Breast Cancer: A Survey

EPIDEMIOLOGY

GENERAL

Incidence: leading type of newly diagnosed cancer in women (U.S)
Mortality: second leading cause or mortality in women (U.S)

NATURAL HISTORY

The survival at 5 yrs depends on stage ad Dx: 100% for STAGE I
20% if metastatic
Most potent prognostic factor for disease progression: **axillary node involvement**

RFs for BRCA

Female gender
Age
FHx of cancer syndrome: Ovarian + BRCA in same proband or family (nuclear)
Bilateral BRCA in the same premenopausal proband
BRCA-1, BRCA-2 mutations
HNPCC (Lynch) Syndrome
BRCA-1 and BRCA-2 are associated with 5 – 10% of all carcinomas
More commen in females of Jewish ancestry
Lifetime risk is 40 – 85% for BRCA, and 20 – 50% for Ovarian Cancer
Risk of ovarian cancer is also increased
Hx of ovarian carcinoma
Ionizing XRT to breasts or chest wall (in young females, usually due to HL)
Increased lifetime Estrogen exposure
Early Menarche
Nulliparity or Late Maternity
Delayed Menopause
Hormone Replacement Therapy (HRT) and OCs : minor risks
Breast Atypia (lobular carcinoma *in situ*)
(Diet)
(Exercise)
(EtOH)

SCREENING

MAMMOGRAPHY

The main benefit is detection of early-stage non-palpable cancers
MMG does not reduce mortality if done in patients 40 – 49 yrs
Recommendation (USPTF)
Evidence Base: mammography at > 50 yrs reduces BRCA mortality
Between 40 – 49 yrs, MMG offers a *slightly* decreased mortality, but NNT is too high to warrant widespread testing
The strongest evidence exists for the 50 – 69 yrs age group

MMG may be offered to pts > 70 yrs if the life expectancy is sufficiency high

BREAST SELF-EXAM

Evidence Base : BSE does **NOT** decrease the mortality due to BRCA

In fact, it increases the incidence of false positives on Bx

The appropriate use of BSE is self-monitoring for recurrent lesions in patients with prior BRCA currently in remission

CLINICIAN BREAST EXAM

Specificity approaches > 97.5%

For lesions undetectable on MMG, the CBE is positive in 5% of cases

PATHOGENESIS

BRCA follows a course of malignant transformation similar to many other carcinomas:

Benign tissue → (hormonal changes) → epithelial hyperplasia → (beginning of genetic instability) → atypia → carcinoma *in situ* (DCIS and LCIS) → acquisition of more mutations in TS and PO genes → increased expression of matrix proteases + loss of surface adhesion ligands → invasive carcinoma

HISTOPATHOLOGY

All BRCA arises from the terminal duct lobular units (unrelated to ductal and lobular carcinoma)

BRCA can be classified as *in situ* carcinoma or invasive carcinoma

Both types of carcinoma demonstrate ductal and lobular morphologies

Ductal Carcinoma In Situ (DCIS) is the precursor lesion to invasive ductal carcinoma

This tumor is clonal, with acquisition of multiple mutations

The cells are confined within the myoepithelial layers (surrounding the glandular epithelium)

There are no lymphatic vessels within the myoepithelial compartment, so there is no risk of metastasis *for a non-invasive clone*

Although the cancer is *in situ*, untreated lesions will eventually invade and metastasize

Goals of therapy: treat as if it is BRCA (resection, XRT, endocrine therapy)

Lobular Carcinoma In Situ (LCIS) predisposes the patient to BRCA

The entire breast parenchyma is at higher risk of malignant transformation

Goals of therapy: prevent occurrence of overt BRCA

Invasive Lobular Carcinoma is essentially equivalent to Invasive Ductal Carcinoma

EXCEPT: It is more difficult to detect by clinical palpations

It tends to be multifocal or bilateral

DIAGNOSIS

FNA: does not distinguish between *in situ* and invasive carcinoma
Core Needle Bx: does not provide tumor size
Lumpectomy or **Mastectomy**: does not r/o nodal disease

THUS: Sentinel node biopsy with exploratory surgical pathology is the most informative method for staging

RECURRENCE OF BREAST CANCER

RFs for **RECURRENT BRCA**

Post-surgical margins: the strongest risk factor
Axillary nodes
Larger tumor volume
High-grade lesions
Higher stages of disease
Overexpression of HER2 (EGF receptor): *more likely in postmenopausal women*
E-R and P-R negative tumors : *more likely in premenopausal women*

Age
Extracapsular Extension
Lymphativ Invasion

Recurrent lesions may be distant metastasis, local relapsing lesions, or new primary tumors

STAGING

STAGE I: Tumor < 2 cm, N0, M0
STAGE II: Tumor 2 – 5 cm, fluctuant axillary nodes, N0
Tumor > 5 cm, N0, M0
STAGE III: Any size tumor, fixed nodal disease (axillary or internal mammary), extramammilary extension (skin, pectoralis, chest wall)
STAGE IV: M1

Higher stage is a strong RF for recurrence

METASTASIS: Some patients will have microscopic metastasis at the time of Dx. Eventually, these lesions grow to be appreciable.

TREATMENT

SURGERY

The evidence shows that MASTECOMY is **equivalent** to BREAST-CONSERVATIVE SURGERY (Lumpectomy + Adjuvant XRT)

Mastectomy

May be preferred in advanced local BRCA

Also indicated for recurrent BRCA after treatment with Breast-Conservative Surgery

Breast-Conservative

Excision (lumpectomy, partial mastectomy, tylectomy) + adjuvant XRT

Even if the surgical margins are negative, there is a significant risk of recurrence if XRT is not delivered

Thus, this is the preferred strategy for early-stage tumors

Sentinel Node Bx

A radioactive tracer is injected and collects in metabolically upregulated axillary nodes

The sentinel node is examined for uptake by LM

If positive for disease, a full axiallary node dissection is performed

ARs: chronic lymphedema of the arm

RADIATION

IN BREAST-CONSERVATIVE THERAPY

XRT improves local control, with statistical significant seen immediately

This is due to the ability of ionizing radiation to sterilize microscopic disease

Without XRT, the rate of local recurrence tends to plateau at 30% within 5 – 10 yrs. XRT reduces this risk to 10% at 15 yrs.

XRT improves survival, but the statistical benefit is only seen at 15 yrs

AS ADJUVANT THERAPY for **COMPLETE MASTECTOMY + CHEMOTHERAPY**

XRT improves local control, with effect similar to BCT

XRT improves Disease-Free Survival (10 yrs)

Effect on overall survival is unknown

HOWEVER, this benefit is only seen in certain patient risk groups:

Tumor size> 5 cm

≥ 4 nodes on axillary dissection

≤ 3 nodes for higher grade lesions or extracapsular extension

Deep or close margins

Cutaneous Involvement

CHEMOTHERAPY and HORMONAL ANTAGONIST THERAPY

The utility of chemotherapy strongly depends on the baseline risk of recurrence

Chemotherapy: the standard is adjuvant cyclophosphamide + methotraxate + 5-FU
Molecular Therapy: Trastuzumab is an antagonist at the HER/neu receptor for EGF

Average Benefits of **Intervention**

30 – 50% of post-surgical patients who are **not definitively free** of disease will benefit from adjuvant therapy (pooled chemotherapy and hormonal modulation)

Chemotherapy reduces the baseline risk by 20 – 30%
Hormonal therapy reduces the baseline risk by 30 – 50% in E-R+/P-R+ tumors only

Thus, combined therapy has the greatest efficacy when the baseline risk is HIGH. There is only a marginal benefit when the baseline risk is LOW.

PREVENTION

Approximately 65% of BRCA is ER+, and thus responsive to estrogen receptor antagonism
In high-risk females, **TAMOXIFEN** reduces the risk of

- Invasive carcinoma
- Progression of LCIS to DCIS (*in situ* carcinoma)
- Osteoporotic Fractures

However, the risk of some adverse outcomes was increased:

- Strokes (ischemic)
- VTE and Pulmonary Embolism
- Endometrial Carcinoma
- Cataracts