بوی باران، بوی سبزه، بوی خاک
عطر نرگس، رقص باد
آمده اینک بهار
خوش به حال روزگار

هفت سین ایرانی

Panel subject:
LOCALLY ADVANCED BREAST CANCER

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- **Case 1**

- A 39 year old woman who is a lawyer has come to you with the complaint of an enlarging painless and firm mass in her left breast.

- She tells that has had this mass since 5 months ago, firstly was smaller, but she did not care, with passing the time it became larger and firm, but has no pain, no other complaint.

- PMH: mild HTN since 3 years ago
- FH: -
- HH: -

- **What further Qs do you ask and why?**

- Other symptoms such as: WL, cough, bone pain, headache …

- **What do you do now?**

- **Ph/E?**

Alert and conscious, not pale,

no LAPs, Lung and spines: Nl

AP: Nl.

Wt: 63 Kg, Ht: 167 cm

Breasts: a 3*3 fixed non-tender mass in lt breast, about at 3 o'clock and a 2*1 mobile non-tender LN in lt axilla

What do you do now?

- Can we do surgery now?
- Or further W/U needed, then make correct decision?

- Imaging (mammo, sono)

- Mammo: BIRADs 4b

- Sono: Breasts: a 34*32 mm mass in lt breast, at 2 o'clock and a 22*11 mm mobile LN in lt axilla

  (probably breast mass: malignant, but axilla:benign)

- **Lab data includes:**

CBC, BUN/Cr, LFT, FBS&Lip: Nl,

ESR, LDH, Ca/P: Nl,

CEA, CA15-3: Nl,

PT, PTT, BT: Nl

- **What do you do now?**

- **Now what should you do?**

- **Can we start treatment now?**

- **NO, Biopsy needed.**

- **Core needle biopsy:**

  IDC, G3

  IHC: HR+, HER2/Neu: 2+, Ki67: 40%, p53: +

Now do surgery or nCht?

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PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known Benefits of Preoperative Systemic Therapy

- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities

- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides excellent research platform to test novel therapies and predictive biomarkers

Cautions

- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for Preoperative Systemic Therapy

- Patients with inoperable breast cancer:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - HER2-positive disease and TNBC, if ≥cT2 or ≥cN1
    - Large primary tumor relative to breast size in a patient who desires breast conservation
    - cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

A very important point:

Complete staging

before initiation of nCht

is critical.

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WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

CLINICAL STAGE

c≥T2[rr] or cN+ and M0
or
cT1c, cN0 HER2-positive disease
or
cT1c, cN0 TNBC
(For preoperative systemic therapy criteria, see BINV-M, 1 of 2)[pp]

ADDITIONAL WORKUP[a]

- Axillary assessment with exam
  - Consider ultrasound
  - Percutaneous biopsy of suspicious nodes[qq]
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase

Additional tests to consider:[h]
- Chest diagnostic CT ± contrast
- Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
- Bone scan or sodium fluoride PET/CT[ss] (category 2B)
- FDG PET/CT[tt] (optional)
- Breast MRI[b] (optional), with special consideration for mammographically occult tumors, if not previously done

For operable breast cancers: See Breast and Axillary Evaluation Prior to Preoperative Systemic Therapy (BINV-13)

For inoperable breast cancers: See Preoperative Systemic Therapy (BINV-15)

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]

Preferred Regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[c]
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[c]
- TC (docetaxel and cyclophosphamide)
- Olaparib, if germline *BRCA1/2* mutations[d,e]
- High-risk[f] triple-negative breast cancer (TNBC): Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab
- TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine

Useful in Certain Circumstances:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by weekly paclitaxel[c]
- Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)

Other Recommended Regimens:

- AC followed by docetaxel every 3 weeks[c]
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Select patients with TNBC:[g]
  - Paclitaxel + carboplatin[g] (various schedules)
  - Docetaxel + carboplatin[g] (preoperative setting only)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive

Preferred Regimens:

- Paclitaxel + trastuzumab[h]
- TCH (docetaxel/carboplatin/trastuzumab)
- TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]

Useful in Certain Circumstances:

- Docetaxel + cyclophosphamide + trastuzumab
- AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)
- Neratinib[i] (adjuvant setting only)
- Paclitaxel + trastuzumab + pertuzumab[j]
- Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)

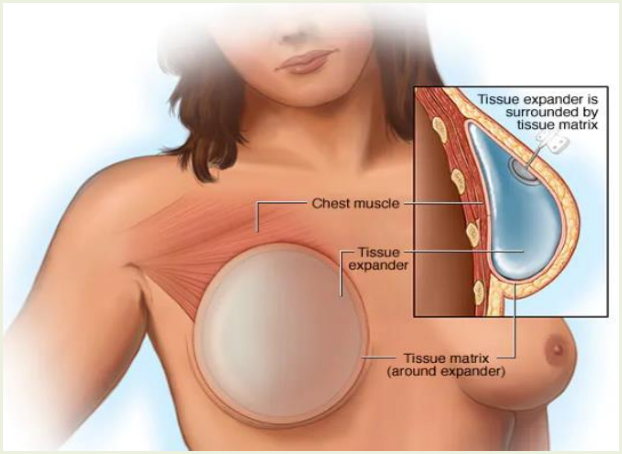
Other Recommended Regimens:

- AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
- AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

- After 4AC + 4TH, BCT + SLNB done
- Pathology report: pCR

- XRT?



- Reconstruction?

- Adjuvant endocrine tx

  (Tmx 10 yrs + Zoladex)

- SOFT and TEXT trial

- F/U

- After 4 yrs of starting Tmx, she has had pain in her back which doesn't respond to rest and medication.

- What do you do now?

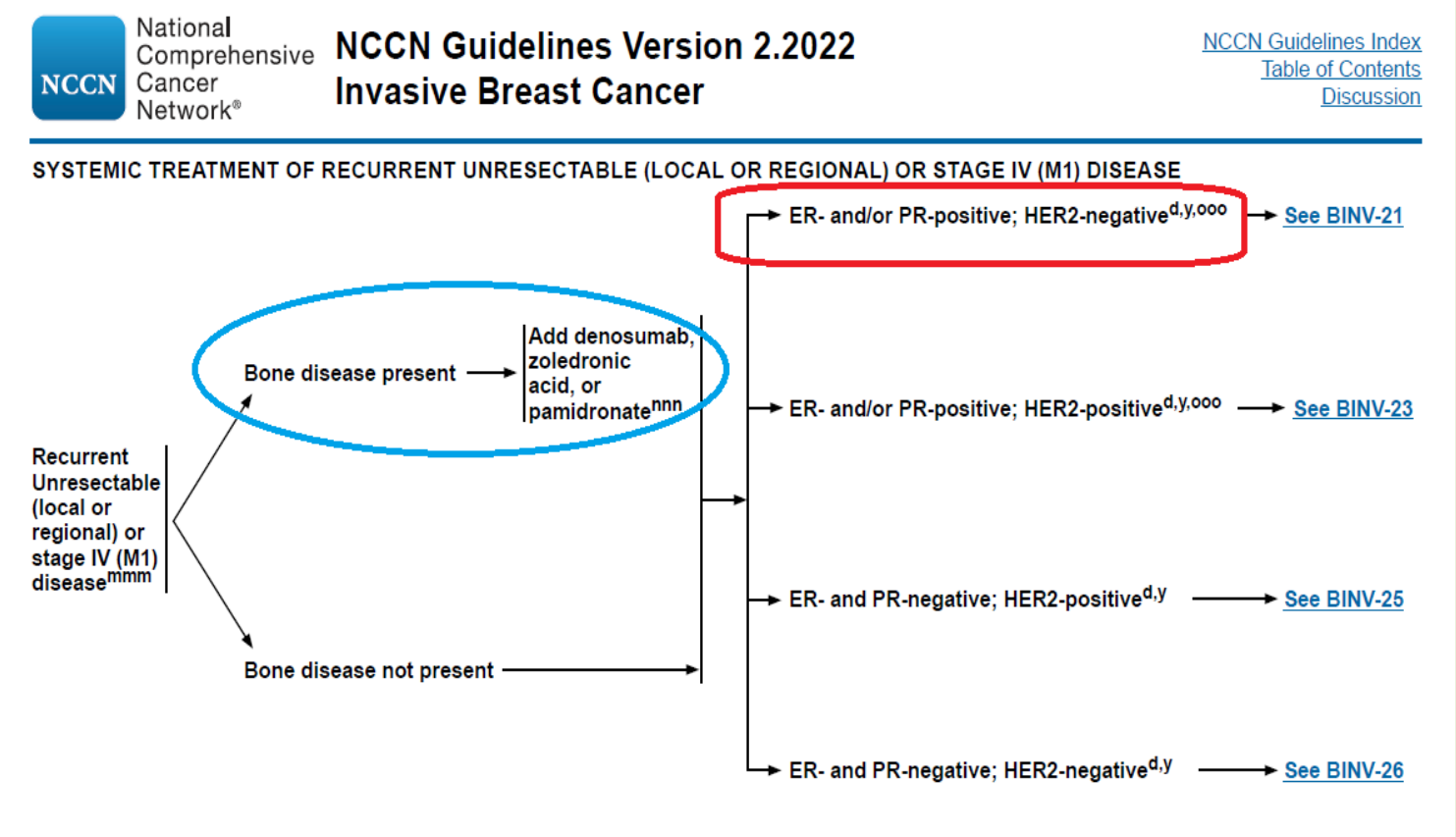
- W/U includes lab data and imaging (WBS, MRI+/-GAD or PET/CT) needed.

- Ph/E
- CA15-3: 98
- WBS: uptake in L5 body

- **Is biopsy needed?**
- **Other W/U needed?**

- Biopsy of L5: IDC, HR+, HER-
- APC CT with contrast: Nl

- **Tx?**



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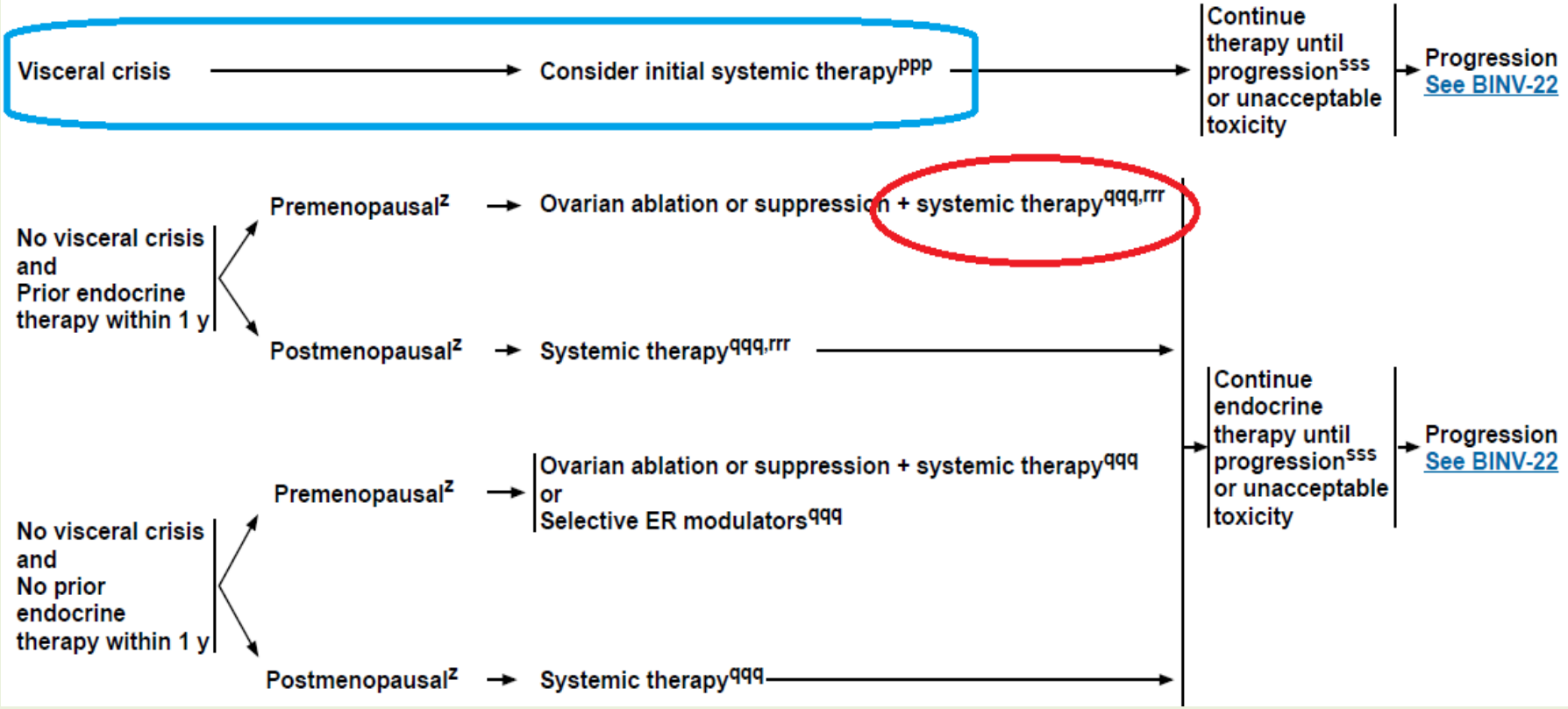
SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d]



ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[c]	Category 1	Preferred second- or subsequent-line therapy
TNBC	PD-L1 expression (using 22C3 antibody) Threshold for positivity combined positive score ≥10	IHC	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[d]	Category 1	Preferred first-line therapy[h]
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[d,f] Dostarlimab-gxly[g]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[d,f]	Category 2A	

Thank you for your attention