predictive markers are well known in oncology community, multi-disciplinary team surgeons, pathologists, & radiologists, and includes; ER, PgR & HER2 neu expression on immune-histochemistry or gene amplification (on fluorescent in-situ hybridization (FISH)/ or in-situ hybridization (ISH). Treatment has evolved over decades of scientific research through randomized phase II/III trials and meta-analyses. Chemotherapy and hormonal therapy has remained the mainstay of treatment, while targeted therapy (trastuzumab) found its definitive role in early 2003. Newer antibodies, like pertuzumab are approved in neo-adjuvant as well as adjuvant setting.[7]

Modified radical mastectomy (MRM) remains a suitable option in underdeveloped World, poverty ridden societies, with lack of surgical expertise and where the patients' follow-up is doubtful. However, a recent large randomised trial (San Antonio 2015) reveals increased postoperative complications (infection) with MRM, especially in age $\geq$65 years. We also know lumpectomy followed by breast radiotherapy preserves breast and its cosmetic appearance in experienced hands.[8] Breast surgery teams are confident at breast preservation having the ability of skin sparing mastectomy as well as reconstructive surgeries (silicone implant or autologous tissue/ flaps) when indicated. Survival advantage with axillary lymph node dissection (ALND) is very small, which become evident when the absolute rate of local recurrence is reduced by 10%.[9] Patient's having sentinel lymph node (SLN) positivity (clinically N0, $N1_{mic}$ <2 SLN, no extra nodal extension) may avoid ALND and associated morbidity, as long as they receive adjuvant chemotherapy and radiotherapy. The risk of local recurrence remains at ~1% with either ALND or axillary radiotherapy without detrimental effects on overall survival (OS).[10–13] At least 2 (preferably more) SLN should be dissected using combined blue dye & technetium ($Tc^{99m}$) radioisotope methods to reduce false negativity. Patients having palpable ALN who receive neo-adjuvant chemotherapy (NAC) may also opt for SLNB after axillary remission (~40% pathological CR), but the false negative rate remains ~12.5%.[14,15] Once the SLN revert to remission, NSABP B-51/ Radiation Therapy Oncology Group (RTOG) 1304 trial randomly assigns patients to nodal radiotherapy vs. no nodal radiotherapy (without further surgery) and if the SLN remains diseased, Alliance A11202 study randomly assigns patients to ALND vs. no axillary dissection (with nodal radiotherapy for all patients), and results of these are awaited. Palliative toilet mastectomies are reserved for patients with fungation and repeated infections, bleeding tumours, intractable pain or for cosmesis. Individualized decisions for modified radical mastectomy may be feasible for solitary metastases in bones and brain that may have simultaneous resections, prostheses placement (former) and adjuvant radiotherapy. All require systemic therapy based on final predictive biomarkers.[7]

NAC is increasingly practiced and enables downsizing the tumour, either by facilitating patients' breast preservation, or their surgeons' in attaining negative surgical margins after mastectomy for large tumours. It also carries the potential advantage of attaining a complete remission in ALN, saving it from ALND and hence morbidity, provided the SLN is negative. Initiating chemotherapy earlier in the course of therapy addresses micro-metastases, and defines chemo-responsiveness of the disease. Taxanes are sequentially added to increase pathological complete responses (pCR) as well as to non-responders if initially offered induction anthracyclines and vice versa, while others are offered salvage surgery.[16] In elderly females, poor performance status (PS), and poor cardiac reserves often find a place for neo-adjuvant hormonal therapy for down-sizing large tumours, which are

quite effective but require longer time to attain a reasonable response (3-4 months). In hormone receptor (HR) negative disease, combination chemotherapy is equally effective as seen in young patients but is more toxic.[17] Adjuvant weekly paclitaxel x 12 may be used,[18] while single agent capecitabine (ICE trial) is found no better than not offering chemotherapy in the elderly (25% of patients in this trial >75 years, 10% frail - Charlson comorbidity index of 2, 15%-17% show reduced physical function and disabilities) at 3 years.[19] There is an increasing tendency to use chemotherapeutics, while neo-adjuvant endocrine therapy is exclusively reserved for postmenopausal females with HR positive disease.

Adjuvant systemic therapy is often over-utilized and seldom under-utilized. It is used for occult disease ($<10^6$ cells) which is associated proportionally with higher risk of relapse without pathological evidence, and absence of clinical or radiological disease at the time of decision making. These are the patients who require treatment after definitive breast surgery (breast conservation or mastectomy). Clinical guidelines can be approached through various hand-held devices e.g. National Comprehensive Cancer Network (www.nccn.org), National Cancer Institute (http://www.cancer.gov/cancertopics), British Columbia Cancer Agency http://www.bccancer.bc.ca/default.htm), European Society of Clinical Oncology (http://www.esmo.org/Guidelines), St. Gallens (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683952/), etc. Therapeutic decisions of systemic agent's rests on the patients age (<35 years), tumour size (>0.5–1 cm), high tumour grade, presence of lympho-vascular invasion, metastasis in ALN, estrogen (ER) & progesterone receptor (PgR) status and human epidermal growth factor receptor (HER2-neu) protein expression (IHC 3+) or gene amplification on FISH/ ISH (HER2-neu: chromosome 17 copy number, ratio>2).[6,20]

The debate whether chemotherapy should be given prior to or after surgery has subsided with the consensus that neo-adjuvant chemotherapy is superior for reasons given in the proceeding paragraphs, and more so, due to the fact that patients achieving a pCR have the longest survival and continue to live a normal life cosmetically (preserved breast). Chemotherapy adds to anti-estrogens in survival at 5 years, which is substantially higher in reproductive females (<50 years) (absolute gain 7.6% $p$=0.00001) compared to post-menopausal females (50–69 years) (absolute gain 4.9% $p$=0.00001).[21] Anti-oestrogens are always used sequentially.

CMF regimen is scarcely used while anthracyclines and taxanes are overtly used in forefronts of our day to day clinical practice. A recent study finds AC x4 regimen to be as effective as $FE^{100}C$ x 6 regimen.[22] Some HR positive breast cancers do not benefit from addition of adjuvant chemotherapy, or have intrinsic resistance to chemotherapy, but otherwise have an excellent prognosis with endocrine therapy alone. Oxford review confirms an absolute gain in survival of 13% at 15 years in HR positive tumours ($p$=0.00001) with tamoxifen use in adjuvant setting, while chemotherapy induced amenorrhea has also been associated with improvements in disease free survival (DFS). In a 20 years follow-up after 5 years of tamoxifen use, there is a 31% risk reduction in breast cancer (absolute benefit 3.4%), according to International Breast Cancer Study Group (SABCS 2014), however, the study paradoxically shows increase in breast cancer mortality.[23,24] Ten years of adjuvant tamoxifen use is associated with reduced breast cancer recurrences (28% vs. 32% $p$=0.03) in a key randomized trial, and so is the use of letrozole sequenced with tamoxifen. On the contrary, aromatase inhibitors (AIs), i.e., letrozole, anestrazole, exemestane have emerged as first line therapy for HR positive postmenopausal females in improving DFS & OS, but with a different toxicity profile.[6,25,26] AIs are subsequent therapy after tamoxifen failure in metastatic setting, and also proven to be practice changing for HR positive pre-menopausal females after adjuvant chemotherapy. Prudence Francis in ASCO 2014 presented the SOFT trial where exemestane-ovarian function suppression (LHRH agonists, or pelvic radiotherapy, or bilateral salpingo-oophorectomy (BSO), increased DFS (HR 0.66 95% CI, $p$=<0.001) and reduced risk of disease recurrence, second invasive cancer or death (HR 0.72 95% CI, $p$<0.001), without adding toxicity.[27]

Adjuvant post-mastectomy therapeutic radiation is reserved for tumours that exceed 5 cm (T3-T4a-d), in presence of metastatic axillary lymph node/s (ALN), close (<1 mm), positive or unknown surgical margins.[7] Wider margin status (>1 mm) varies inversely with risk of local recurrence. Radiation boost to the tumour bed or operative scar is reserved for positive or close surgical margins that may not be re-excised, age <50 years and for grade 3 tumors.[28] Radiotherapy is also mandatory after breast conservation surgery or high scoring DCIS. Modified Van Nuys' Prognostic Index refines therapy, and 12-gene

Oncotype Dx DCIS score (Genomic Health) predicts patients' risk of recurrence or invasive cancer.[29] Immediate radiotherapy after tissue expander placement and implant reconstruction is a suitable practice, compared to delayed placement following radiotherapy which may result in tissue expansion of irradiated skin flaps leading to capsular contracture, implant exposure, malposition and poor cosmesis.[7] Randomized trials after trials and meta-analyses have endorsed and validated chest wall radiotherapy to reduce local recurrences at 10 years which is maintained at 20 years (20% risk reduction; $p$=0.0001), reduce metastases free survival and enhance OS at 20 years (6% increase; $p$=0.0001).[30] Two dimensional radiotherapy is old fashioned, yet practiced in many centres in the under-developed World. On the contrary, in developed and developing countries the practice of whole-breast radiotherapy has gradually shifted to 3D-conformal radiotherapy (3D-CRT) & intensity modulated radiotherapy (IMRT) which results in net gains in therapeutic ratio. Cambridge breast IMRT trial has shown improvement in cosmesis and telangiectasis at 5 years using forward planning IMRT, while meta-analyses failed to show superiority of IMRT over standard tangential radiotherapy necessitating further testing. IMRT (VMAT) has a dosimetric advantage in the left breast or chest wall radiotherapy. It reduces the dose to the heart, contralateral breast and lung, but theoretically increases the risk of second cancer due to increase in volume of tissues receiving relatively low dose.[31–33] The ongoing UK SUPREMO trial shall determine role of radiotherapy in intermediate risk tumours e.g. pT2N0M0, high grade, with lymphatic vascular invasion, as well as in presence of 1–3 metastatic ALN.[34] The START trial uses 4000 cGy in 15 fractions with equivalent results to conventional radiotherapy (200 cGy x 25 fractions) for early breast cancer (pT1-3aN0-1M0).[35] The ongoing Fast Forward trial is investigating use of one week of radiotherapy. Trials are underway and partial breast irradiation individually practiced to attain local control.[36] Localized radiotherapy as a boost has been tried using intraoperative electron therapy, or mamosite, or interstitial implants in low risk invasive cancer in specialized centres, and is considered to be cosmetically superior and convenient. Radiotherapy is also attempted to control symptoms of cord compression, superior vena cava syndrome, symptomatic brain and painful bone metastases (+bisphosphonates) and for impending pathological fractures in weight bearing bones. HER2 neu amplified patients receive trastuzumab. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 & North Central Cancer Treatment Group (NCCTG) N9831 trials, the addition of trastuzumab to paclitaxel following doxorubicin/ cyclophosphamide (AC) reduced breast cancer deaths by 37% with absolute improvement in DFS of 11.5% at 10 years and 40% risk reduction in relapse ($p$= <0.0001).[37] The targeted agent is very well tolerated, with risk of having reduction in left ventricular ejection fraction (LVEF) and CCF. Trastuzumab associated fall in LVEF is managed with ACEi (lisinopril) and closely followed with echocardiography not necessitating discontinuation because of the risk-benefit ration in favour of the agent.[38] The agent is intermittently interrupted only in symptomatic patients or those having frank heart failure. In a UK based retrospective analysis, 80 consecutive patients with breast cancer are found to have brain metastases during follow-up, and are co-related with biomarkers: ALN involvement (40 %), ER/PgR negative (53.75 vs. 61.25 %), TNBC (28.75 %) & HER2+ status (40 %) are associated with brain metastasis.[39] Selected patients underwent surgical resection followed by whole brain radiotherapy plus tumour bed radiation boosts, which are associated with better long-term survival. Dual targeted therapy (trastuzumab + lapatinib) in adjuvant setting shows no additional benefit, whereas its use in neoadjuvant setting doubles the pathological response rates.[40] Pertuzumab addition to trastuzumab and a taxane in neoadjuvant setting (>T2 >N1 disease) enhances the pathological complete response (CR) rates (39.3% vs 21.5% $p$=0.0063), and the magnitude of improvement is much higher in HR negative patients (54.4% vs. 29.8%) compared to HR positive patients.

Adjuvant zoledronic acid improves DFS in postmenopausal females, and in pre-menopausal females treated with LHRH analogues. The relative risk reduction in bone recurrence is 34% ($p$=0.000001) and in breast cancer related deaths by 17% ($p$=0.004).[41,42] It remains to be defined whether its action is enhanced in low estrogen environment. The agent is also used (6 monthly for 2 years) with AIs to prevent or treat osteoporosis in clinical practice. Obesity and hyperinsulinemia increases recurrence risk which is lowered by the use of metformin in diabetics and by maintaining BMI between 20–25.[7,43] In an exploratory sub-group analysis of WINS trial, weight reduction (specially in TNBC) is associated with superior survival.[44] Palliative systemic therapy is offered for symptomatic improvement and for maintaining good quality of life. Metastatic patients are generally treated with sequential single agent chemotherapy to reduce toxicity, while combination chemotherapy is reserved for symptomatic patients (visceral crises). Endocrine therapy (tamoxifen, fulvestrant or AIs:

letrozole, anestrazole, exemestane is reserved for HR positive indolent and slow growing disease.[45] A phase II (FIRST) trial reveals, that first line use of fulvistrant (SERM) enhances time to progression and OS as first line treatment in postmenopausal HR positive locally advanced or metastatic disease.[46] This may be practice changing provided the phase III (FALCON) study validates these findings (Clinicaltrials.gov NCT01602380). These agents are also useful and invariably used for HR positive frail, elderly, poor performance and poor cardiac reserve patients, those having multiple co-morbids, or who refuse chemotherapy.

AIs are also used in combination with mTOR inhibitors (everolimus) to counter drug resistance to tamoxifen at progression in metastasis. Hormones are generally reserved for HR positive indolent, slow growing non-visceral metastases (in BALERO 2 study 35% patients have visceral metastases).[47] The PALOMA3 study (San Antonio 2015) assessed the efficacy of palbociclib and fulvestrant, where the combination improved PFS in hormone receptor positive advanced breast cancer that had progressed on prior endocrine therapy. Drug conjugates like trastuzumab emtansine (TDM-1) have recently emerged as standard systemic therapy in refractory progressive metastatsis and prior exposure to taxanes (TH3RESA trial- San Antonio 2015).[48] In fit, elderly (>70 years) HR positive patients who progress on endocrine therapy, or have visceral crises, decision to give chemotherapy rests on comprehensive geriatric assessment, potential toxicity and aims at achieving adequate quality of life without functional decline. Weekly paclitaxel is well tolerated, time tested and commonly practiced at our facility.[18]

Trastuzumab continuation in combination with subsequent salvage chemotherapy, or its re-challenge, lapatinib, pertuzumab and TDM-1 are monoclonal antibodies (former) and drug conjugates (later)[48] that are particularly helpful at disease progression in clinical practice. TDM-1 is also being tested in adjuvant setting. Everolimus has emerged as salvage therapy when it is combined with trastuzumab and vinorelbine for disease that has progressed after induction trastuzumab, as well as when combined with paclitaxel and trastuzumab where it enhances PFS in HR negative patients by 7 months (HR 0.66 95% CI, $p$=0.0049) in a recent randomized trial (BALERO 1) on its subset analyses. This should be read with caution as this is not the primary endpoint of the trial.[49,50]

Trastuzumab and lapatinib doublet is equally effective and well tolerated in HER2-neu patients not willing, or unsuitable for chemotherapy. Short course chemotherapy and re-initiation of salvage hormonal agents with trastuzumab in HR positive cases, is a frequent practice. The breast cancer patient's treatment may be optimized and individualized based on molecular classification, as identified by protein expression on IHC – table-2, and categorized systemic treatment as depicted in – table-3. Standard high-risk features are always kept in mind while making therapeutic decisions.[6] Intention is to treat biology, rather than the stage. The following text describes the characteristics and management of these sub-types in brief:

**Table-2: Breast cancer molecular classification (Intrinsic subtypes)**

| *IHC Markers* | 1. Luminal A | 2.Luminal B | Luminal B (HER2 like) | 3.HER2 like | 4.TNBC |
|---|---|---|---|---|---|
| Ki67 | <14% | ≥14% | usually high | very high | not matters |
| ER PgR | positive | positive | positive | negative | negative |
| HER2 neu | negative | negative | positive | positive | negative |
| SQUH Breast unit | 23% | 20% | 21% | 15% | 21% |

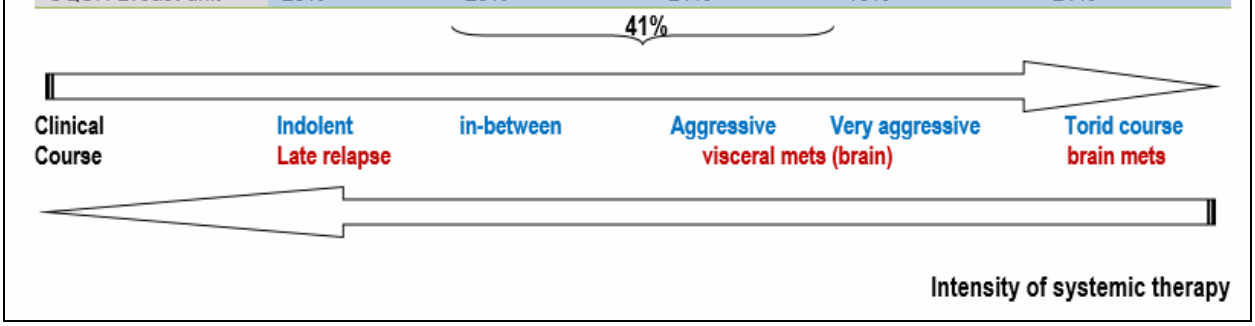

**Table-3: Proposed adjuvant systemic therapy protocols for intrinsic sub-types[75]**

| Molecular SUBTYPE | Treatment OPTIONS | |
|---|---|---|
| | Premenopausal*** | Postmenopausal |
| **LUMINAL A** | | |
| **pT1/3N0-N$_{1mic}$M0** | (seek Oncotype Dx) If not accessible, use AC x 4 ~ CMF x 6 | |
| - (low risk) | Tamox ± LHRH agonist/ or AIs + LHRH | AIs |
| - (intermediate risk) | AC x 4 + Tamox*** | AC x 4/ or CMF x 6 + AIs |
| - (high risk) | CAF x 6 + Tamox*** | CAF x 6/ or FE$^{100}$C x 6/ or DC + AIs |
| **pT4N+M0** | AC x + Dx x 4 + Tamox*** | FE$^{100}$C x 3 + Dx x 3/ or CAF x 6 + AIs |
| | **high risk clinic-pathological risk features (LN-ive); young age ≤35 years, G3, LVI+, T2, low ER/PgR+ivity* | |
| | ***IntClust2 subtype is notorious for late relapses (10-15 y), ideal candidates for extended adjuvant hormonal therapy* | |
| | ****Exemestane + Ovarian Function Supression (LHRH agonist, or BSO or pelvic XRT)* | |
| **LUMINAL B** | | |
| **<pT1N0M0** | CAF x 6/ or FE$^{100}$C x 6 + Tamox*** | CAF x 6/ FE$^{100}$C x 6 + AIs |
| **≥pT1N+M0** | AC x 4 + Dx x 4 + Tamox*** | AC x 4 + Dx x 4, DC* + AIs |
| **LUMINAL B, HER2 like** | | |
| **<pT1N0M0** | DCH x 6 + H x 1 yr + Tamox*** | DCH x 6/ PacH x 12 wk/ or + H x 1 yr + AIs |
| **≥pT1N+M0** | AC x 4 + DH x 4 + H + P + Tamox*** | AC x 4 + DH x 4 or PacH x 12 wk +H+P+ AIs |
| **HER2 amplified** | | |
| **T1aN0M0** | DCH x 6 + H x 1 yr | No adjuvant therapy |
| **<pT1N0M0** | DCH x 6 + H x 1 y | DCH x 6 + H x 1 yr/ or Pac x wk x 12 +H x1y |
| **≥pT1N+M0** | AC x 4 + DH x 4 ± P or TAC x 6 + H | AC x 4 + DxH + Pert x 4 + H x 1yr |
| **TNBC** | | |
| **T1a N0M0** (*M/ AC CA) | No adjuvant chemotherapy | No adjuvant chemotherapy |
| **T1aN0M0** | AC x 4 + Dx x 4 | No adjuvant chemotherapy |
| **pT1-4N+M0** | dense dose AC x 4 + Dx x 4 or TAC x 6 | AC x 4 + Dx x 4 or TAC x 6 or Pac x wk x 12 |
| **BRCA 1$_{mut}$** | ddAC x 4 – DC (cisplatin)/ CDDP/ Gemcitabine | CDDP/ Gemcitabine / or DC x 6 |
| **Frail, elderly, poor PS** | | weekly Pac x 12 |

A Adriamycin, C Cyclophosphamide, F 5-Fluorouracil, E Epirubicin,
Dx Docetaxel, C(DCH) Carboplatin, CDDP Cisplatin, H Herceptin,
Pert Pertuzumab, Tamox Tamoxifen, T Taxane, Pac Paclitaxel, AIs Aromatase Inhibitors
*M Medullary carcinoma, AC Adenoid cystic carcinoma

- **IHC based molecular classification of breast cancers:**

Breast carcinomas are a heterogenous group of cancers with different tumor biology. Immunostains are used to identify key predictive markers and subsequently describe four distinct sub-types: Luminal A, luminal B (includes luminal B,HER2 like) HER2 amplified, & TNBC – table-2.[51,52] There are two other sub-types: claudin like and normal like of unknown therapeutic significance. Claudin 1 is expressed in basal sub-type of TNBC and directly participates in promoting breast cancer progression, possibly through the alteration of expression of epithelial-mesenchymal-transition genes. The accuracy of the sub-typing is 80% compared to genomic determination, and is neither validated nor commonly practiced. Sub-typing definitely predicts prognosis but its predictive role in defining therapy requires gene expression array which is costly. The intensity of systemic treatment is escalated and optimized with the increasing aggression of the biologic sub-type.

1. **Luminal A:** is a sub-type that has an indolent natural history, tumours are generally small sized, axillary lymph glands are normal (N0), tumor proliferates slowly (Ki67 <14%) and grades are low (grade 1). These tumours have good prognosis, low p53 mutations (12%), moderate PI3K mutations (30-50%) but exhibit relative chemo-resistance.[53] Tumour tissues are subjected to tissue microarray in the Oncotype Dx test, and low risk stratified patients (score <18) receive anti-oestrogens, as the 10-year risk of distant recurrence remains low (6.8%) and chemotherapy in this subset does add to toxicity without any substantial gains in efficacy. Young patients may be offered combined estrogen blockade. Despite its meaningful utility in low risk luminal A, chemotherapy use in intermediate risk strata (risk score 18–30: 10 year risk of distant recurrence 14%) and ALN positivity remains ambiguous and until results from TAILORx (Clinicaltrials.gov NCT003101800), RxPONDER (RS <25) (Clinicaltrials.gov NCT01272037) & MINDACT trials (70 gene signature) (Clinicaltrials.gov NCT00433589) are available, clinico-pathological risk factors continue to determine whether these require chemotherapy –

table-3. High risk (risk score >31: 10-year risk of distant recurrence 30%) are additionally offered chemotherapy with sequential endocrine therapy that adds 28% absolute benefit in survival at 10 years.[54] There is another unfavourable group (IntClust2 group) within this sub-type, which is notorious for late relapses (after 10–15 years), and this is the sub-type that may benefit from extended adjuvant hormonal therapy.[55]

2. **Luminal B sub-type:** The proliferative rate is high (Ki67>14%), the rate of p53 mutation is frequent (30%), the tumour size is relatively large, grade is high and this may often harbour ALN metastases. This is relatively more aggressive compared to luminal A sub-type. It is treated with sequential triplet chemotherapy and endocrine therapy. Luminal B, HER2 like are more aggressive tumours with expression of HER2-neu. Tumours are larger, grades and Ki67 are high. This tumour sub-type warrants standard chemotherapeutic agents, monoclonal antibody & endocrine agents – table-3.
3. **HER2 amplified:** is clearly aggressive sub-type with high Ki67, rapid clinical course and early systemic metastases in the absence of targeted therapy. This sub-type harbours intrinsic resistance to tamoxifen and non-anthracyclines which requires trastuzumab addition to override it. This sub-type warrants three chemotherapy agents: TAC x 6 in young age or AC x 4 – Dx x 4. Weekly paclitaxel x 12 may be reserved for weak, frail, elderly having poor performance status combined with trastuzumab therapy for a year in adjuvant setting.[56–58] The absolute benefit of trastuzumab outweighs that of poly-chemotherapy (11.5% vs. 8%) in favour of targeted therapy.

   In a recent provocative retrospective analysis of NCCTG N9831 study (945 patients) presented by Perez *et al*, presence of stromal tumour infiltrating lymphocytes ($ST_r$TILS) (approximately ~10% of tumour samples) do not show benefit from addition of trastuzumab to chemotherapy. This is because trastuzumab stimulates adaptive immunity, but remains useful when the immune cells are low in the tumour micro-environment, and hence the substantial gains in 10-year relapse free survival (RFS) of 79.6% with its addition to chemotherapy vs. 64% with chemotherapy alone ($p$=<0.0001). The 10 years RFS with high $ST_r$TILS is 91% with chemotherapy alone and 80% with the addition of trastuzumab to chemotherapy ($p$=0.22).[59] Therefore $ST_r$TILS levels, essentially provide a biomarker, that could predict response to trastuzumab where high levels benefit from chemotherapy alone, saving costs, preventing inconvenience, and toxicity from trastuzumab. The monoclonal antibody is never given in tandem with anthracyclines to prevent cardiotoxicity. With early use of trastuzumab and its continuation beyond disease progression with salvage sequential single agent chemotherapy, the corresponding survival rates in advanced/ metastatic breast cancers (MBC) are high – table-1. Addition of pertuzumab to trastuzumab and chemotherapy in MBC is associated with 15.7 months OS benefit (HR 0.68).[60] Oral pan-HER irreversible tyrosine kinases e.g. niratinib and afatinib are undergoing phase II & III trials (Clinicaltrials.gov NCT01125566) as singlets or in combination with cytotoxics.
4. **Triple negative breast cancer (TNBC):** are notorious for occurring in young age, and with Afro-American/ Hispanic preponderance. It is defined by the lack of expression of the three receptors, i.e., ER, PgR, & HER2-neu. This is a sub-type unfamiliar prior to 2006, found its way into minds of oncologists for its rampant clinical course, and early relapses despite intensified therapy – table 3.

   These tumours in general exhibit large size and high grade, frequent ALN metastasis, and are associated with CK5/6 positivity. Breast tumours and their germ line DNA samples are analyzed using six technology platforms in one study and describes molecular characteristics of basal subtype of TNBC, i.e., frequent TP53 mutation (68-80%), RB-1 (5%), BRCA1 (19%) & BRCA2 (15%) function, MYC amplification, & phosphatidyl-inositol 3-kinase (PIK3) pathway activation (90%), epidermal growth factor receptor (EGFR) over-expression (60%), MDM2/4 amplification (7%) & PTEN mutations.[61] This is a heterogenous sub-type which either fails to respond to chemotherapy or is associated with higher clinical response. The course is rampant and notorious for early distant relapses (<2 years) and brain metastases, as well as local/ or in breast relapses. Unfortunately, chemotherapy is the only known therapy and everything else is a theory. The molecular features are also shared by high grade serous ovarian carcinomas which are treated with paclitaxel carboplatin combinations.

Medullary & adenoid cystic carcinoma are considered good prognosis and hence treated with adjuvant radiotherapy.[7] Metaplastic carcinoma (carcinosarcoma) is treated in same line as other TNBC. The standard of care for TNBC is AC x 4 followed by Taxanes x 4 or toxic regimens like TAC and dense dose AC followed by taxanes in young patients. Patients who are elderly, frail or have poor PS and have toxicity concerns, may be offered weekly paclitaxel, or DC, or CMF. Cisplatin based chemotherapy has been extensively used by

various groups and TNBC shows excellent pCR rates, as high as 60–80% in BRCA 1 mutation, but only ~20% in sporadic TNBC.[62,63] Addition of iniparib to gemcitabine and cisplatin doublets, yields response rates of 30%. The PARP inhibitors (poly ADP-ribose polymerase) also show promise in BRCA 1 mutation carriers, where they result in 'synthetic lethality' and enhance cell kill.[64,65] Combination of ixabepilone and capecitabine as salvage therapy associated with pCR of 26% and enhances the PFS,[66] while bevacizumab came into (ECOG 2100 & RIBBON 2 trial) and left the horizon of breast cancer treatment in the metastatic setting (RIBBON 1 trial), and its clinical use remains an individualized decision. However, in a recent finding from a randomized trial (443 patients) having stage II/ III TNBC (314 basal like), the addition of either carboplatin or bevacizumab to paclitaxel was associated with higher pCR breast (45% with paclitaxel alone to 64% with bevacizumab $p$=0.0009) and combined breast & axilla (43% with paclitaxel alone to 57% with bevacizumab $p$=0.014) rates in patients harbouring basal-like cancers: bevacizumab is toxic and is associated with higher discontinuation rates. The addition of carboplatin to paclitaxel in the basal-like subtype demonstrated a 14% higher pCR rate in the breast ($p$=0.014) and 13% higher pCR rate in the breast & axilla ($p$=0.018). Carboplatin's pCR rate is the same in non-basal like sub-types. It is also seen that expression of high proliferation mRNA gene signatures ($p$=0.0017), poor ER expression ($p$=0.0002), or high TP53 expression ($p$=0.0017) is associated with superior outcomes with neoadjuvant bevacizumab. The 11 immune signatures and tumour infiltrating lymphocytes could also predict benefit of adding neoadjuvant carboplatin.[67,68]

Gemcitabine cisplatin is used as first salvage in TNBC developing metastasis, and trials are underway to evaluate its efficacy as first-line combination. O'Shaughnessy J. *et al* used eribulin (EMBRACE trial) that improves OS in heavily pre-treated locally recurrent and MBC by 3.5 months ($p$ 0–04).[69] TNBC do not do well with early relapses and is generally associated with fatal outcomes. Localized recurrences (in breast tumor relapse, chest wall, ALN) are excised, followed by re-irradiation (if possible, using electron therapy) and subjected to adjuvant poly-chemotherapy for 3–6 cycles, which is associated with improvement in DFS at 5 years (69% with chemotherapy vs. 57% without).[70]

**Future considerations: TNBC Dilemma or an Opening**

The cancer genome atlas (TCGA) research network has undertaken gene expression profiling based on 3247 gene expression profiles (587 TNBC samples with unique gene expression patterns from 21 breast cancer data set), and described six TNBC sub-types in pre-clinical models[71,72] – table-4.

1. basal-like 1(BL1)
2. basal like 2 (BL2: BRCA 1 rich)
3. immunomodulatory sub-type (IM)
4. mesenchymal sub-type (M)
5. mesenchymal stem–like (MSL) &
6. luminal androgen receptor (LAR) subtype

These sub-types have opened a panorama of druggable targets. Findings from representative cell lines of TNBC sub-types by Leh-mann *et al* on-gene expression, is later evaluated by Masuda *et al*, who confirms a RR of NAC in 130 patients: standard treatment of AC x 4 followed by taxanes x 4 cycles, produce a pCR as high as 52% in BL 1, 0% in BL 2 and barely 10% in LAR sub-type of TNBC.[73,74]

**Table-4: TNBC sub-types, cellular pathways/ druggable target[71,72]**

| TNBC Subtype | Cellular pathways/ Targets | Therapeutic interventions |
|---|---|---|
| **BL 1 subtype** | heavily enriched in cell-cycle and cell-division pathway – DNA damage response genes | **TKIs, Cetuximab AUTHORS' CONTRIBUTION x 4 (pCR 52%)** |
| **BL 2 subtype** | involves the growth factor signalling pathway; BRCA1 loss | **PARPi + Carboplatin CDDP Gemcitabine CDDP CPT-11 AC x 4 – Taxanes x 4 (pCR 0%)** |
| **IM subtype** | enriched in immune cell processes | **? Immunotherapy; Nivolumab, pembrolizumab** |
| **M subtype** | is heavily enriched in pathways involved in cell motility, extracellular matrix (ECM) receptor interaction, and cell diff. pathways | **PI3K/ mTORi, Dasatinib** |
| **MSL subtype** | adds growth factor signalling pathways n angiogenesis | **Bevacizumab, PI3K/ mTORi, Dasatinib** |
| **LAR subtype** | is enriched in androgen-regulated pathways; production of amphiregulin (aggressive sub-type) | **Biclutamide (Clinicaltrials.gov NCT00468715), MDV3100, mTORi, PI3Ki** |

PARPi Poly (ADP) ribose polymerase inhibitors; Phosphoinositide -3-kinase (PI3K) inhibitors; CDDP Cisplatin, Mammamalian target of rapamycin inhibitors (mTORi).

## CONCLUSIONS

The breast cancers can easily be classified on immune-histochemistry, facilitating treatment and unifying clinical practices. It appears very convenient, cheap, presentable and a reproducible method and Oncologist may feel more confident in customizing treatment based on subtyping, but should have no hesitation in incorporating clinico-pathological characteristics, where the classification is unable to direct treatment decisions. The classification however, awaits validation through tissue microarray and in the setting of a prospective randomized trial. Long term follow-up is essential to provide data on survival outcomes and evaluate patterns of relapse with molecular classification. There are also series of ongoing randomized phase I, II & III trials evaluating drugable targets, and others countering drug resistance.

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|---|---|---|

# Address for Correspondence:

**Dr. Muhammad Furrukh,** Clinical Oncology (Medicine), SHIFA College of Medicine, SHIFA International Hospital, Islamabad-Pakistan.
**Cell:** +92 336 222 3555
**Email:** furrukh_1@yahoo.com