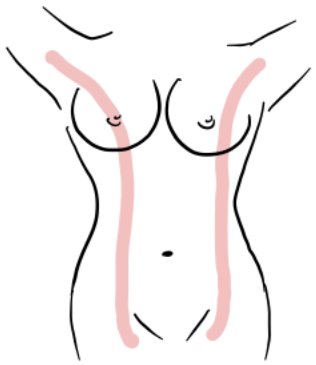
BREAST. ANATOMY

EMBRYOLOGY

5th-6th week of intrauterine life - 2 ventral ectodermal ridges from axilla to inguinal region
↓
Mammary ridges / Milk lines



ingrowth of ectoderm ⟶ primary tissue bud is formed in the mesenchyme
↓
15-20 secondary buds
↓
Epithelial cords (lactiferous ducts)

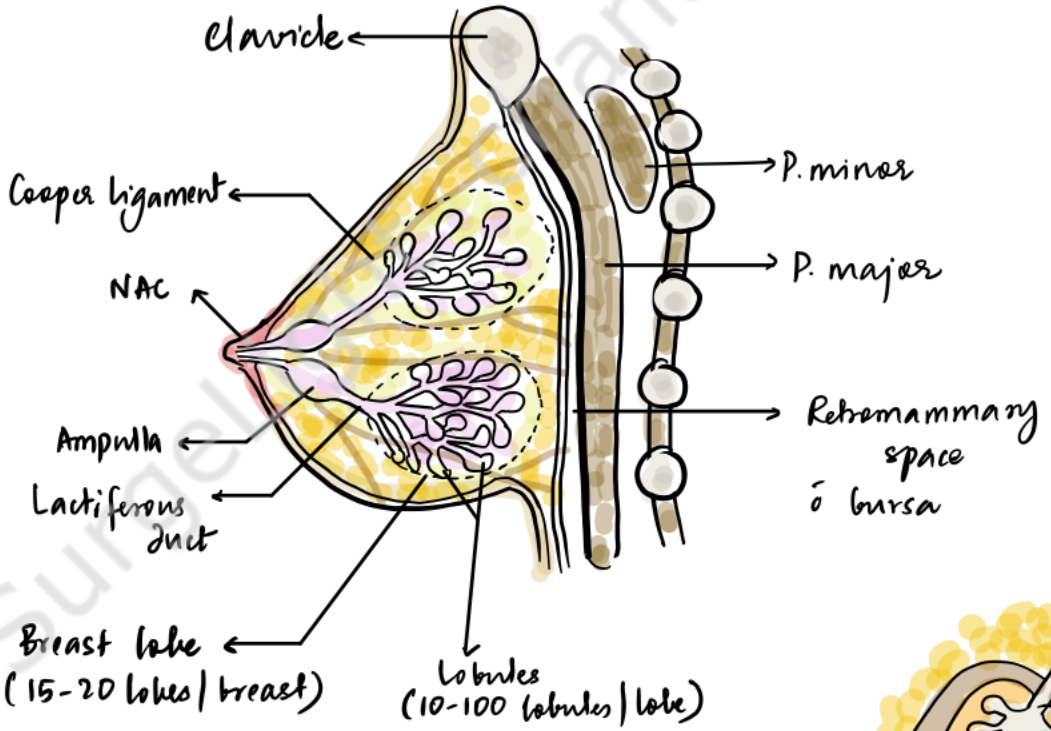
Polythelia - multiple nipples draining a single breast

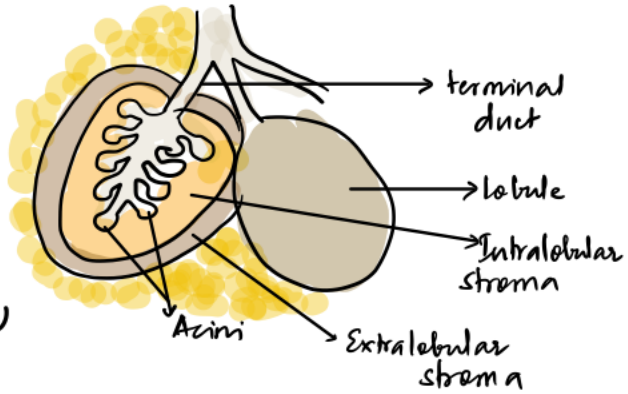
Supernumerary nipples - rudimentary nipples occuring anywhere along milk line

ANATOMY

- Lies between subdermal fat and pectoral fascia

- Extent
  - 2nd ⟶ 6th rib / inframammary fold
  - Lateral border of sternum to anterior axillary line (AAL)
  - Axillary tail of Spence extends laterally across AAL
  - Upper outer quadrant - max. breast tissue

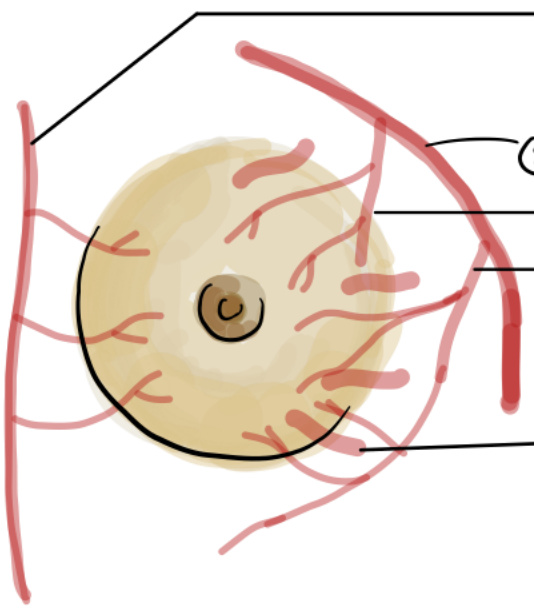




TDLU

Mature breast
- Glandular epithelium → TDLU
- Stroma → Myoepithelium cells.
- Adipose tissue

BLOOD SUPPLY



1. Internal mammary artery (perforating branches)
2. AXILLARY ARTERY
   - Thoraco-acromial artery
   - Lateral thoracic artery
3. Lateral branches from posterior intercostal As

VENOUS DRAINAGE

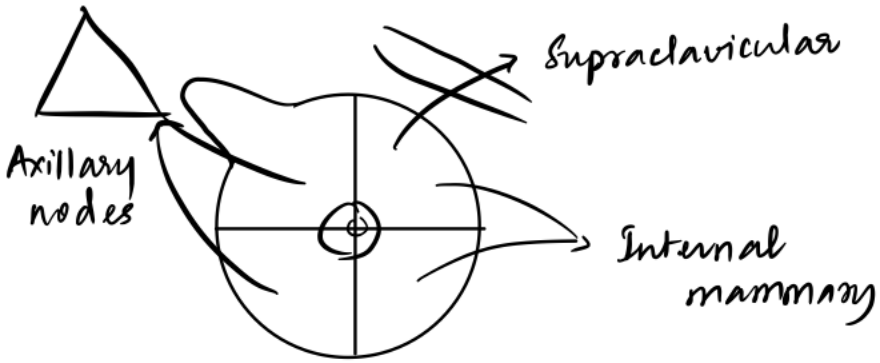
- parallels the arterial supply
- Batson's venous plexus
  - invests the vertebrae from skull base to sacrum
  - receives posterior intercostal veins

NERVE SUPPLY

- Lateral cutaneous branches of 3th - 6th intercostal nerves (via spaces between the slips of serratous anterior)
- T_2 - Intercostobrachial nerve - also medial aspect of arm
- Cutaneous branches of cervical plexus

LYMPHATIC DRAINAGE OF THE BREAST

a) Skin over the breast



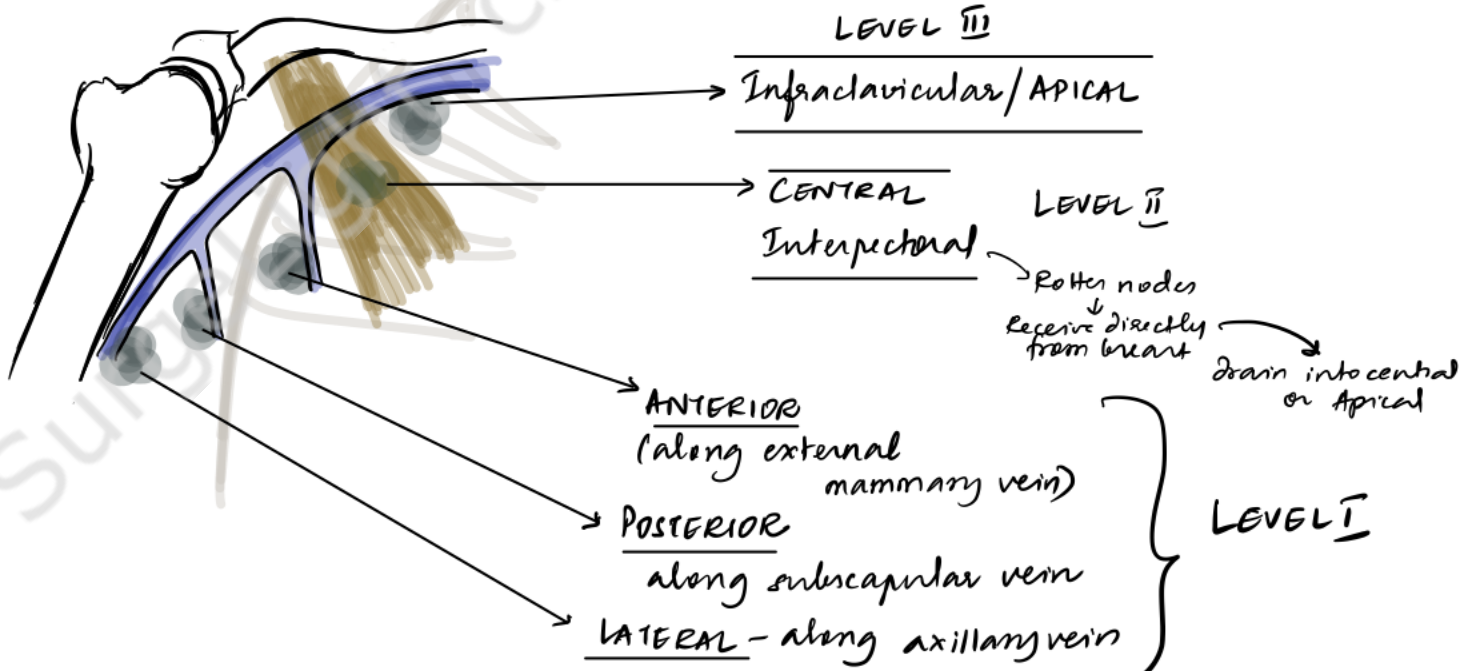
b) Nipple areola complex
↓
Subareolar plexus of Sappey

c) Breast parenchyma
- ↓ Internal mammary nodes
- → Axillary nodes

INTERNAL MAMMARY NODES

- Along internal mammary vessels 1-2cm from sternal margin
- Receive from inner quadrants
- Communicate c/l internal mammary nodes across midline

Levels of Axillary nodes - BERG's LEVELS



Path of Gerota : Lymphatics from lower inner quadrant form a plexus on rectus sheath → this plexus communicates c subdiaphragmatic lymphatic plexus & peritoneal lymphatics → ? liver involvement, transcoelomic spread

BENIGN BREAST DISEASES

ANDI - Aberrations in normal development & involution of the breast

Spectrum of conditions : normal → disorder → disease

	NORMAL	DISORDER	DISEASE
EARLY REPRODUCTIVE YEARS - 15-25y	Lobular development →	Fibroadenoma →	Giant Fibroadenoma
	Stromal development →	Adolescent hypertrophy →	Gigantomastia
	Nipple eversion →	Nipple invasion (↓ development of major ducts → short ducts - prevents protrusion) →	(when major duct obstruction occurs) • Subareolar abscess • Mammary duct fistula
LATER REPRODUCTIVE YEARS 25-40y	Cyclical changes of menstruation →	Premenstrual enlargement; Cyclical mastalgia ± nodularity (FIBROADENOSIS) →	Incapacitating mastalgia; Painful nodularity persisting > 1wk
	Epithelial hyperplasia of pregnancy →	Bloody nipple discharge	
INVOLUTION 35-55y	Lobular involution →	• Macrocysts • Sclerosing lesions	
	Duct involution: Dilatation →	Duct ectasia →	Periductal mastitis → periductal fibrosis → NIPPLE RETRACTION
	Sclerosis →	Nipple retraction	
	Epithelial turnover →	Epithelial hyperplasia →	Epithelial hyperplasia ± ATYPIA

CLASSIFICATION OF BENIGN BREAST DISORDERS

NON PROLIFERATIVE DISORDERS

- Cysts
- Apocrine metaplasia
- Calcifications
- Fibroadenoma

PROLIFERATIVE DISORDERS

WITHOUT ATYPIA

- Sclerosing adenosis
- Radial scar
- Ductal epithelial hyperplasia
- Intraductal papilloma

WITH ATYPIA

- Atypical Ductal Hyperplasia
- Atypical Lobular Hyperplasia

Breast cancer risk

- No increased risk – Non proliferative lesions
  Sclerosing adenosis
  Intraductal Papilloma
- 1.5-2x ↑ risk – Florid hyperplasia
- 4x ↑ risk – ADH, ALH
- 7x ↑ risk – ADH ± ductal involvement
- >10x ↑ risk – DCIS, LCIS

} Premalignant

FIBROADENOMA

- benign lesion of the breast
- Proliferation of both glandular & stromal elements of TDLU
- TYPES

Pericanalicular
- Hard, smaller
- seen in younger age
- arises from the tissue outside the elastic lamina covering the ductules
- can be easily enucleated
- Duct & glandular tissue compressed into linear branching structures by stroma

Intracanalicular
- Soft, larger
- older patients
- arises from the tissue within the elastic lamina covering the ductules
- stroma proliferates around patent ducts

- 'Breast mouse'
  > 3cm - Giant fibroadenoma | > 5cm acc to Bailey

VARIANTS

Myxoid fibroadenoma - Myxoid stromal change
Cellular fibroadenoma - Diffuse stromal hypercellularity
Juvenile fibroadenoma
Complex fibroadenoma
- a/c cysts, sclerosing adenosis
- epithelial microcalcifications
- papillary apocrine metaplasia

→ Risk of malignancy

Evaluation
- Younger pt - clinical
- older - Mammo, FNAC } r/o Ca breast

Rx

Excision
- Circumareolar incision - Webster
- Sub-mammary - Gaillard Thomas incision
- Radial incision
- Along RSTL / Langer's lines

DUCTAL AND LOBULAR CARCINOMA IN SITU

Non invasive breast cancer: malignant cells are confined within natural ductal/alveolar boundaries without any invasion into the surrounding stroma through the basement membrane

DCIS

DCIS : LCIS :: >2 : 1

Areas of invasion may be minute ⇒ accurate dx of DCIS necessitates the analysis of multiple microscopic sections to exclude invasion

- DCIS is predominantly seen in the female breast; but accounts for ~5% male Ca breast
- Mammogram - microcalcifications - palpable/ non palpable

PATHOLOGY

- Proliferation of the epithelium lining the minor ducts → papillary growths within ductal lamina

HISTOLOGICAL SUBTYPES

NON COMEDO	INTERMEDIATE	COMEDO
Papillary / Cribriform / Solid patterns	mixture of multiple non-comedo patterns	Necrotic
Low grade	Intermediate grade	High grade
No necrosis	± focal necrosis	Extensive necrosis

PROGRESSION OF DCIS GRADES

Non comedo → (Necrosis (cells outstrip blood supply)) → Comedo

Micropapillary / Papillary / Cribriform / Solid

- Coalesce to form clumps ± spaces in between
- spaces obliterated

Calcium deposition in areas of necrosis

- Risk of invasive Ca ~ 5x in DCIS
  - in ipsilateral breast in the same quadrant as DCIS

} ⇒ DCIS is an anatomic precursor

PROGNOSTIC INDICES

1) VAN-NUY'S

	1	2	3
Size	< 1.5cm	1.5 – 4cm	> 4cm
Margin	≥ 10mm	1 – 10mm	< 1mm
Grade, Necrosis	↓/↔ No necrosis	↓/↔ Necrosis +	↑, Necrosis +

- 4-6 → BCS c̄ or ̄ RT
  - 1% rec ; 5YS – 97-99%
- 7-9 → BCS + RT
  - 20% rec ; 5YS – 73-84%
- 10-12 → Mastectomy
  - 50% rec ; 5YS – 34-51%

2) NOTTINGHAM PROGNOSTIC INDEX

(0.2 × tumor size in cm) + LN stage + Grade

- < 3.4 → Good prognosis — 15YS – 80%
- 3.4 - 5.4 → Moderate prognosis — 40%
- > 5.4 → Poor prognosis — 15%

MANAGEMENT

DCIS
Tis N₀ M₀

↓

Diagnostic B/L Mammogram
ER status
± Breast MRI

For non palpable DCIS - needle localization / image guided techniques
↓
specimen mammography

→ **Lumpectomy**
c̄ margin of atleast 2mm
- Radiotherapy to decrease ipsilateral breast tumor recurrence
  - WBRT ↓ prefered
  - ABPI - may be considered in low risk patients c̄ tumor size ≤ 2.5cm, margins > 3mm, low/ intermediate grade

→ **Mastectomy**
- in larger lesions (esp >4cm)
- when lumpectomy c̄ adequate margins is not feasible
- ± SLNB

↓

Adjuvant Tamoxifen considered for ER+

LCIS

- originates from the terminal ductal lobular units → distension & distortion of TDLU by cells ± large size & cytoplasmic mucoid globules
- DEVELOPS **ONLY** in female breast

- Mammography - NEIGHBORHOOD CALCIFICATION
- Average age at Dx - 45y
- American : African american :: 12 : 1

Invasive cancer - ~25-35% of women ± LCIS
- may develop in any breast, irrespective of the one ± LCIS
- Multicentricity ++
- in women ± h/o LCIS ; 65% of ca are Ductal carcinoma

LCIS is a marker of ↑ invasive cancer risk ; NOT an anatomic precursor

Rx - Observation, chemoprevention ± tamoxifen / Risk reducing B/L mastectomy

LCIS	DCIS
~45y	~55y
2-5% incidence	5-10%
No clinical features	Mass / Pain / Nipple discharge
No characteristic mammo signs of lesion - Neighborhood calcification	Microcalcification on mammo
Invasive carcinoma	
synchronous - 5%	2-46%
Incidence - 25-35%	~25-70%
Bilateral	Ipsilateral
Multicentricity 60-90%	40-80%

(Schwartz 564pg)

NON PALPABLE BREAST LESIONS

Mammographic abnormalities that cannot be detected by physical examination

Eg: Microcalcifications
masses
architectural distortions
asymmetries

BIRADS - 3 ⟶ followup using short-interval mammograms over a 2-year period

75-80% of diagnostic biopsies for non-palpable lesions ⟶ BENIGN

Approach

Wire localisation
or
Seed localisation - 4.5mm ^{125}I seeds } at a mammographic suite or · USG · Stereotactic techniques

↓

FNAC - discordant
Eg - ADH

↓ Excision biopsy

↓

Specimen radiography

BREAST CANCER - TYPES

(Invasive)

INVASIVE DUCTAL CARCINOMA (NOS)

80 %

Syn: Scirrhous
Simplex
NST

- Perimenopausal & post menopausal women
- 5th - 6th decades
- Firm - hard mass
- Poorly defined margins
- cut surface - central stellate configuration
- 'Gritty'
- Chalky white / yellow streaks extending into surrounding tissue

-75 % ER +ve

INVASIVE LOBULAR CARCINOMA

10 %

small cells
- rounded nuclei
- inconspicuous nucleoli
- scant cytoplasm

- intracytoplasmic mucin (IHC)
↓
displaces nucleus (signet cell)

Clinically inapparent
↓
Poorly defined diffuse mass

Multifocal, Multicentric, Bilateral

90 % - ER +ve

MEDULLARY CARCINOMA

4 %

frequent phenotype of BRCA-1

Soft
hemorrhagic
Bulky
Deep seated

20 % B/L

- Dense lympho-reticular infiltrate (enlarged LN may be reactive)
- Pleomorphic nuclei
- sheet like

50 % a/i DCIS

<10 % ER +ve

MUCINOUS CARCINOMA

2 %

Syn: Colloid Ca

Older pts
Bulky

Extracellular pools of mucin surrounding aggregates of low GRADE cells

Glistening

Fibrosis ±
↓
firm consistency

90 % ER +ve

PAPILLARY CARCINOMA

2 %

7th decade

NON WHITE

Small, <3cm

Papillae
- fibrovascular stalks i multilayered epithelium

↓ Axillary LN mets

87 % ER +ve

TUBULAR CARCINOMA

2 %

Perimenopausal
early menopausal

invasive cribriform Ca is a closely related variant

LN & distant mets are rare

LONG TERM SURVIVAL NEARLY 100 %

94 % ER +ve

Very rare variants – Adenoid cystic, Squamous cell, apocrine

MOLECULAR TYPES OF BREAST CANCER

LUMINAL 'A'

ER/PR +
HER 2 −
↓ Ki67

Low grade
Good outcome

LUMINAL 'B'

ER/PR ±
HER ±
↑ Ki67

Int / High Grade
Int. outcome

a/i BRCA-2

BASAL-LIKE

Triple negative
↑ Ki67
BASAL MARKERS +
P53 mutations +

High grade
Poor outcome

a/i BRCA1

HER 2+ / ER −

ER −
PR ±
HER 2 ±
↑ Ki67

High grade
Poor prognosis

Molecular apocrine

ER/PR −
HER ±
↑ Ki67
Apocrine markers

Poor prognosis

BREAST USG, MRI

USG of the Breast

- Solid vs cystic
- Demonstrates echogenic qualities of specific solid abnormalities
- helps resolve equivocal mammographic findings
- Imaging regional nodes
  - → 35-82% Sensitivity, 73-97% specificity
  - Cortical thickening
  - Oval → Circular
  - ≥ 1cm
  - Loss of fatty hilum
  - hypoechoic internal echoes
- cannot reliably detect lesions ≤ 1cm
- Important adjunct to mammography
- Useful in younger women & dense breasts

Combined sensitivity of USG + Mammo > Mammo alone

- helps in guided biopsies

Indications for Breast MRI

- Women with ≥ 20-25% lifetime risk of Ca breast

Screening

- BRCA 1/2 carriers
- 1st degree relative of BRCA 1/2 (themselves not tested)
- H/o chest irradiation at 10-30y of age
- Carriers of / 1° relatives of
  - Li Fraumen So
  - Cowden So
  - Bannayan Riley Ruvalcaba syndrome

- Women with Moderate risk - 15-20% lifetime risk
  - Personal h/o breast cancer, DCIS / LCIS / ADH / ALH
  - Extremely dense breasts on mammogram

- Axillary LN with Ca Breast with mammographically unidentified primary
- Paget's disease of the nipple with radiologically unidentified primary

- Imaging in women with implants
- helps detect multicentric / multifocal disease in index breast or contralateral breast
  - very sensitive for DCIS

- Use of specialized dedicated breast coils

Breast Cancer Risk Assessment

Average lifetime risk - 12%

Gail risk assessment model - Cumulative breast cancer risk according to decade
- 5 year risk
- Lifetime risk

① Age at menarche
- < 12 → 1.21
- 12-13
- ≥ 14

② Breast biopsy / h/o benign breast disease
- 0
- 1
- ≥ 2
  - < 50y - 2.88
  - ≥ 50y - 1.62

③ Age at first live birth
- < 20y
- 20-24
- 25-29
- ≥ 30y

→ Number of first degree relatives with h/o breast cancer
- 0
- 1
- ≥ 2

Other models

Claus model - incorporates more info about family history
- risk acc. to decade of life

Tyrer Cuzick model - Family history + Individual risk information

Variable	Gail	Claus	Ford	Tyrer–Cuzick	Manual
Personal information					
Age	Yes	Yes	Yes	Yes	Yes
Body mass index	No	No	No	Yes	No
Hormonal factors					
Menarche	Yes	No	No	Yes	Yes
First live birth	Yes	No	No	Yes	Yes
Menopause	No	No	No	Yes	Yes
Personal breast disease					
Breast biopsies	Yes	No	No	Yes	Yes
Atypical hyperplasia	Yes	No	No	Yes	Yes
LCIS	No	No	No	Yes	Yes
Family history					
First degree relatives	Yes	Yes	Yes	Yes	Yes
Second degree relatives	No	Yes	Yes	Yes	Yes
Age of onset of cancer	No	Yes	Yes	Yes	Yes
Bilateral breast cancer	No	No	Yes	Yes	Yes
Ovarian cancer	No	No	Yes	Yes	Yes
Male breast cancer	No	No	Yes	No	Yes

MAMMOGRAPHY

Radiographic modality wherein the breast is compressed between plates to
- reduce the thickness of the tissue through which radiation must pass
- separate adjacent structures
- improve resolution

on mammo - fat absorbs relatively little radiation & provides contrasting BG
∴ sensitivity of mammo is limited by breast density

Earlier - Xeromammography
conventional film-screen mammography → Digital mammography

↓
Delivers ~0.1cGy / study
↓
Equivalent to 4-5 x Rays

↓
allows manipulation & enhancement of images (useful in dense breasts; < 50y)
↓
facilitates interpretation

No ↑ breast cancer risk a/i radiation dose delivered using mammography

SCREENING MAMMOGRAPHY

- Performed in asymptomatic women to detect breast cancer

2 views

CRANIOCAUDAL VIEW (CC)
- provides better visualisation of the MEDIAL ASPECT of the breast
- permits greater breast compression

(MLO) MEDIOLATERAL OBLIQUE VIEW
- images the greatest volume of breast tissue including
  - upper outer quadrant
  - axillary tail of Spence

DIAGNOSTIC MAMMOGRAPHY → used to evaluate women i abnormal findings such as breast mass / nipple discharge

ADDITIONAL VIEWS (apart from CC, MLO)

90° LATERAL VIEW
↓
used along with craniocaudal view to triangulate the exact location of an abnormality

SPOT COMPRESSION VIEW
↓
compression device is directly placed over a mammographic abnormality obscured by overlying tissues
- minimizes motion artefacts
- improves definition & resolution
- ↓ radiation dose needed to penetrate tissue

Combined i magnification techniques to resolve calcifications & margins

MAMMOGRAPHIC GUIDANCE : for needle localisation, needle biopsy

DIGITAL BREAST TOMOSYNTHESIS

→ 3D images

→ to mitigate the shortcomings of standard 2D mammography such as: • obscured findings due to - Parenchymal density
- Superimposition of breast tissue

Multiple projection images are reconstructed to allow review of thin breast sections (~0.5mm)

- better characterisation of non-calcified lesions

MAMMOGRAPHIC FEATURES

- Solid mass ± stellate features
- asymmetric thickening of breast tissue / architectural distortions
- clustered microcalcifications (<0.5mm size ; >5 particles in a volume of $1cm^3$
- spiculated margins

BIRADS

0 - Incomplete assessment → needs: additional evaluation / prior mammo for comparison

1 - NEGATIVE

2 - Benign - routine annual screening suffices

3 - Probably benign (<2% malignant)

4 - Suspicious abnormality (2-95% malignant) → consider biopsy

5 - Highly suggestive of malignancy (>95%)

6 - Biopsy proven malignancy

SCREENING MAMMOGRAPHY RECOMMENDATIONS

Annual screening mammography ≥ 40y (American cancer society)

≥ 50y → screening reduces mortality d/t Breast cancer by 20-25%

∴ Targetted screening mammography in pts <50y → using risk assessment models

BREAST USG, MRI

USG of the Breast

- Solid vs cystic
- Demonstrates echogenic qualities of specific solid abnormalities
- helps resolve equivocal mammographic findings
- Imaging regional nodes
  - → 35-82% Sensitivity, 73-97% specificity
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  - Personal h/o breast cancer, DCIS / LCIS / ADH / ALH
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FAMILIAL & HEREDITARY BREAST CANCER

Sporadic breast cancer - 65-75%.

FAMILIAL - 20-30%.
HEREDITARY - 5-10%.

1) BRCA-1 - 17q → 45%.
2) BRCA-2 - 13q → 35%.
3) p53 / Li Fraumeni - 17p — Sarcoma, lymphoma, adrenal
4) STK11 / LKB - Peutz Jeghers - 19p
5) PTEN / Cowden - 10q — Thyroid + GI + skin
6) MSH-2 / MLH-1 - Muir Torre
7) ATM
8) Hereditary diffuse Gastric Ca SO - CDH-1 mutation
9) Unknown → 20%.

(3)–(8): < 1%.

BRCA

- Autosomal dominant inheritance ; high penetrance → chance that mutation carriers develop disease
- early age of onset, B/c breast cancer

	GENERAL POPULATION	BRCA-1	BRCA-2
Breast cancer risk (lifetime)	~12%.	50-90%.	30-80%.
Risk of 2nd primary breast cancer	2% in 5y	21% in 10y 83% in 70y age	10.8% in 10y 62% in 70y age
Lifetime risk of ovarian Ca	1-2%.	40%-60%	20-30%.
Male breast cancer	0.1%.	1.2%.	~10%.
Prostate cancer (in males)	6% at 69y	8.6% at 65y	15% by age 65 20% lifetime
Pancreatic cancer	0.50%.	1-3%	2-7%.
		Other Ca: Colon	↑ risk of melanoma (Cutaneous & Ocular) GB cancer, Bile duct cancer Stomach cancer
HISTOPATHOLOGY		Poorly diff IDC Triple negative (Basal type) 66% of BRCA-1 DCIS is ER-ve (No use of Tamoxifen prophylaxis)	Well diff IDC Luminal type Hormone +ve

CANCER PREVENTION IN BRCA mutation carriers

1) Risk-reducing B/L mastectomy & reconstruction
2) Risk reducing B/L salpingo-oophorectomy
3) Intensive surveillance of breast & ovarian cancer
4) Chemoprevention

B/L Mastectomy → 90% ↓ in breast cancer risk

Until then - clinical breast examination 6 monthly
Annual mammo from 25y
MRI for screening

Risk-reducing BSO - 90% ↓ in risk of Ca Ovary
50% ↓ in risk of Ca breast
4-5% ↓ in risk of 1° Peritoneal cancer

Timing - after family completion
→ before 40y of age

Chemoprophylaxis

1) Not much evidence to support routine use of Tamoxifen in BRCA-1

because, BRCA 1 CA breast is high grade
Hormone receptor negative

66% of BRCA 1 DCIS is ER negative

2) 62% reduction in incidence of breast cancer c̄ BRCA-2 carriers
c̄ Tamoxifen

CHEMOPREVENTION IN BREAST CANCER

2 Drugs have been approved - Tamoxifen
Raloxifene

Trial Data

EBCTCG - Tamoxifen ↓ risk of 2nd primary breast cancer

NSABP-P-1 – Tamoxifen, when given in patients ↑ ≥1.66 5y RR,
overall risk reduction (for IDC) → 49%.
in patients ↑ LCIS → 51%.
in pts ↑ ADH, ALH → 86%.

NSABP-P-2 – Raloxifene vs Tamoxifen
(STAR)
(study of Tamoxifen & Raloxifene) → better toxicity profile

MAP-3 - Chemoprevention in post-menopausal women ↑
Aromatase inhibitor - Exemestane
→ ~65% ↓ in annual incidence of invasive CaB

IBIS-II trial - Chemoprevention in post-menopausal women ↑
Aromatase inhibitor - Anastrozole
→ ~50% ↓ in annual incidence of invasive CaB

Breast Self Examination

HC marbella

Breast self-examination

1

With your arms relaxed by your side, look for changes in shape and color or if the nipple has changed direction.

2

Place your hands on your hips and press firmly. Bend forwards and backwards looking for any changes.

3

Standing and with one hand behind your head, explore your entire breast, starting with the armpit and finishing with the nipple.

4

With the tips of the fingers together, feel your breast up and downwards. Also in round movements, starting from the outer part and pull inward toward the nipple.

5

Lying with a cushion under your back, repeat all previous movements.

6

Place your thumb and forefinger on the tissue around the nipple and press. Look for any abnormal discharge.

Early detection is fundamental

HC Marbella International Hospital

www.hcmarbella.com

Done once a month after the menstrual period

Recommended to start at 20y of age or atleast 10y before the youngest age of Dx of breast cancer in a family member

Average Risk

- Age 20 to 34
  - Monthly self-examination
  - Examination by a trained professional every three years
- Age 35 to 39
  - Monthly self-examination
  - Examination by a trained professional every three years
- Age 40 and over
  - Monthly self-examination
  - Annual examination by a trained professional
  - Annual mammogram

Average risk may increase based on:

- Personal history of breast abnormalities
- Current age
- Breast cancer history of close relatives
- Whether a woman has had a breast biopsy
- Obesity
- Physical inactivity
- Race

High-risk: Family history of disease (at least one first-degree relative—parent or sibling—who has had breast cancer)

- Women should be aware of any changes in their breasts. Monthly breast self-examination beginning at 20 years old is optional, but highly recommended.
- Clinical examination every six months starting 10 years before the age at which the youngest family member was diagnosed with the disease.
- Annual mammography starting 10 years before the age of the youngest family member with the disease (but no earlier than 25 and no later than 40).
- Consider annual MRI (consult with your physician).

PAGET'S DISEASE OF THE NIPPLE

- represents in-situ carcinoma in the nipple-epidermis

CLINICALLY - eczematoid changes, crusting, redness, irritation, erosion, discharge ± retraction, inversion

PATHOLOGICALLY - classical PAGET cells - large cells ± clear cytoplasm, atypical nuclei } within nipple epidermis in rete pegs

Generally unilateral
Almost confined to females

Paget's disease occurs in the nipple a/w

1. underlying invasive cancer → staging acc. to inv cancer
   - adjacent to nipple OR peripheral
   - → 90%
2. underlying DCIS → staged as Tis
   OR
3. neither invasive cancer nor DCIS → staged as Tis

THEORIES OF ORIGIN OF PAGET'S DISEASE

INTRA-EPIDERMAL THEORY

↓

Paget's disease is PRIMARILY an IN-SITU INTRA-EPIDERMAL MALIGNANCY with secondary extension to adjacent structures

EPIDERMOTROPIC THEORY

↓

Migration of tumor cells into nipple epidermis from an underlying carcinoma of the breast

Mean age at Dx - 55y

PAGET'S DISEASE	ECZEMA
Generally unilateral	Generally Bilateral
m/c in menopausal women	m/c in lactating women
NAC destruction ⊕	NAC generally spared
a/w underlying breast lump	a/w other features of eczema like flexural lesions

Evaluation - Mammo/Sonomammo to look for underlying DCIS/Ca
CNB/FNAC of underlying lump
Punch biopsy of nipple lesion — needs to be diff from superficial spreading melanoma
IHC - S-100

Management

Traditionally - mastectomy
or
BCT - with excision of the full NAC with a cone of underlying retroareolar tissue + all radiological abnormality

↓

Whole breast irradiation (based on criteria for DCIS / invasive cancer)

Axilla - treated as per DCIS / invasive cancer
↘ SLNB

Adjuvant systemic therapy depends on final pathology

EXTRAMAMMARY PAGET'S DISEASE

↳ m/c seen on genitalia of older patients ; rarely axilla

- Extramammary paget's disease of vulva - rare, non squamous intraepithelial lesion

↓

PAGET cells

derived from the apocrine cells in stratum germinatum of epidermis

Post menopausal women - vulval weeping, itching

HPV Negative

5-10% - a/i underlying adenocarcinoma

- Anal Paget's Disease - intraepithelial adenocarcinoma arising from the dermal apocrine sweat glands

females, older patients

Associated ī invasive cancers
- 7-24% - tuboovarian adenocarcinoma
- 12-14% - GI cancer

can progress to invasive disease in 5y.

INFLAMMATORY BREAST CANCER

- Rare and aggressive form of LABC
- Clinical diagnosis - Erythema & peau d'orange > 1/3rd of the skin over the breast within 6 months of onset
  - d/t blockage of dermal lymphatics by tumor emboli
    - demonstrable by biopsy

T4d N0-3 M0 - Stage III

- m/c - hormone negative - basal & HER-2 over-expression → m/c

Ddx - Cellulitis
Mastitis

Radiology - skin thickening
- occasionally - underlying mass

Advisable to complete NAC4 - Anthracycline based ± taxanes

↓

Mastectomy + Axillary clearance

↓

Trastuzumab if HER2 + x 1y

↓

RT

STAGING WORKUP

All cases - Triple assessment

NCCN
- History & Physical exam
- B/L DIAGNOSTIC MAMMO
  - USG if necessary
- Determination of tumor pathology
  HR & HER 2 status

CBC & LFT → no added benefit in detecting underlying metastatic disease in asymptomatic Early Breast cancer

NCCN panel - Routine Systemic imaging
↘ not indicated in EBC in the absence of signs/symptoms of mets

% of bone mets detected on Bone scan in EBC

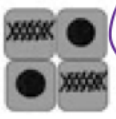
Stg I - 5.1 %
Stg II - 5.6 %
Stg III - 14.1 %

III → LABC - symptomatic
↑ ALP
$T_3 N_{\geq 2} M_0$
} Bone scan

~~Routine use of FDG PET~~ — ↑ false positive
false -ve in lesions < 1cm

FDG PET - helpful only when std staging is equivocal/suspicious

NOTTINGHAM GRADE

Parameter	Score 1	2	3
 Tubule formation	>75%	10-75%	<10%
 Nuclear pleomorphism	Absent*	Moderate	Marked
 Mitotic count**	<9	9-17	>17

Final score	3 4 5	6 7	8 9
	Grade I	Grade II	Grade III

MANAGEMENT

Early breast cancer

- Stage I
  - IA : $T_1 N_0 M_0$
  - IB : $T_0 N_{1mic} M_0$, $T_1 N_{1mic} M_0$
- Stage II
  - IIA – $T_1 N_1 M_0$, $T_2 N_0 M_0$
  - IIB – $T_2 N_1 M_0$, $T_3 N_0 M_0$

Lumpectomy BCT / Mastectomy c̄ SLNB or ALND → Adjuvant RT (±) + Adj CT + Adj HT or TT (Based on Receptor status)

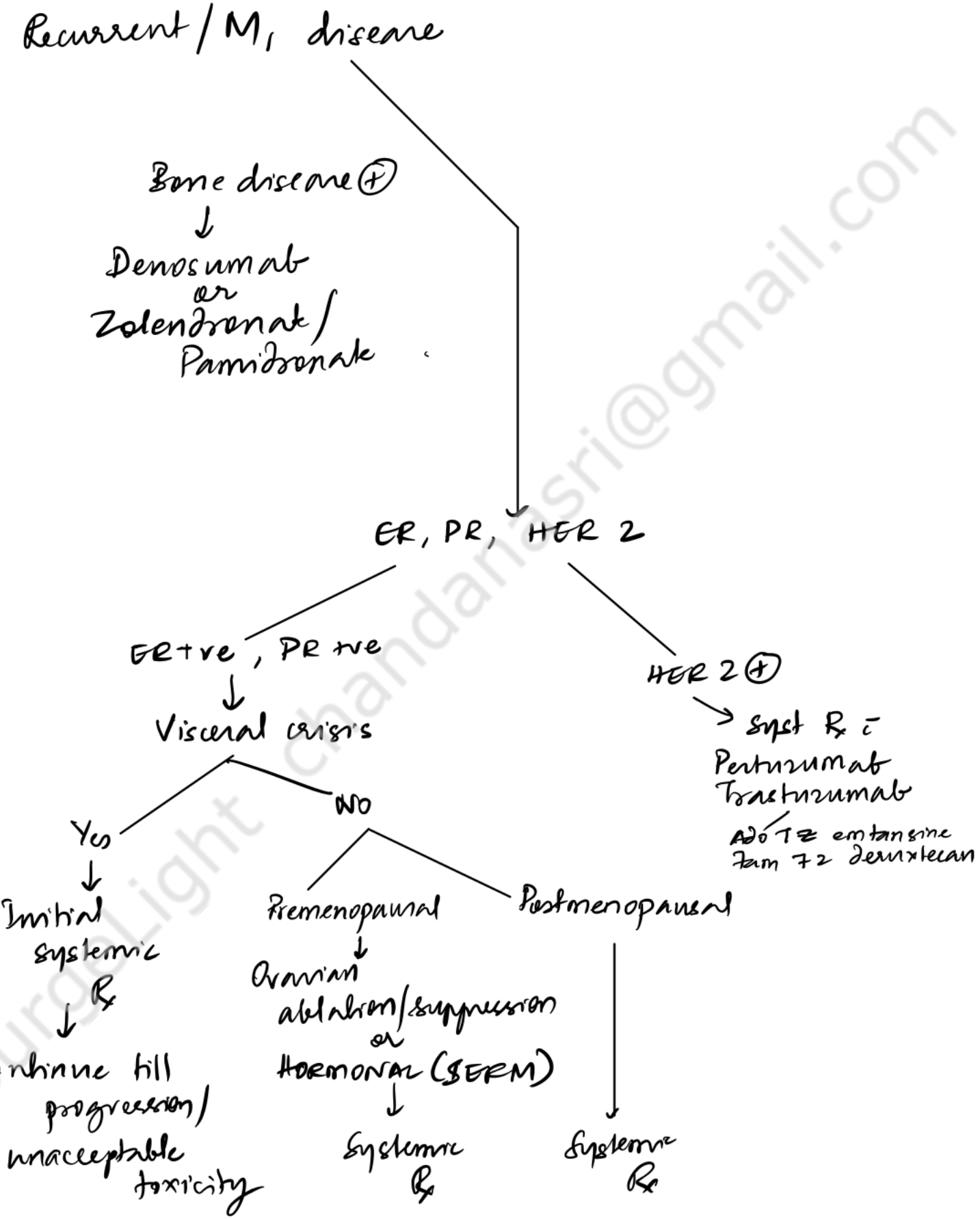
- Adjuvant RT:
  - Always i/c/o BCT
  - Other ind
    - ≥4 nodes
    - (1–3 nodes ±)
    - ↑ Grade
    - +ve / close margins
    - Age < 50y
    - LVI
- Adj CT: not necessary in T < 0.5cm N_0 → others → can decide based on assays

Locally advanced breast cancer

- Stage III
  - IIIA – $T_3 N_1 M_0$, $T_{0-3} N_2 M_0$
  - IIIB – $T_4 N_{0-2} M_0$
  - IIIC – Any T $N_3 M_0$

- Operable
  - ↳ $T_3 N_1 M_0$ → Sx – Adj
- Inoperable → NACT → Sx → Adj

Metastatic



BREAST CONSERVATION SURGERY

- Excision of the tumor along with a surrounding rim of grossly normal parenchyma with the preservation of the rest of the breast

Syn: lumpectomy, partial mastectomy, segmental mastectomy, segmentectomy, tylectomy, quadrantectomy, wide local excision

Mastectomy and breast conservation therapy have been shown to be equivalent in terms of patient survival for the majority of women with stage I & II Ca Breast

CONTRAINDICATIONS

- [Pregnant patients, who would require post op radiation during pregnancy] CI to RT
- Diffuse microcalcifications (s/o malignancy) on mammography
- Widespread disease (multicentric) that cannot be incorporated into a single specimen through a single incision with a satisfactory cosmetic result
- Repeated +ve surgical margins

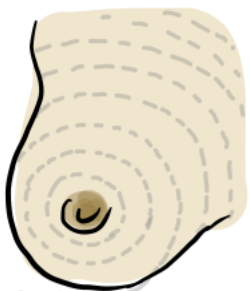
RELATIVE CONTRAINDICATIONS

- Relative contraindications to radiation
  - Previous radiation to breast / chest wall
  - Active connective tissue disorders - Scleroderma, Lupus (pts also should not be taking immunosuppressants like Mtx → they sensitize tissue to radiation damage)
  - Severe pulmonary disease
  - Severe cardiac disease (if tumor is left sided)
  - p53 mutation - ↑ susceptibility to radiation-induced cancers
- Strong family history / BRCA 1 & 2 mutation carriers
- Tumor size - large tumor in a small breast - generally >5cm (Cat 2B)
- ≥ N_2

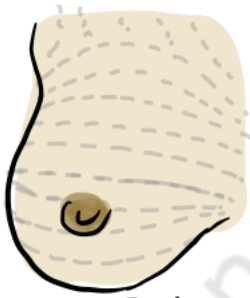
Good candidates - T_1, T_2, N_0, N_1
Single clinical & mammographic lesion | Motivated for f/u & RT

TECHNICAL ASPECTS

- **Incision -**
  - should lie within the domain of a possible subsequent mastectomy incision
  - should be oriented with Langer's lines / RSTL in mind
  - should be placed as directly over the lesion as possible – **TUNNELLING** IS NOT PREFERRED
    - compromises margins
    - makes re-excision unnecessarily difficult
  - excising the overlying skin is necessary only if the tumor is very superficial & skin is tethered



Langer's lines – correspond to the predominant orientation of collagen bundles in the skin



Resting skin tension lines of Kraissl
- lines of maximum resting skin tension

Closer to areola – circumareolar

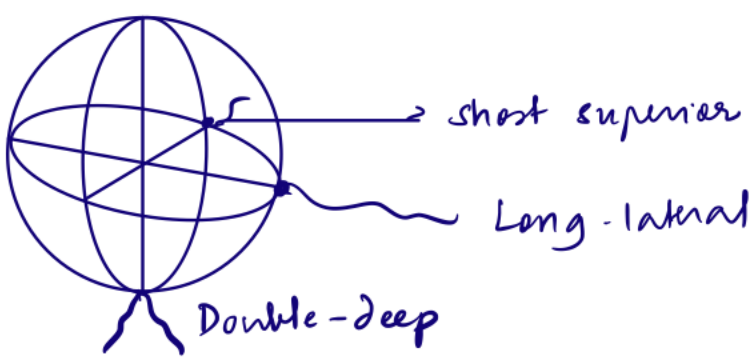
Lower hemisphere – radial incisions produce ↓ NAC displacement

In general, scars which are parallel to both produce best cosmesis & least keloids or hypertrophic scars

Flaps elevated 1-2cm beyond edge of tumor

- **Margins**
  - Aim for ~1cm margin – no ink on tumor is satisfactory
  - Mark the specimen & orient it

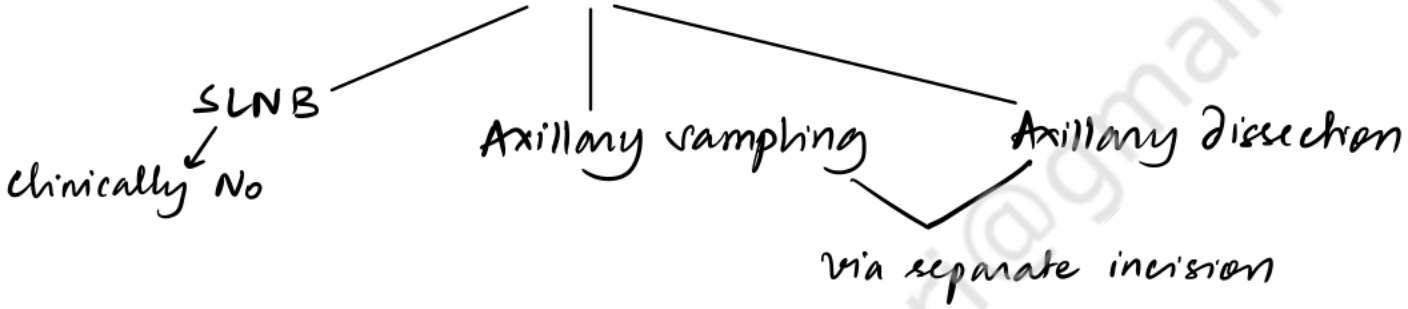
Depth – go up to pectoral fascia ↓ not necessary to excise unless it is involved



Wire localisation & stereotactic guidance may be used

- Wound closure
  - Good hemostasis to avoid hematoma
  - Surgical clips in lumpectomy cavity for orientation
  - No drain
  - Close ī subcuticular / tissue glue

- AXILLA MANAGEMENT



Always followed by radiotherapy

BREAST RECONSTRUCTION

POST MASTECTOMY BREAST RECONSTRUCTION

Timing

Immediate

Pros
- Psychological benefit
- Better preservation of inframammary fold
  ↓
  Better aesthetics
- Skin flaps more pliable

Cons
- Chemotherapy and radiation can interfere with post-operative healing & outcomes - volume loss
- Delay in CT/RT to optimise flaps ⟶ adverse oncological outcomes

Delayed

Pros
Prioritises oncological outcomes

Cons
- psychological issues
- Loss of native skin envelope
- New IMF needed
- exploration/ dissection of irradiated tissue

RECONSTRUCTION OPTIONS

Combination Procedures
LD / TRAM ± Implant

AUTOLOGOUS

- Abdomen based flaps
  - TRAM flap
    - Single pedicle flap
    - Double pedicle flap
    - Free flap
  - DIEP flap
  - SIEP flap
  - Vertical abdominal flap
  - Inked abdominal flap
- Latissimus Dorsi myocutaneous flap
- Gluteal Flap - Superiorly based
  Inferiorly based
  - musculocutaneous
  - GAP
- Ruben's flap (Deep circumflex iliac A flap)
- Thoracoepigastric flap
- TUG (Transverse upper gracilis flap)

ALLOPLASTIC

- Silicone gel implant
- Silicone implant ± saline fill
- Smooth wall implant
- Textured wall implant
- Round implant
- Anatomic shaped implant

IMPLANT BASED RECONSTRUCTIONS

INDICATIONS

1) Bilateral reconstruction - best opportunity for symmetry
2) Pt requests augmentation in addition to reconstruction
3) Long surgical times not feasible
4) Reluctance for additional scars over back / abdomen
5) Lack of adequate abdominal tissue
6) Small breast mound i minimal ptosis

RELATIVE CONTRAINDICATIONS

1) Young age - implant may have to be replaced multiple times
2) Very large & ptotic breast (Implant will look like 'rock in a sock!')
3) Silicone allergy
4) Previous failed implants

Types - Textured vs smooth
→ reduces • implant movement & maintains orientation
• rate & degree of capsular contracture

Anatomical vs round
→ • ↓ upper pole fullness (ⓝ breasts have supra-areolar flattening)
• ↑ Projection than round implants of same volume

Placement: Subcutaneous vs Submuscular pockets

Subcutaneous
cons: visible rippling below thin layer of skin
↑ incidence of CAPSULAR CONTRACTURE (contracture of FB capsule around implant)

Beneath pectoralis major
- Full muscle coverage → additionally using Serratus anterior Rectus abdominis fascia (pg 868 - Sabiston 20E)
- Coverage of inferior pole of implant i Bioprosthetics: Allograft - human porcine bovine

Timing
- Tissue expander placed at mastectomy → later exchanged for implant
- Immediate permanent implant placement

Complications: Implant rupture / infection → Linguini sign on MRI
Capsular contracture
Flap necrosis

AUTOLOGOUS RECONSTRUCTIONS

A) ABDOMINAL BASED FLAPS

Pros

- Similar consistency
  - ↓
  - like is replaced i like
- acceptable donor scar
- improvement of abdominal contour in some patients
- suitable for breasts of all sizes
- suitable even for ptotic breasts

Cons

- High metabolic demand
  - ? flap survival
- Time consuming
- Longer recovery period - 4-6 weeks
- Abdominal weakness / ↑ hernia risk
- Not suitable in :
  - Smokers
  - h/o abdominal liposuction / previous abdominal surgeries
  - Pulmonary disease
  - Obesity

ABDOMINAL BASED FLAPS

Myocutaneous flaps

- Pedicled TRAM
  - ↓
  - usually based on the Superior epigastric vessels
  - ↓
  - tunneled into the mastectomy defect (Ipsilateral / Contralateral)
  - ↓
  - Drawback - epigastric muscle bulge raised by the pedicle
- Free TRAM
  - ↓
  - usually based on Inferior epigastric vessels
  - ↓
  - microvascular anastomosis to
    - Thoracodorsal vessels
    - Internal mammary vessels

Muscle sparing flaps

ms TRAM

↓

only muscle fibres around the pedicle are included in the flap

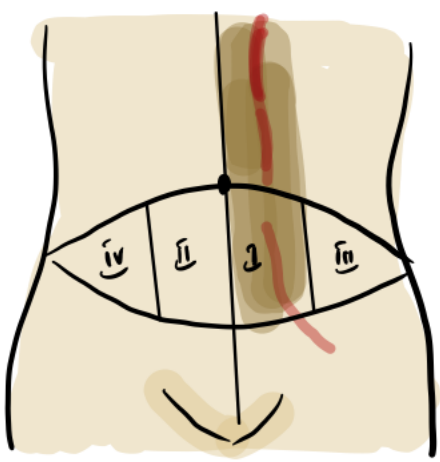
Perforator flaps

↓

muscle need not be taken

DIEP flap

SIEA flap

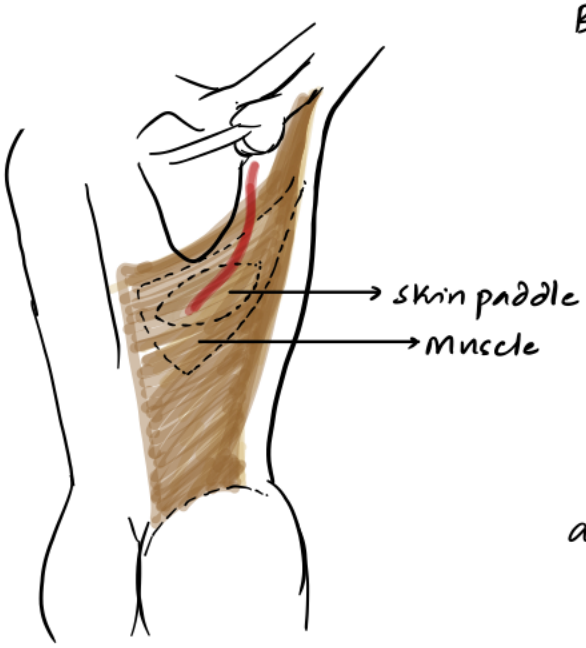


MOON & TAYLOR PERFUSION ZONES

↓

VASCULAR TERRITORIES OF UNILATERAL TRAM

B) LATISSIMUS DORSI MYOCUTANEOUS FLAP



Based on thoracodorsal vessels

- Pedicled
- Free

Can be used for autologous breast reconstruction
- Immediate
- Delayed

- total autologous
- combined (+ implant)

NIPPLE AREOLAR RECONSTRUCTION

Nipple reconstruction – local flap techniques over the reconstructed mound

Areola reconstruction
- Full thickness grafts from areas with darker skin → Eg. Groin
- Pigment tattoos

Generally done 2-3 months after creation of breast mound or completion of adjuvant therapy

ONCOPLASTIC BREAST SURGERY

Oncoplasty - Combining the principles of oncology and plastic surgery to enhance outcomes in breast cancer surgery

More attention is paid towards - planning skin incisions
- tissue excision

↓

ONCOLOGICAL CLEARANCE + aesthetic closure ⟶ Restoring skin continuity, breast contour, NAC position

" BCT without oncoplastic techniques becomes breast distortion "

INDICATIONS FOR ONCOPLASTIC SURGERY

- Breast cancer for which a standard BCS is seemingly impossible
  - = Larger tumors
  - Multifocal disease

  requiring resection of >10-20% breast volume
- Tumors in any location

CONTRAINDICATIONS FOR ONCOPLASTIC SURGERY

- Large tumors that require mastectomy to achieve clear margins
- Insufficient residual breast after excision
- Multicentric disease
- Inflammatory carcinoma
- Previous irradiation
- Multiple co-morbidities
- Chronic smoking

LEVELS OF ONCOPLASTY (Clough)

Level I ⟶ ≤ 20% of breast volume excised
→ does not require skin excision/mammoplasty for reshaping

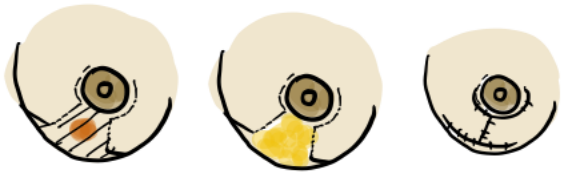
Level II ⟶ 20-50% volume excision
→ requires mammoplasty techniques

TYPES OF ONCOPLASTIC TECHNIQUES

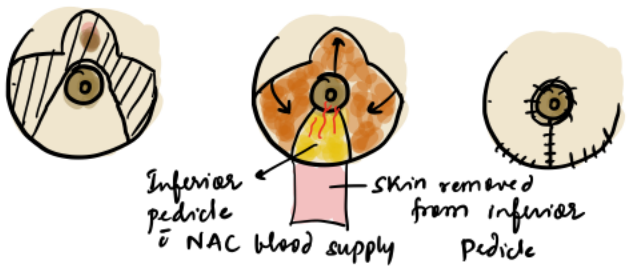
Volume DISPLACEMENT

Resected defect is reconstructed by moving local glandular / dermoglandular tissue into the defect
'ADJACENT TISSUE REARRANGEMENT'

- SUPERIOR PEDICLE BREAST REDUCTION
  - for tumors in lower part of breast'

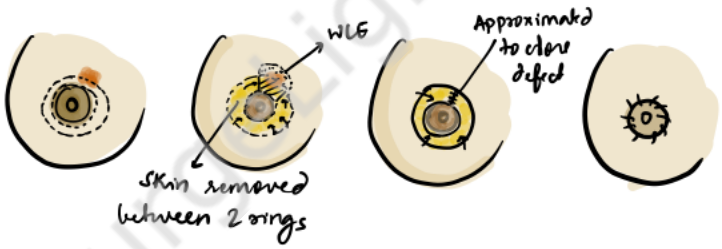


- INFERIOR PEDICLE BREAST REDUCTION
  - for tumors in the upper / medial / lateral parts



- GRISOTTI ADVANCEMENT ROTATION FLAP
  - for retroareolar tumors

- ROUND BLOCK TECHNIQUE - tumors near NAC



- Local glandular flaps
- Lateral Mammoplasty
- Batwing mammoplasty

Volume REPLACEMENT

Extensive resections in the breast should be replaced with a similar volume of autologous tissue from an extramammary site

↓

Musculocutaneous flaps

↙ Pedicled ↘ Free

m/c → Latissimus dorsi myocutaneous flap

↓

very versatile
can reach any quadrant

mini-LD flap - may be used if skin is not required from donor site

↓

Anterolateral / Lateral mammary crease incision

↓

Can be used for both tumor excision & mini LD flap harvest

Other flaps - TDAP - Thoracodorsal artery perforator flap - (minus muscle)

Lateral thoracic artery flap

Lateral intercostal artery flap

SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER

Indications

- Early breast cancer : clinicoradiologically node negative axilla
(- T_3 N_0 → 75% will have nodal mets on HPE)

- Can also be used in patients after NACT who were node-negative at presentation

SLNB is not recommended in

Inflammatory breast cancer
Biopsy proven mets
DCIS without mastectomy
Prior axillary surgery
Pregnancy
(some studies say it may be safe if done : radioisotope alone)

PRINCIPLE

- Sentinel node is the first lymphnode that drains the area under consideration (tumor)

- when mapping agents are injected subareolar / subdermally in the site of the primary tumor (peritumorally), the material passes through the lymphatics to the sentinel node which is then identified and biopsied.

- Patients with negative sentinel nodes can avoid the morbidity of an ALND

PROCEDURE

① Pre-operative lymphoscintigraphy – may or may not be done

A dose of 2.5mCi of ^{99m}Tc-labelled sulfur colloid is injected on the day before surgery

↓

films obtained

↳ adequate activity persists in the sentinel node the next day → allows lymphatic mapping without the need for reinjection

[Inability to demonstrate a sentinel node on pre-op scintigraphy
DOES NOT MEAN YOU CAN'T IDENTIFY IT BY SLNB
On the contrary, the likelihood of sentinel node being +ve is ↑ in such a case)

② On the day of the surgery - 0.5mCi of ^{99m}Tc Sulfur colloid injected peritumorally or in subareolar location or at prior biopsy site

③ On the operating table → 3-5ml of blue dye (Isosulfan/Methylene blue) is injected into the breast parenchyma near the tumor / subareolar (Subdermal avoided → tattooing/necrosis)
- massaged gently to facilitate dye movement through lymphatics

④ Using a hand-held γ camera, the area of ↑ radioactivity in the axilla is identified transcutaneously
↓
Incision is placed over it
↓
Blue lymphatic channels can be visualised leading up to the sentinel node
↓
also corresponds to area of highest radioactivity in the axilla

Before sentinel node is removed, a 10-second in vivo radioactivity count is obtained
↓
SLN removed
↓
10 second ex vivo radioactive count → sent for HPE
↓
Best results: Remove all blue nodes & all lymphnodes ≥ 10% of the radioactivity of the 10 sec ex-vivo count of sentinel node harvested (10% rule)

Not necessary to remove >4 nodes on SLNB for accurate staging of axilla

Combination of intra-op γ probe detection of radioactive colloid & intra-op visualisation of blue dye → more accurate than either of the two used in isolation

---

Sentinel node can be successfully identified in 97% women

MASTECTOMY

SIMPLE MASTECTOMY / TOTAL MASTECTOMY - Removal of the entire tissue i an ellipse of skin + NAC

RADICAL MASTECTOMY (HALSTED)

Disfiguring surgery

STRUCTURES REMOVED

1) Whole breast
2) NAC
3) Skin overlying the breast
4) Subcutaneous fat & fascia
   - clavicle → upper rectus sheath
   - sternum → Ant border of lat. dorsi
5) Pectoralis major
6) Pectoralis minor
7) Clavipectoral fascia
8) Few digitations of S. anterior
9) Axillary nodes - level I, II, III

STRUCTURES SAVED

Axillary vein
Bell's nerve
Cephalic vein

+ Internal Mammary nodes = Extended Radical

MODIFIED RADICAL MASTECTOMY

PATEY

Whole breast i ellipse of skin + NAC removed

Pectoralis Major & Minor Preserved

P. minor divided from its insertion at the CORACOID PROCESS for access to level III nodes

Level I, II & III removed

SCHANLON

Whole breast i ellipse of skin + NAC removed

Pectoralis Major & Minor Preserved

P. minor incised for access to level III nodes

Level I & II removed

AUCHINCLOSS

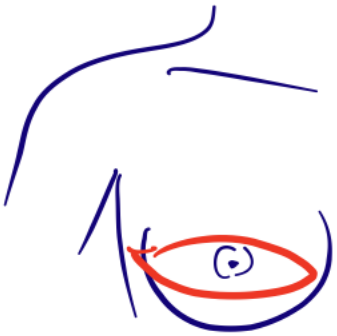
Whole breast i ellipse of skin + NAC removed

Pectoralis Major & Minor Preserved

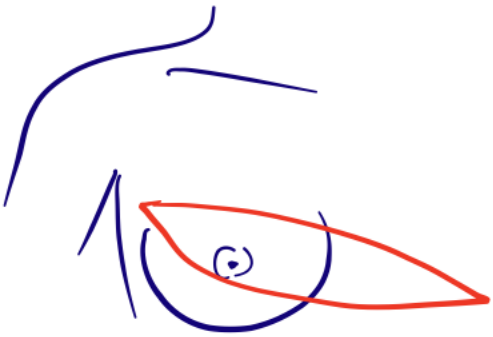
P. minor retracted for access to level II nodes

Level I & II removed

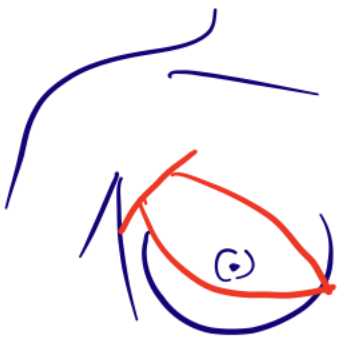
INCISIONS



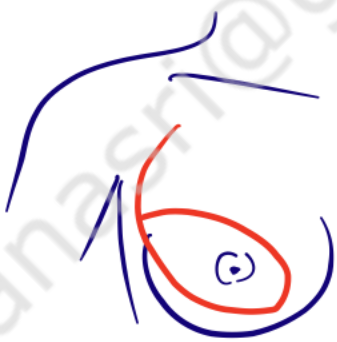
STEWART



GRAY



GREENOUGH



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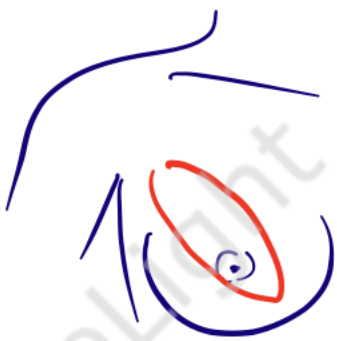

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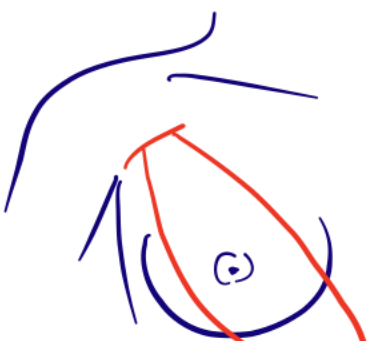

RODMAN

Others : Skin sparing
Nipple sparing
Areola sparing

Complications

- Injury/ thrombosis of axillary V
- Shoulder weakness
  - Injury to thoracodorsals
- Winging of scapula
  - Bell's (N) injury
- Atrophy to pectorals
  - Medial & lateral pectoral N injury
- Upper medial arm loss of sensation
  - intercostobrachial N injury

Seroma

Flap necrosis

SSI

Lymphedema

Lymphangiosarcoma

AXILLA- SURGICAL MANAGEMENT

ALND- standard of care for N+ disease

in clinical N+ disease

↳ NCCN panel RECOMMENDS pathologic confirmation of malignancy by FNAC / CNB

ALND (traditional = removal of level I & II) → limited to pts i proven axillary mets

↳ Atleast 10 nodes should be removed in Level I & II

ALND for accurate staging

Level III included only if gross disease apparent in level II & III

SKIN SPARING MASTECTOMY

→ removal of whole breast parenchyma + NAC

↓

+ preservation of original skin envelope

↓

Recon → Autogenous
Implant
Composite

→ CI in Paget's, nipple discharge

NAC sparing mastectomy

→ idea is to preserve nipple sensation + cosmesis

Assessment of nipple margins – mandatory

Can be considered in biologically favourable cases

Nottingham grade 1 & 2
Node negative
HER 2 neu -ve
LVI absent

DCIS
Peripherally located
→ >2cm from nipple

CHEMOTHERAPY IN BREAST CANCER

CANDIDATES FOR PRE-OPERATIVE SYSTEMIC THERAPY

1) Patients ε inoperable breast cancer
   - IBC
   - Bulky / matted N_2 axillary nodes
   - N_3 nodal disease
   - T_4 tumors

2) In patients ε operable breast cancer,
   HER 2+ disease & TNBC if $T \geq T_2$ or $N \geq N_1$

3) Large primary tumor relative to breast size in a patient who desires breast conservation

Adjuvant chemotherapy indications

- All non-metastatic breast cancer except $T \leq 0.5cm$, pN_0
- Multigene assays may be performed to determine benefit of adding adjuvant chemotherapy in early breast cancer ($T_{1b/c}, T_2, N_0$)
  - 21-gene assay - Oncotype Dx
  - 70-gene assay - Mammaprint
  - 50-gene assay - PAM 50 / Prosigma
  - 12-gene assay - EndoPredict
  - Breast cancer Index

Regimens

HER-2 Negative

AC ⟶ Paclitaxel (Q2week)

AC ⟶ Paclitaxel (Q1week)

TC (Docetaxel, Cyclophosphamide)

Others
- CMF
- EF

HER-2 Positive

AC ⟶ Paclitaxel + Trastuzumab ± Pertuzumab

Paclitaxel + trastuzumab

TCH - Docetaxel, Carboplatin, Herceptin

Doses: Doxorubicin (A) - 60mg/m²
Cyclophosphamide - 600mg/m², Fluorouracil - 600mg/m²

Carboplatin - AUC 6
Paclitaxel 80mg/m²

Cisplatin - 75mg/m²

ENDOCRINE THERAPY IN BREAST CANCER

PRINCIPLE

Estrogen receptor is a nuclear receptor through which estrogen exerts its action.
It is physically expressed in the breast tissue (ovulation suppresses expression)

Estrogen has both genomic & non genomic actions

- genomic → binds to nuclear receptor → acts on estrogen response elements in the genetic material → transcription of growth promoting genes, including PR
- non genomic → hormone-dependent activation of membrane-bound or cytosolic ERs (non nuclear ERs) → activation of important growth regulatory kinases EGFR, IGFR-1

In breast cancer, there are ALTERATIONS IN THE ER SIGNALING PATHWAYS
→ Gene amplification → ER over-expression
→ ER mutations causing constitutive activation of the pathway

ER pathway is a target for breast cancer therapy

→ STRATEGIES

1) Inhibition of the pathway by substances that bind to the ER - SERMs
Tamoxifen
Raloxifene
Fulvestrant

2) Decreasing the production of endogenous estrogen

- Ovarian ablation
  - Drugs
    - GnRH agonists: Goserelin, Triptorelin, Leuprolide
    - Surgical oophorectomy
- Aromatase inhibitors
  - Non steroidal: - Letrozole, - Anastrazole
  - Steroidal: Exemestane
  - Palbociclib → CDK4/6 inhibitor

TAMOXIFEN

- ↓ locoregional recurrence, distant mets
- ↓ contralateral breast cancer (39% risk reduction)

Adverse effects

Bone pain
Hot flashes
Nausea & vomiting
Fluid retention
Thrombotic events (<3%)
Cataract
Endometrial hyperplasia & cancer

RALOXIFENE - 2nd generation SERM

Actions: Antioestrogenic (Breast, Uterine) | Oestrogenic (Bone, Lipid, Coagulation)

Better side effect profile - Helps preserve bone mineral density
Does not ↑ risk of endometrial cancer

Risk - Thromboembolic events

Tamoxifen — 10mg BD PO x 10y (initially 5 years - now 10y is proven to be better)

Exemestane - 25mg PO OD

- chemoprevention → 5y
- Adjuvant breast cancer hormonal therapy - switch to Exemestane after 2-3y Tamoxifene
- Metastatic Post menopausal ER+ Ca Breast - indefinitely

Letrozole - 2.5mg PO OD x 5y

Anastrozole - 1mg PO OD x 5y

TARGETED THERAPY IN BREAST CANCER

Growth factor receptor pathways → mutations are implicated in breast cancer

- **HER 2**

Human epidermal growth factor receptor 2

(Syn: EGFR-2/ ErbB2)

HER 2 - does not have any physiological ligand
- (polymerisation) → has some influence on G1/S phase of cell cycle
- → over-expression causes accelerated cell growth & proliferation

Molecules

1) Trastuzumab - monoclonal anti HER-2 antibody
   - both locoregional & metastatic HER 2+ cancer
2) Pertuzumab - targets HER-2 ⟶ HER-3 heterodimerization site
3) Lapatinib
4) Neratinib
5) TDM-1 / Trastuzumab emtansine - drug conjugate allowing HER-2 targeted delivery of an antimicrotubule agent

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- **CDK - Cyclin Dependent Kinase**

CDK-4/6 inhibitors - Palbociclib, Ribociclib, Abemaciclib

- PARP (Poly adenosine Ribose phosphate polymerase)

PARP inhibitor - Olaparib → for BRCA associated breast cancer

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TRASTUZUMAB - 52 weeks = 1 year

Adjuvant - 4mg/kg over 90min (week 1) ⟶ 2mg/kg (week 2-12/18) ⟶ 6mg/kg (week 13/19-52)

Metastatic - 4mg/kg (week 1) ⟶ 2mg/kg/week (till 52 weeks)

Adverse effects - Cardiomyopathy, Pulmonary toxicity, Fetotoxicity, Neutropenia (exacerbation of chemo-induced ↓ LC)

Breast Radiotherapy

Post BCS | Post MRM | for DCIS

Post BCS RT

WBRT ± Tumor bed boost | APBI

1) WBRT + Tumor Bed Boost

- Whole Breast RT (WBRT)

50 Gy in 25 fractions

↓

5 fractions x 5 weeks per week (5 days a week)

(Sat, Sun ✗ 🙏)

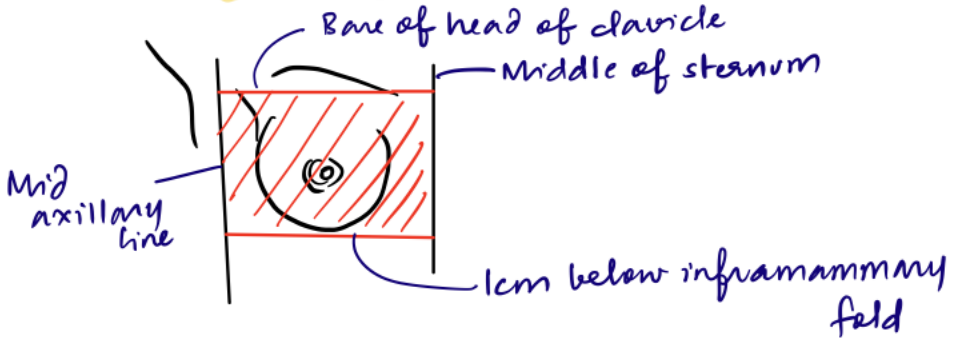
- Tumor Bed Boost

16 Gy (10-18 Gy) in 4-8 fr

Indications:

Age < 50y
High Grade
focally +ve Margins

- For women who undergo breast-conserving surgery, the target volume for whole-breast RT extends medially to the middle of the sternum and generally laterally to the mid-axillary line. The field usually extends 1 cm beyond the palpable border of breast tissue. The inferior edge of the field is approximately 1 cm below the inframammary fold in the intact breast. Superiorly, the field typically ends at the base of the head of the clavicle.



Whole Breast Radiation

- **Target definition is the breast tissue in entirety.**
- **RT dosing:**
  - **The whole breast should receive a dose of 45–50.4 Gy in 25–28 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred).**
  - **A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.**
- **All dose schedules are given 5 days per week.**

2) APBI - Accelerated Partial Breast Irradiation

- Hypofractionated doses
  - (↑ dose over fewer sittings)
- Alternative to WBCT

34 Gy - 10 fractions (twice a day x 5 days) → Brachytherapy

38.5 Gy - 10 fractions (twice a day x 5 days) → EBRT

Accelerated Partial Breast Irradiation (APBI) (NCCN)

- **Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing.**
  - **Patients are encouraged to participate in clinical trials.**
  - **The NCCN Panel accepts the updated 2016 version of the ASTRO APBI guideline, which now defines patients "suitable" for APBI to be one of the following:**
    - **1) 50 years or older with invasive ductal carcinoma measuring ≤2 cm (T1 disease) with negative margin widths of ≥2 mm, no LVI, ER positive, and *BRCA* negative; or**
    - **2) low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.**
  - **RT Dosing:**
    - **A course of 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is typically prescribed to the tumor bed.**
    - **Other fractionation schemes are currently under investigation.**

- ≥ 50y
- T1
- Margins ≥ 2mm
- No LVI
- ER +ve
- BRCA -ve

low/int grade DCIS

Delivery Of APBI

ACCELERATED PARTIAL BREAST IRRADIATION — Accelerated partial breast irradiation (APBI) refers to the use of focused radiation therapy (RT) to a limited portion of the breast. Options for the delivery of APBI include brachytherapy, intraoperative radiotherapy, or external beam radiation. Conformal external beam radiation is the most commonly used delivery system in the United States. The indications and results following APBI are discussed separately. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Accelerated partial breast irradiation'.)

External beam radiation therapy — APBI using external beam RT is delivered postoperatively, which allows final review of the pathology, including an assessment of surgical margins. In addition, the treatment is noninvasive, and standard dosimetry and treatment equipment are employed.

1) **Conformal external beam radiotherapy** — Three-dimensional conformal external beam radiotherapy requires virtual simulation and combines multiple RT fields to deliver a specific dose of radiotherapy to the tumor bed region while sparing the majority of normal surrounding tissue and solid organs [14,15]. The dose typically delivered ranges from 35 to 38.5 Gy in 10 fractions. Treatment is usually administered twice a day, over one week. (See "Radiation therapy techniques in cancer treatment", section on 'Conformal therapy'.)

2) **Intensity-modulated radiotherapy** — Intensity-modulated radiotherapy (IMRT) uses a linear accelerator to deliver focused small beams of radiation that follow the exact contours of a tumor or target volume. Higher radiation doses can be used because the damage to surrounding tissue is limited, possibly resulting in more effective treatment. Computer imaging is used to evaluate the tumor throughout the course of treatment, permitting the most precise dose and treatment changes based on the changing tumor characteristics. IMRT requires special equipment that is available at most hospitals and radiation centers, but its use in breast cancer for APBI delivery has been limited [16-18]. A more general discussion of IMRT is covered separately. (See "Radiation therapy techniques in cancer treatment", section on 'Intensity-modulated radiation therapy'.)

Brachytherapy — Brachytherapy for breast cancer involves the temporary placement of radioactive material into body tissues for local radiation treatment. Brachytherapy can be delivered with interstitial, intracavitary, or intraoperative delivery systems. (See "Radiation therapy techniques in cancer treatment", section on 'Brachytherapy'.)

1) **Interstitial brachytherapy** — For interstitial brachytherapy, several small hollow catheters are placed into the breast surrounding the partial mastectomy site (figure 3) [19]. Potential disadvantages of this approach include the risk of infection and poor cosmesis with scarring due to the multiple catheters, although these complications have largely been seen in older studies. (See 'RT boost' below.)

- **Catheter placement –** The number of catheters used is dependent upon the size and shape of the target. The placement of the catheters is determined using RT planning software along with stereotactic mammography, ultrasound, or computed tomography guidance.

- **Radioactive seed insertion** – High or low dose-rate radioactive seeds are inserted into the catheters as described above. The catheters are removed when treatment is completed. (See 'Technical considerations' below.)

2) **Intracavitary brachytherapy** — For intracavitary brachytherapy, a radiation delivery device is placed into the partial mastectomy site [20]. Single lumen and multi-lumen balloon catheter and non-balloon devices have all been used successfully (picture 1 and figure 4) [21-23]. The presumed advantage of the multi-lumen devices as compared with single lumen catheters is more precise dosimetric planning and safer treatment delivery, avoiding skin and other organ damage.

- **Placement of the device** – Consideration of intracavitary brachytherapy requires a surgical cavity large enough to accommodate the device (figure 5) [24,25].

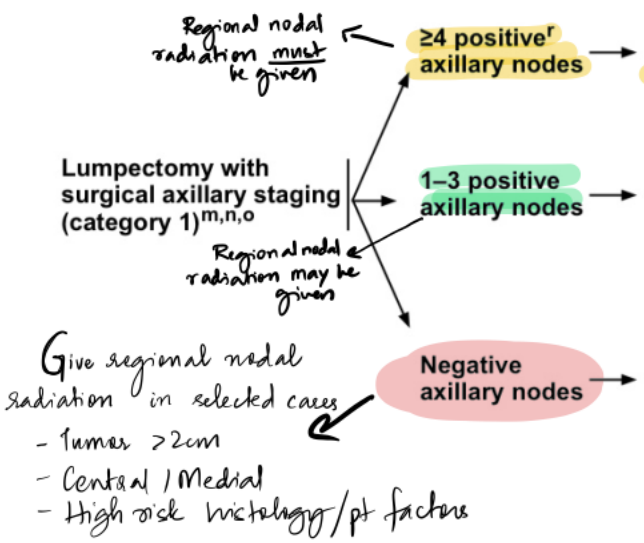
  The device can be placed at the time of lumpectomy ("open technique") or several days later under ultrasound guidance ("closed technique"). The closed technique is preferable because, if the device is placed during surgery, final pathology results may require the device to be removed due to involved margins or positive lymph nodes [20]. The device can usually be placed percutaneously in the office setting after final pathology results are available. In addition, infection rates are lower with the closed technique [26].

  A cavity evaluation device may be placed initially in the operating room and then exchanged for the treatment device (figure 6). The cavity evaluation device is used to assess the partial mastectomy cavity, evaluate skin spacing, and assist in the selection of the correct balloon size applicator for delivery of intracavitary radiotherapy.

3) **Intraoperative radiation therapy** — Intraoperative RT condenses the entire therapeutic dose into a single fraction, permitting surgery and radiation to be completed in one day. Potential advantages include accurate delivery of radiotherapy directly to the surgical margins and a decreased dose of radiation to skin and subcutaneous tissue since these can be retracted during treatment. Drawbacks to the use of intraoperative radiation include the extended time in the operating room, the inability to verify the radiation dosimetry, and the lack of final pathology information at the time of radiation.

FIELDS TO BE IRRADIATED FOLLOWING BCS

LOCOREGIONAL TREATMENT OF T1-3,N0-1,M0 DISEASE[a]



Radiation therapy to whole breast with or without boost[s] to tumor bed (category 1), infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk (category 1). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

Radiation therapy to whole breast with or without boost[r] to tumor bed (category 1). Strongly consider radiation therapy to infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

Radiation therapy to whole breast with or without boost[s] to tumor bed, and consider regional nodal irradiation with exclusion of the dissected portion of the axilla in patients with central/medial tumors or tumors >2 cm with other high-risk features (young age or extensive lymphovascular invasion [LVI]).
or
Consideration of APBI in selected low-risk patients.[s,t]
It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.[u]

- All cases post-BCS MUST receive radiotherapy to the breast
- RT to regional nodal areas is given based on the scenario

≥4 +ve nodes → WBRT + Infraclavicular, Supraclavicular, Internal mammary, Axilla } RT

(1-3 +ve nodes → strongly consider)

-ve nodes → WBRT + Regional nodal RT i/d/d

↑ risk - central tumors >2cm
young age
LVI

Post Mastectomy RT (PMRT)

POSTMASTECTOMY RADIATION THERAPY — For women who undergo a mastectomy, the chest wall can be treated with tangential photon fields, similar to the intact breast. The field borders are the same, as are the considerations regarding the underlying volume of heart and lung.

Delivery of an adequate dose to the chest wall skin is important, and the skin-sparing effect of photons must be taken into consideration. When the photon beam strikes the absorbing surface, there is an initial build-up of dose that reaches a maximum, the depth of which increases with increasing energy and then attenuates. This skin-sparing effect is desirable when treating a deep lesion but not superficial tissues such as the chest wall skin. In these cases, a bolus (a material with similar density to tissue that is placed directly on the skin surface) must be used to ensure that the skin receives a therapeutic radiation dose. The beam strikes the absorbing surface at the bolus, whose thickness is calculated so that the maximum dose to the target volume occurs closer to the skin surface.

If a bolus is used, patients should be informed that skin erythema is an expected effect. The reaction peaks toward the end of therapy and then quickly heals. If skin erythema occurs too early in the patient course or is more than desired, the bolus can be discontinued.

Satisfactory treatment of the chest wall can also be accomplished with electrons [32-34]. However, electrons deposit a high dose to the superficial skin, which cannot be modified from day to day, unlike the placement of a bolus during photon beam therapy. Patients with sensitive skin can develop a brisk skin reaction before the treatment is concluded, making the last few days of treatment uncomfortable. Use of electrons can also increase dose to the underlying lung pending electron energy. Careful planning not only of field arrangements but also electron energies is needed if electrons are used to treat the chest wall.

- For women who have undergone a mastectomy, the lateral field edge should extend to the mid-axillary line with the inferior edge extending to the contralateral inframammary fold. As with RT to the intact breast, the superior field typically extends to the base of the head of the clavicle. The area to be treated should encompass the full length of the mastectomy scar.
- The primary field may consist of high tangential fields that extend to just below the humeral head. This ensures coverage of the level I and in the majority of patients, a portion of level II of the axilla in a patient who will not receive dedicated regional RT fields (figure 2). (See 'Regional field' below.)

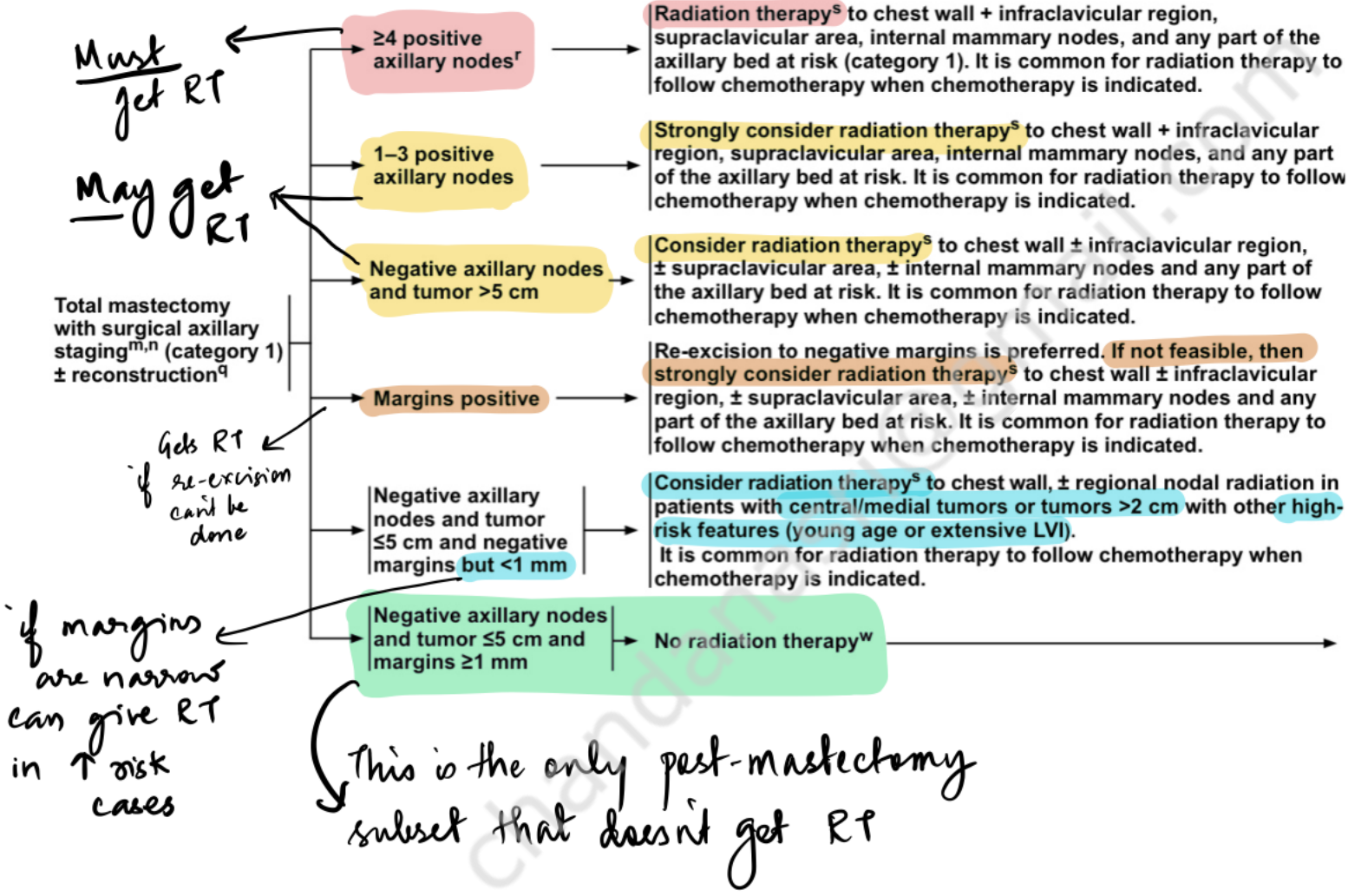
NCCN Recommendations

Chest Wall Radiation (including breast reconstruction)

- **The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated.**
  - **Depending on whether or not the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate.**
  - **CT-based treatment planning is encouraged in order to identify lung and heart volumes and minimize exposure of these organs.**
  - **Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate.**
  - **RT Dosing:**
    - **Dose is 45–50.4 Gy in 25–28 fractions to the chest wall ± scar boost, at 1.8–2 Gy per fraction, to a total dose of approximately 60 Gy.**
- **All dose schedules are given 5 days per week.**

Indications for PMRT (Chest wall RT + Regional Nodal RT)

LOCOREGIONAL TREATMENT OF T1-3,N0-1,M0 DISEASE[a,v]



Fields

Postmastectomy RT fields — In our practice, we deliver postmastectomy RT to both the chest wall and to the regional nodes. These include the supraclavicular and infraclavicular nodes. We also include RT to the axilla except in patients who underwent complete axillary dissection. Additionally, we generally include the internal mammary nodes, although an individualized approach is necessary. (See 'Radiation of internal mammary nodes' below.)

For women who undergo a complete axillary dissection, administering RT to a more limited field (ie, omitting a full axillary field and instead radiating only the supraclavicular/infraclavicular regions, with or without internal mammary nodes) is our preferred option given the risk of subsequent lymphedema, which in one series approached 40 percent following axillary RT [40]. By contrast, in a series where RT was restricted to the supraclavicular/infraclavicular fields, the rate of arm edema was only 3 percent [59]. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer", section on 'Regional node radiation therapy'.)

For DCIS

DIAGNOSIS	WORKUP	PRIMARY TREATMENT
DCIS Tis,N0,M0 →	• History and physical exam • Diagnostic bilateral mammogram • Pathology review[a] • Determination of tumor estrogen receptor (ER) status • Genetic counseling if patient is at risk[b] for hereditary breast cancer • Breast MRI[c,d] as indicated →	Lumpectomy[e] without lymph node surgery[f] + whole breast radiation therapy (category 1) with or without boost to tumor bed[g,h,i,j] or Total mastectomy with or without sentinel node biopsy[f,h] + reconstruction (optional)[k] or Lumpectomy[e] without lymph node surgery[f] + accelerated partial breast irradiation (APBI)[g,h,i,j] or Lumpectomy[e] without lymph node surgery[f] without radiation therapy[g,h,i,j] (category 2B)

Decision of lumpectomy vs mastectomy depends on feasibility of adequate margins

DCIS

- For patients with pure DCIS treated by BCS and whole breast radiation therapy (WBRT), a quantitative description of any tumor close to margin resection width of at least 2 mm is associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths, while the routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment can be applied to determine if re-excision might be avoided in individual cases.
- For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.
- DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤1 mm in size, should refer to the DCIS margin definition when considering the optimal margin width (>2 mm), given that the majority of DCIS-M is comprised of DCIS and systemic therapy utilization for this lesion more closely reflects the treatment pattern for DCIS than for invasive carcinoma.

1) Basically, aim for a margin of ≥2mm

2) Radiotherapy is better than excision alone

3) WBRT is preferred; think of APBI in pts c̄ low risk features and wider surgical margins

Whole-breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and physician view the individual risk as "low," some patients may be treated by excision alone. Select patients with low-risk DCIS may be considered suitable for APBI if they meet all aspects of the definition of low-risk DCIS from the RTOG 9804 trial, including screen-detected DCIS, low to intermediate nuclear grade, tumor size ≤2.5 cm, and surgical resection with margins negative at >3 mm.

→ High risk factors

→ Try APBI

PHYLLODES TUMOR

(syn: cerocystic disease of Brodie; Cystosarcoma phyllodes)

- includes a group of lesions with varying malignant potential (Benign, Borderline, Malignant)
- FIBROEPITHELIAL ORIGIN
- generally affects women - 35-55y
- ~1% of all breast tumors
- typically large - mean diameter 4-5cm

Bosselated lesions, cystic areas
skin - stretched over tumor, prominent veins, warm
skin ulceration ⊕ in large tumors
↘ usually d/t pressure necrosis rather than skin infiltration by the malignant cells (PROBE TEST)

HISTOLOGICALLY:
/ more cellularity than fibroadenoma
epithelial elements + connective tissue stroma → leaf-like projections into cystic spaces. (gross cut surface)

CLASSIFIED as benign/ borderline/ malignant based on
(Benign/Borderline)
- nature of tumor margins (pushing / infiltrative)
- presence of cellular atypia/ pleomorphism
- mitotic activity
- stromal overgrowth (strong predictor of distant spread)

Benign	Borderline	Malignant
<3/ 10 HPF	4-9/10 HPF	>10/10 HPF

- smaller lesions can be mammographically indistinguishable from fibroadenoma

NATURAL HISTORY, PATTERNS OF SPREAD

~70 % Benign
~25 % malignant

Local recurrence: 5-20% - benign tumors
20-40% - malignant tumors
↳ typically salvageable ± mastectomy, do not affect overall survival

Axillary nodal spread - <1%

Distant metastasis: 25-40% of malignant tumors
↳ m/c site → lung > bone > mediastinum

MANAGEMENT OF PHYLLODES TUMOR (MD Anderson Algorithm)

CLINICAL SUSPICION OF PHYLLODES TUMOR

- Palpable mass
- Rapid growth
- Imaging suggestive

↓

→ HISTORY & PHYSICAL EXAMINATION
→ USG
→ Mammogram if ≥30y

Mammographic e/o of calcifications & morphological e/o necrosis cannot distinguish benign / borderline / malignant

↓

CORE NEEDLE BIOPSY

(FNAC / Core needle biopsy may not yield definitive diagnosis due to tumor heterogeneity)

↙ Phyllodes tumor

↓

WIDE EXCISION

traditionally - 1cm margin

Large phyllodes may require mastectomy

↓ NO axillary staging

(Benign - complete excision & negative margin suffices)

↘ Fibroepithelial lesion / indeterminate pathology

↓

EXCISIONAL BIOPSY

(Complete mass removal without much emphasis on obtaining histologically negative margin)

Most malignant phyllodes - hypo/rhabdo sarcomatous elements rather than fibrosarcomatous

↓

REVIEW FINAL PATHOLOGY

↙ Benign / Borderline

↓

Observe

↓ If malignant, consider XRT in (No RCT data)

close margins, e/o infiltration

↘ >5cm stromal overgrowth

↓

Treat as STS

No established role of RT / chemo / Hormonal Rx

GYNECOMASTIA

- Enlarged breast tissue in a male
- generally d/t excessive circulating estrogens in relation to circulating testosterone

PHYSIOLOGICAL GYNECOMASTIA

- Neonatal gynecomastia - d/t action of placental estrogens on neonatal breast tissue
- Adolescent / Pubertal gynecomastia - ↑ estradiol w.r.t testosterone
  - often unilateral
  - 12-15y
- Senescent Gynecomastia - Relative hyperestrinism d/t fall in circulating testosterone (testicular atrophy)
  - usually bilateral

PATHOLOGICAL GYNECOMASTIA

ESTROGEN EXCESS STATES

- Gonadal origin
  - True hermaphroditism
  - Tumors
    - → Germ cell tumors
      - Choriocarcinoma
      - Seminoma
      - teratoma
      - embryonal carcinoma
    - → Stromal tumors
      - Leydig cell tumor
      - Sertoli cell tumor
      - Granulosa-theca cell tumor
- Extragonadal origin
  - Tumors - Adrenal cortex Ca
    Lung Ca
    Hepatocellular Ca
  - Endocrine disorders - Thy
  - Liver failure - ↓ estrogen metabolism
  - Nutritional disturbances - Refeeding gynecomastia - resumption of pituitary GnRH
  - Drugs -
    Estrogenic activity - digitalis
    anabolic steroids
    ↑ estrogen synthesis : hCG

ANDROGEN DEFICIENCY STATES

- Primary testicular failure
  - Klinefelter syndrome (XXY)
    - generally a/i ↑ risk of male breast cancer
  - Kallmann syndrome
  - Eunuchoidal state
  - Hereditary deficiencies of androgen biosynthesis
  - ACTH deficiency
- Secondary testicular failure
  - Trauma
  - Orchitis
  - Cryptorchidism
  - Irradiation
- Renal failure
- Drugs - inhibitors of androgen synthesis / action
  - Cimetidine
  - Ketoconazole
  - phenytoin
  - Spironolactone

Idiopathic mechanisms: Systemic illness, Reserpine, TCAs, furosemide, Verapamil, theophylline

→ In the non-obese male, breast tissue measuring ≥ 2cm → gynecomastia

→ In gynecomastia, ductal structures of male breast enlarge, elongate & branch ↑ concomitant in epithelium

GRADING OF GYNECOMASTIA

- I – mild breast enlargement; no skin redundancy
- II – moderate breast enlargement
  - IIa – without skin redundancy
  - IIb – with skin redundancy
- III – marked breast enlargement ± skin redundancy & ptosis

Evaluation

- To evaluate cause
- USG / Mammography – to differentiate fat from breast tissue
  - to r/o Ca breast
- FNAC if Ca breast is suspected

MANAGEMENT

- Specific cause ⟶ specific therapy
- If gynecomastia is d/t. androgen deficiency ⟶ Rx testosterone supplementation
  - estrogen excess → DANAZOL → Regression of breast
    - Androgenic side effects
- Progressive gynecomastia not responding to other treatments
  - → SURGERY
    - Local excision
    - Liposuction
    - Subcutaneous mastectomy

NIPPLE DISCHARGE

Unilateral vs Bilateral

Spontaneous, unilateral discharge localised to a single duct in a woman ≥ 40y
- blood stained
- a/i mass

→ suggestive of Ca breast

usually multiductal
- Lactation
- Prolactin secreting pituitary adenomas
- Blue-green discharge in older women - duct ectasia

Single duct / Multiple ducts

Intraductal Papilloma
Intraductal carcinoma

Carcinoma
Infection
Duct ectasia
Lactation
Fibrocystic disease

from the 'surface' → Paget's disease

Type of discharge

Clear / Serous
- Physiological in parous women
- Duct papilloma
- Mammary dysplasia

Blood stained
- Duct papilloma
- Carcinoma
- Duct ectasia

Black / green
- Duct ectasia
- Ductal Papilloma

EVALUATION

- Mammography in ≥35y ± USG
- Ductoscopy - using a microendoscope
- Ductography
  - Duct is enlarged with a dilator
  - small blunt cannula inserted under sterile conditions into the nipple ampulla
  - with patient in supine position, 0.1-0.2ml of dilute contrast media is injected

CC & MLO mammographic views are obtained without compression
Intraductal papilloma - small filling defect surrounded by contrast
Cancer - irregular masses / multiple intraluminal filling defects

- Discharge cytology for malignant cells

Management

- Always r/o carcinoma
- Surgery if discharge is troublesome; to r/o Ca

MICRODOCHECTOMY

- lacrimal probe / stiff nylon suture is inserted into the discharging duct
- Tenni's Raquet / Periareolar incision
  ↓
  nipple flap → duct excised

Papillomas - usually 4-5cm from duct orifice

HADFIELD SUBAREOLAR CONE EXCISION OF MAJOR DUCTS

Cone of tissue excised using periareolar incision
↓
entire major duct system → HPE

→ Pectoral fascia

- cannot breast feed
- altered nipple sensation

MULTIPLE ENDOCRINE NEOPLASIA

Hereditary cancer syndromes characterised by neoplastic transformation in multiple target endocrine tissues & pathological involvement of some non-endocrine tissues - Autosomal Dominant inheritance

Genes: MEN-1 - a tumor suppressor gene - chromosome 11 → MENIN
RET (Rearranged during transfection) - proto oncogene - chromosome 10

MEN-1 - Wermer's Syndrome

ENDOCRINE FEATURES		NON-ENDOCRINE FEATURES
PRIMARY HYPERPARATHYROIDISM (90%) - multiglandular disease (all 4 glands) - Parathyroid Hyperplasia - M=F - mainly benign **PANCREATIC NEUROENDOCRINE TUMORS (30-70%)** (Potentially malignant) • Gastrinoma (20-40%) - Zollinger Ellison • Insulinoma (10%) • VIPoma / Glucagenoma / Somatostatinoma (2%) • Non functioning; PP (20-55%) **PITUITARY ADENOMAS (30-40%)** • Prolactinomas (20%) • GH, ACTH, TSH **FOREGUT CARCINOIDS** Thymic, Bronchial (2%) Gastric enterochromaffin-like (10%) (non functional) **ADRENAL CORTICAL TUMORS (40%)**		1. Facial angiofibromas 2. Collagenomas 3. Lipomas 4 Ependymomas

Screening - Biochemical - S. Calcium - cheaper than Genetic screening
∴ Virtually all cases have parathyroid involvement

SURGERY in MEN-1

① Primary Hyperparathyroidism → d/t hyperplasia

- Symptomatic / marked Hypercalcemia
- Nephrolithiasis
- ↓ Bone density / pathological fracture

↓

PARATHYROIDECTOMY

- Total parathyroidectomy ± heterotopic intramuscular gland implantation

(OR)

- Subtotal (3½) parathyroidectomy - ± vascularised remnant in neck

Not much role for pre-op localisation studies

② Gastrinoma - 60-70% of MEN-1 Gastrinomas are MALIGNANT

- severe peptic ulcer disease
- more commonly found in

DUODENAL MUCOSA > INTRAPANCREATIC SITE

→ Primarily Rx ± PPIs → Sx - DPPD

③ Insulinoma - Surgery recommended

④ Pituitary adenoma - similar to sporadic tumors

⑤ Adrenal tumors - operate if functional;
Non functional - operate if ≥ 4cm

MEN 2 Syndromes - MEN 2A, MEN 2B

1. MEN-2A

A. Classical MEN 2A

1) Medullary Thyroid Cancer - 100 %.
2) Pheochromocytoma - 50 %.
3) Primary Hyperparathyroidism 10-25 %. - often mild & asymptomatic
   - multiglandular

B. MEN2A + Cutaneous Lichen Amyloidosis

pruritic, scaly, papular, pigmented lesions over
INTERSCAPULAR REGION
Extensor surfaces of extremities

Histology - Amyloid deposition

C. MEN 2A + Hirschsprung Disease

↳ absence of autonomic ganglion cells within distal colonic sympathetic plexus

D. FMTC - variant + strong predisposition to MTC & not other features of MEN2A (Pheo, PHPT)

2. MEN2B

- Medullary Thyroid Cancer
- Pheochromocytoma
- Other -

Mucosal neuromas -
unencapsulated - lips, tongue, GB mucosa, vocal cord supra 'unchira

Intestinal ganglioneuromas (Megacolon)

Marfanoid habitus - long, thin extremities & digits

Surgery

- MTC -

Total thyroidectomy + Central Neck Dissection ± U/L / B/L Lateral neck dissection
↓
Based on pre-op imaging or central node involvement

Parathyroids - 3½ Sx ± autotransplantation in SCM / forearm

Prophylactic Thyroidectomy in carriers

MEN 2A - ≤ 5 y
MEN 2B - ≤ 1 y
FMTC - ≤ 5-10 y

} if calcitonin < 40 pg/mL
↓
can skip central dissection & parathyroidectomy

- Pheochromocytomas are NOT malignant in MEN2
- Parathyroid - 4 gland parathyroidectomy ± autotransplantation

SOLITARY NODULE OF THYROID

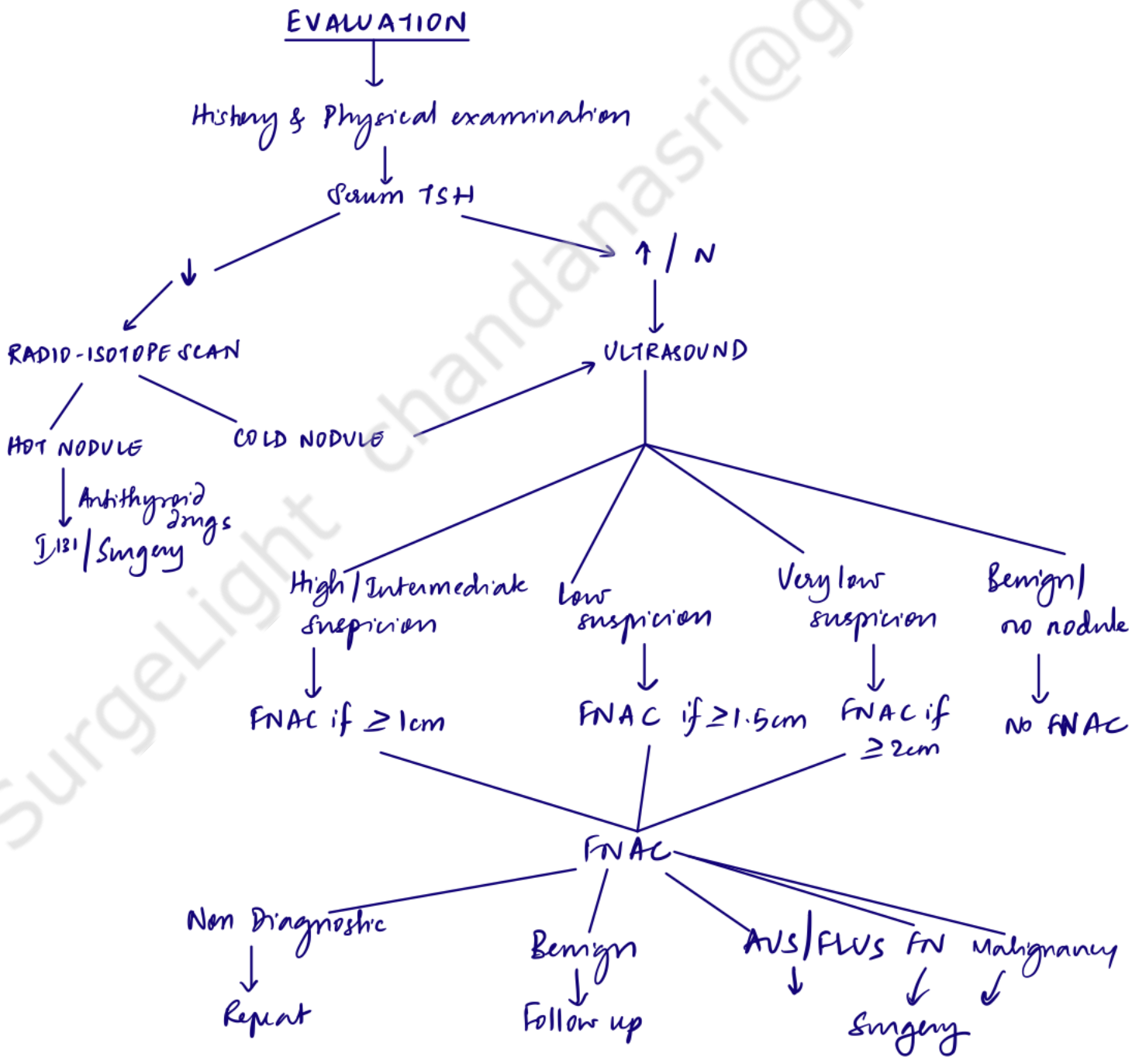
Definition: A thyroid nodule is a discrete lesion within the thyroid gland, distinct from adjacent thyroid parenchyma on clinical or radiological examination.

Occurs in ~4% of the population

ISOLATED / SOLITARY (70%) – discrete swelling in an otherwise impalpable gland

DOMINANT (30%) – discrete swelling in a gland + clinical evidence of generalised abnormality in the form of
- a palpable contralateral lobe
- generalised mild nodularity

Risk of malignancy in thyroid nodules - ~5%



HYPERTHYROIDISM

THYROTOXICOSIS - symptoms due to raised levels of circulating thyroid hormones

HYPERTHYROIDISM - excessive secretion of thyroid hormones - a cause for thyrotoxicosis

THYROTOXICOSIS

Hyperthyroidism
↑ Hormone synthesis
[↑ RAI uptake]

- GRAVES DISEASE - DIFFUSE TOXIC GOITER
- TOXIC MNG
- TOXIC ADENOMA
- DRUG INDUCED
  Amiodarone
  Iodine - Jod Basedow thyrotoxicosis
- THYROID CANCER (very rarely)
- STRUMA OVARII
- HYDATIDIFORM MOLE
- TSH- SECRETING PITUITARY ADENOMA

↑ Preformed / Circulating Hormone
[↓ RAI uptake]

- THYROIDITIS
  - Acute phase of Hashimoto thyroiditis
  [Hashitoxicosis]
- FACTITIOUS / IATROGENIC thyrotoxicosis
  [↑↑ exogenous thyroid hormones]
- 'Hamburger' thyrotoxicosis

HYPERTHYROIDISM

(This classification is found almost exclusively in DAs)

PRIMARY	SECONDARY
- Autoimmune	- Autonomous nodules
- Younger age of onset	- Older age of onset
- Goiter appears along ± toxic symptoms	Goiter appears first, toxic symptoms appear much later
- Toxic symptoms - abrupt & severe	- Toxic symptoms - insidious & mild
- Neurological symptoms ++	- Cardiovascular symptoms ++
- Goiter - diffuse, soft - firm moderate	- Goiter - nodular, variegated may be quite large
- Eye signs + ++	- Eye signs ±

GRAVE'S DISEASE

- Autoimmune disease
- Strong familial predisposition - HLA-B8, DR-3 - DR, CTLA-4 gene polymorphism
- Female preponderance - 5:1
- Peak incidence ~ 30-50 y
- DIFFUSE GOITER + THYROTOXICOSIS + EXTRATHYROIDAL MANIFESTATIONS
  - Ophthalmopathy
  - Dermopathy
  - Acropachy

PATHOPHYSIOLOGY

Autoimmune mechanism

anti TSH-R abs (stimulatory abs) + ↑ in ~90%

TSAb (Thyroid stimulating Ab)

(+)

Thyrocytes

TROPHIC EFFECT

- GOITER
  - Diffuse smoothly enlarged gland
  - ↑ vascularity
  - BRUIT

SECRETORY EFFECT

HYPERTHYROIDISM

CALORIGENIC EFFECTS
Heat intolerance
↑ Sweating
Weight loss despite good intake

Systemic effects
GI symptoms - ↑ Gut motility
Menstrual disturbances
Rapid bone maturation

ADRENERGIC EFFECTS
Palpitations → A. fib → CHF
Nervousness
Fatigue
Emotional lability
Hyperkinesis
tremors
EYE SIGNS: Lid lag (von Graefe)
Dalrymple sign
Lid retraction

Anti Tg, anti-TPO abs
- non specific
- in about 75%

GAG deposition → Pretibial myxedema

Ocular fibroblasts & muscles share TSH-R (common antigen)
↓
Ophthalmopathy
↓
INFILTRATIVE EYE DISEASE
- Periorbital edema
- Chemosis
- Proptosis
- Restriction of ocular movements
- Keratitis
- Blindness

DIAGNOSTIC TESTS

- ↓↓↓ TSH ± ↑ T_4 | T_3 [If free T_4 (N), check free T_3 → elevated in early Graves disease]
- RAI uptake / Tc^{99m} – increased uptake – diffuse enlargement
- Raised TSH-R Ab, anti TPO, anti Tg
- CT/MRI for Ophthalmopathy

TREATMENT

ANTITHYROID DRUGS + ADJUNCTS

Generally used to prepare the patient for RAI ablation or surgery

Can be 'curative' in
- Small goiters < 40g
- thyroid hormones only mildly elevated
- –/↓ titres of TSAbs
- e/o rapid ↓ in size i antithyroid medications

Drugs

PROPYLTHIOURACIL
CARBIMAZOLE, METHIMAZOLE

- inhibit organic binding of iodine & coupling of iodotyrosines (catalyzed by TPO)

T_4 —PTU→ T_3

Most patients show
- improved symptoms in 2 weeks
- become euthyroid in 6 weeks

- titrate to TSH & T_4 levels
- 'Block & replace regimen'

→ β blocker – Propranolol
CCBs like Verapamil / Diltiazem when BBs CI

RADIOACTIVE IODINE

used in
- older patients i
- small and moderate goiters
- relapse after medical R or Sx
- Intolerance to antithyroid drugs

Antithyroid drugs to achieve euthyroid state
↓
Discontinue antithyroid drugs
↓
RAI – dose acc. to mass determined by imaging – generally 8–12 mCi orally

- most patients become euthyroid within 2 months
- 50% euthyroid at 6 months

remaining → still hyperthyroid / already hypothyroid

CONTRAINDICATIONS – Pregnancy & BF

Relative CIs: Younger age
Toxic NODULAR goiter
OPHTHALMOPATHY
RAI worsens Graves ophthalmopathy, esp in smokers.

SURGERY → RAPID CONTROL

Indications

- Concern for cancer
- Seeks to conceive < 6m of Rx
- Intolerance to antithyroid drugs
- Large goiters i compressive symptoms

- Pt i moderate to severe Graves opthalmopathy (esp. smokers)

- Surgery – perform in T_2

Prep for Sx
- Antithyroid drugs → euthyroid – continue up to day of Sx
- Lugol's Iodine / SSKI 7–10 days preop 3 drops BD
- β blocker
- Steroids

Extent of Surgery

- Severe disease, large goiter → TOTAL THYROIDECTOMY (Ophthalmopathy stabilises / improves)

OTHERWISE,
- SUBTOTAL / HARTLEY DUNHILL PROCEDURE

TOXIC MULTINODULAR GOITER - Plummer's disease

Older individuals i h/o nontoxic multinodular goiter

↓

over several years, enough thyroid nodules become autonomous

can be precipitated by

- low doses of thyroxine given to suppress TSH to treat non toxic goiter
- iodide containing drugs
  - CONTRAST MEDIA
  - AMIODARONE
  (God Bless Bowes)

Excessive thyroid hormone synthesis

↑ T_3, T_4 levels

↓↓ TSH

Dx - RAI uptake scan - ↑ uptake in nodules, suppression of surrounding gland

Treatment

- Preliminary pharmacotherapy
- Surgery - Near total / Total thyroidectomy
- RAI ablation - not preferred; reserved only for elderly (who have poor operative risks)
  - Requires larger doses of RAI in MNG as the uptake is not as much as in Graves Disease
  - RAI induced thyroiditis - higher risk → potential for airway compromise
  - ↑ recurrence

TOXIC ADENOMA

- Hyperthyroidism from a single hyperfunctioning autonomous nodule
- Younger patients
- h/o recent growth of long standing nodule (usually attain ~3cm size before toxicity develops) + toxic symptoms
- somatic mutation in TSH-R gene

RAI - Hot nodule & suppression of the rest of the gland

Rx - hemithyroidectomy

DIFFERENTIATED THYROID CANCER

Papillary Carcinoma | Follicular carcinoma | Hurthle cell carcinoma
↓ often considered a variant of follicular cancer

- Undifferentiated → Anaplastic
- From 'C' cells → MTC
- Others - Lymphomas, secondaries, sarcomas, SCC

PAPILLARY CARCINOMA THYROID

- 80% of all thyroid malignancies in iodine sufficient areas
- F : M :: 2 : 1
- Mean age at presentation - 30-40y
- Predominant thyroid cancer following exposure to external radiation
- Familial Syndromes - Autosomal dominant
  - Werner Syndrome
  - Cowden Syndrome
  - Carney complex
  - Familial polyposis
  - Papillary carcinoma & papillary renal neoplasia

VARIANTS

1. Conventional	65-85%	
2. Follicular variant	15-20%	→ encapsulated variant → indolent → excellent prognosis
3. Tall cell	5-10%	occur in older patients, less favorable prognosis
4. Solid	1-3%	
5. Diffuse sclerosing	1-2%	
6. Columnar	<1%	

PATHOLOGY

Macroscopically - well circumscribed, white

Microscopy → Papillary projections
Cellular & nuclear characteristics
- cuboidal shape
- Nuclear grooving
- Cytoplasmic inclusions
- ORPHAN ANNIE EYE NUCLEI

occult / microcarcinoma
- <1cm
- no evidence of capsular/vascular invasion

Psammoma bodies - calcified deposits of sloughed cells deposited in stroma/lymphatics
↳ 50%

Multifocality → 80% cases

a/c ↑ risk of lymphnode metastasis - 80-80% at presentation

FOLLICULAR CARCINOMA THYROID

- 6-10% of all thyroid malignancies
- most often found in iodine deficient areas (? related to TSH stimulation)
- Female : Male :: 3 : 1
- found in association ± Benign thyroid disorders like endemic goiter
- 5th-6th decades
- No strong association ± radiation exposure

PATHOLOGY

- ranges from virtually normal follicular architecture to severely altered cellular architecture

Histological diagnosis depends on demonstration of follicular cells occupying ABNORMAL POSITIONS, including → CAPSULAR / VASCULAR } invasion

Atypia ± (7 Genes: BRAF, RAS, RET/PTC, PAX, PPARγ)

Dx depends on defining lesion 'architecture' → not possible by FNAC

- MINIMALLY INVASIVE
- WIDELY INVASIVE → distant spread m/c

CLINICAL FEATURES

- Painless thyroid mass - Hoarseness, fixity → poor prognosis
- co-exist ± MNG in 10% cases

Spread via hematogenous routes
10-15%
m/c metastatic manifestations: LYTIC BONE LESIONS
Lung metastasis

Overall prognosis poorer than pap-C

HURTHLE CELL CANCER

- consists of oxyphilic cells → ↑ number of mitochondria → appearance of enlarged granular eosinophilic cytoplasm
- occurs in OLDER patients - 60-75y
- multifocal, bilateral
- AGGRESSIVE BIOLOGICAL BEHAVIOR - ↑ likelihood of local recurrence, less avid to absorb RAI → local nodal + distant mets
- Does not respond to RAI

PROGNOSTIC SCORES

① AGES scoring system

Age - <40y (low risk) ; >40y (high risk)

Grade - well differentiated (low risk) ; poorly differentiated (↑ risk)

Extrathyroidal extension & metastasis → Poor prognosis

Size - < 2cm (low risk) >4cm (high risk)

② MACIS

Metastasis - ⊕ → poor prognosis

Age - <40y (↓ risk); >40y (↑ risk)

Completeness of surgical resection

Invasion → ETE

Size

③ AMES

Age * ♂ - <40y, ♀ - <50y } better prognosis

Metastasis

Extrathyroidal spread

Size (<5cm - ↓ risk ; >5cm - ↑ risk)

④ De Groot

Class I - Intrathyroidal

Class II - Cervical nodal mets

Class III - Extrathyroidal extension

Class IV - Distant metastasis

⑤ Thyroglobulin doubling time - independent prognostic marker

TNM Classification

T

- T_0 – No e/o 1° tumor
- T_x – cannot be assessed
- T_1
  - T_{1a} – ≤ 1cm
  - T_{1b} – 1–2cm
  - } limited to thyroid
- T_2 – 2–4cm limited to thyroid
- T_3
  - T_{3a} – >4cm limited to thyroid
  - T_{3b} – ETE limited to strap muscles
- T_4
  - T_{4a} – ETE – s/c tissue, larynx, trachea, esophagus, RLN
  - T_{4b} – Prevertebral fascia, carotid / mediastinal vessels

N

- N_0 – no locoregional nodes
- N_x – cannot be assessed
- N_1
  - N_{1a} – Level VI, VII
  - N_{1b} – Lateral nodes – I, II, III, IV, V / Retropharyngeal nodes

M

- M_0
- M_1 – Distant mets

STAGE GROUPING – depends on AGE AT DIAGNOSIS ⟶ < 55y → M_0 → Stg I; M_1 → Stg II

- Stage I
  - < 55y – Any T, Any N – M_0
  - > 55y – T_1, T_2 N_0, N_x M_0
- Stage II
  - < 55y – Any T, Any N, M_1
  - > 55y – T_1, T_2 N_1 M_0
    $T_{3a,3b}$ any N M_0
- Stage III ⟶ > 55y – T_{4a}, Any N, M_0
- Stage IV ⟶ > 55y
  - IV A – T_{4b} Any N M_0
  - IV B – Any T, Any N M_1

EVALUATION

- Similar to thyroid nodule evaluation

MANAGEMENT

① SURGERY

PAPILLARY CARCINOMA

APPROACH TO IO

Indications for total thyroidectomy

- Distant metastasis
- ETE
- >4cm
- Cervical LN ⊕
- Poorly diff
- i/c/o h/o Radiation exposure
- B/L nodularity

strongly consider

Consider hemithyroidectomy

- No prior radiation exposure
- No distant mets
- No cervical LN mets
- ≤ 4cm
- No ETE

CONSIDER COMPLETION THYROIDECTOMY

- >4cm
- +ve margins
- Gross ETE
- Macroscopic multifocal disease (>1cm)
- Macroscopic nodal mets (>5mm)
- Vascular invasion

APPROACH TO NECK

2015 ATA Guidelines

- Prophylactic ipsilateral/bilateral neck dissection in T_3 or T_4

→ central neck dissection

- Nodal involvement ⊕ MRND (II) / FND

Dissection of posterior triangle and suprahyoid dissection
- usually not necessary

- done if there is extensive level I, II, IV involvement

Prophylactic lateral node dissection unnecessary in PTC

FOLLICULAR LESION ON FNAC

INDICATIONS FOR TOTAL THYROIDECTOMY

- >4cm
- Atypia
- Family h/o
- ETE
- Metastasis

HEMITHYROIDECTOMY

- Benign
- Encapsulated Follicular variant PTC

→ ACTIVE SURVEILLANCE

Minimally invasive Follicular cancer

→ ACTIVE SURVEILLANCE

Extensively invasive

→ Completion Thyroidectomy

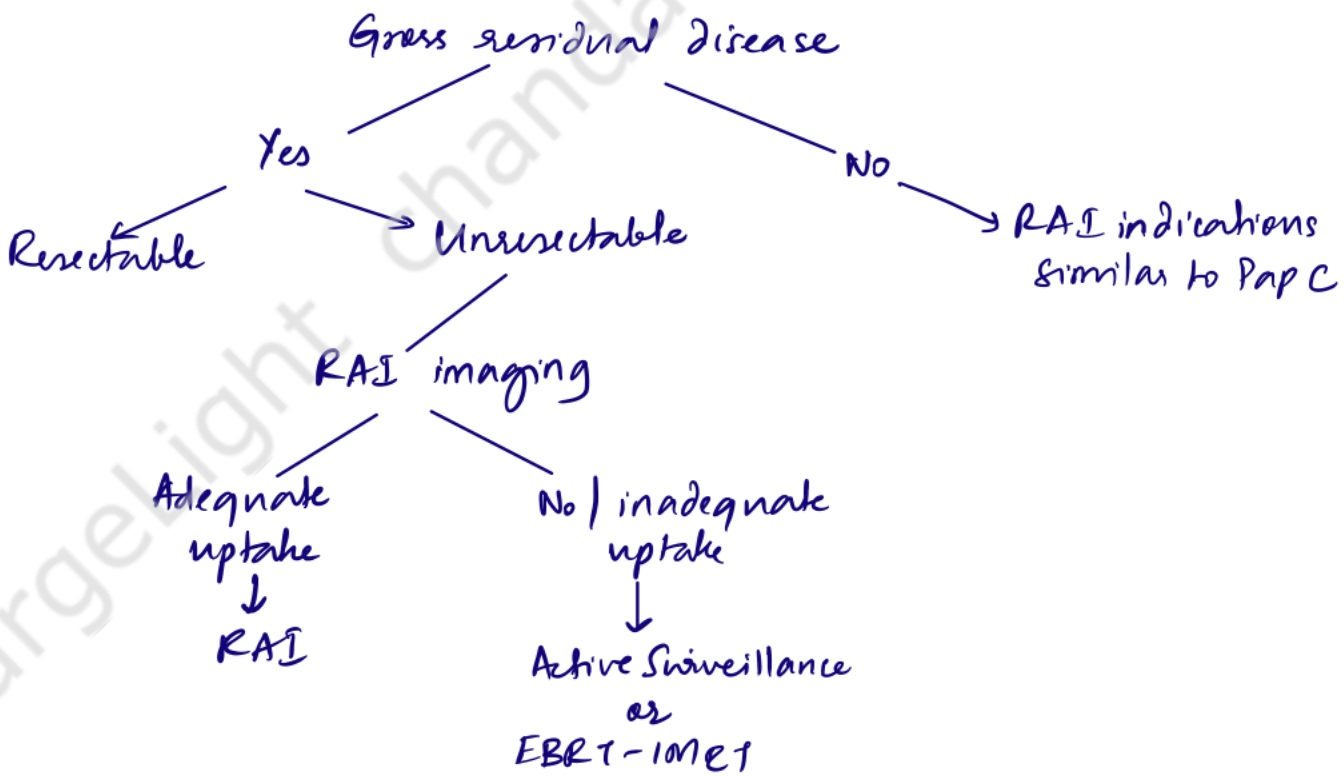
Neck - Therapeutic neck dissection of involved compartments for clinically apparent / biopsy proven disease

② RADIOIODINE THERAPY – Post op

- **PAPILLARY CARCINOMA RISK STRATIFICATION**

LOW RISK	INTERMEDIATE RISK	HIGH RISK
• Classical PAP-C • <2cm - Intrathyroidal • Unifocal • ≤1cm multifocal • No anti Tg abs - Post-op unstimulated Tg <1ng/mL - Negative post-op USG	• High risk histology • 2-4 cm • Lymphatic invasion • Neck nodes (+) • >1cm multifocal • Positive margins (micro) • Post op unstimulated Tg - <5-10ng/mL • +ve post op USG	• Gross ETE - >4 cm • Bulky or >5 +ve LNs • Post op unstimulated Tg >5-10ng/mL • Distant mets (+)
↓	↓	↓
RAI typically not recommended	RAI ±	RAI recommended

- **FOLLICULAR CARCINOMA**



③ TSH suppression therapy – based on risk stratification

TSH goals

↑ risk – <0.1
↔ risk – <0.5
↓ risk – <2

MEDULLARY CARCINOMA THYROID

- ~5% of thyroid malignancies
- arises from parafollicular 'C' cells derived from ultimobranchial bodies
  - → concentrated superolateralli → m/c site of MTC origin
- secrete Calcitonin - 32 amino acid peptide
  - lowers serum calcium (effects minimal in humans)
  - (N) - 0-5 pg/mL ; $t_{1/2}$ - 50-80 min
- Types
  - Sporadic
  - Inherited - 25% { Familial MTC, MEN 2A, MEN 2B } → Germline mutations in RET proto-oncogene

MEN 2A	MEN 2A & Hirschsprung's Disease	Familial MTC	MEN 2B
- MTC	- MTC	MTC	MTC (most aggressive)
- Pheochromocytoma	- Pheochromocytoma	Multifocal, Bilateral MTC & Autosomal dominant inheritance pattern	- Pheochromocytoma
- Primary hyperthyroidism	- Primary hyperthyroidism		- Marfanoid habitus
- Lichen planus	- Hirschsprung's Disease		- Mucocutaneous ganglioneuromatosis
- Amyloidosis			

Clinical features

- F : M :: 1.5 : 1
- 50-60y - sporadic
  familial - younger
- m/c - unilateral (80%) in sporadic
  multicentric in familial (90%)
  - a/i C-cell hyperplasia → Premalignant
- Neck mass & cervical lymphadenopathy (15-20%)
  - Pain
  - Local invasion - Dysphagia, Dyspnea, Dysphonia

Substances secreted - CALCITONIN ($t_{1/2}$ 50-80 min)
- Carcino Embryonic Antigen
- CGRP (Calcitonin gene related peptide)
- Histaminidases
- PGE_2, $F_{2\alpha}$
- Serotonin

Diarrhea d/t ↑ intestinal motility & impaired intestinal water & electrolyte flux

→ Generally seen in EXTENSIVE METASTATIC DISEASE

Distant metastasis
- Liver, bone (Osteoblastic)
- Lung

2-4% - Cushing's - d/t ectopic ACTH

PATHOLOGY - sheets of infiltrating neoplastic cells separated by collagen & amyloid

Polygonal / spindle shaped

IHC - Calcitonin, CEA, CGRP

EVALUATION

- H & P → evaluate central & lateral neck + superior mediastinum
- USG
- FNAC
- ↑ S. calcitonin / CEA
  - more sensitive
  - Better predictor of prognosis

Screening for RET point mutations, pheochromocytoma & hyperparathyroidism in all newly detected MTC (to diff sporadic from familial)

Pheochromocytoma + ⇒ treated first

Hyperparathyroidism → addressed at the time of thyroid Sx

- Pts ± palpable / imaging-detected cervical nodes
  signs & symptoms of metastatic disease
  Calcitonin levels >500pg/mL

NECK & CHEST CT + TRIPLE PHASE LIVER CT
or
Contrast enhanced MRI
+
Axial MRI / Bone scan

STAGING - AJCC-8 Thyroid - Medullary

T
- T_1
  - T_{1a} - ≤ 1cm
  - T_{1b} - 1-2cm

  ] limited to thyroid
- T_2 - 2-4cm
- T_3
  - T_{3a} → 4cm limited to thyroid
  - T_{3b} - Extrathyroidal extension involving strap muscles
- T_4
  - T_{4a} - GTE to neck - s/c tissue, larynx, trachea, esophagus RLN
  - T_{4b} - ETE to spine, main neck vessels, prevertebral fascia

N

Nx - cannot be assessed
N0 - No e/o locoregional nodes
N1 < N1a - Level VI or VII - U/L B/L
↳ Pretracheal, Paratracheal, Prelaryngeal & upper mediastinal
N1b - U/L / B/L / C/L
Lateral neck nodes (I, II, III, IV, V) or retropharyngeal nodes

M1 < M0
M1 - Distant mets (+)

STAGE GROUPING

I - T1 N0 M0

II < T2 N0 M0
T3 N0 M0

III - T1-3 N1a M0

IV < IVA → T4a any N M0
IVB → T1-3 N1b M0, T4b any N M0
IVC → Any T Any N M1

PROGNOSTIC FACTORS

- Nodal involvement - poor prognosis
- Completeness of resection
- Biochemical
  - Calcitonin (0-5 pg/mL (N))
  - CEA (0-3 ng/mL (N))
  - ACTH (<46 pg/mL (N))
- Gene mutations - Familial vs sporadic

TREATMENT

SURGERY - TOTAL THYROIDECTOMY + ROUTINE B/L PROPHYLACTIC CENTRAL NECK NODE DISSECTION

→ clo nodal disease ⊕ ↑ Calcitonin >500pg/ml, Primary tumor ≥1.5cm ⟶ + lateral neck dissection B L

→ locally recurrent/ widely metastatic disease - tumor debulking
↓ pain, flushing, diarrhea
↓ risk of death from neck/mediastinal disease

PROPHYLACTIC THYROIDECTOMY in RET mutation carriers

MEN 2A ⟶ ≤5y of age
MEN 2B ⟶ ≤1y of age
FMTC ⟶ ≤5-10y of age

EBRT - Resected T_4
Unresectable residual/recurrent tumor
Symptomatic bony metastasis

Liver mets - frequently - multiple - not amenable to resection
↳ Rx - RFA, percutaneous ethanol injection

TARGETED THERAPY

Anti RET Kinase - many also inhibit VEGFR 2/t close structural similarities

SORAFENIB
SUNITINIB
LENVATINIB
CABOZANTINIB
} Multikinase inhibitors

Vandetanib - RET Kinase + VEGFR + EGFR inhibitor

Anti CEA monoclonal ab - Labetuzumab

Radioactive Iodine therapy/scan - USELESS in MTC

ANAPLASTIC THYROID CANCER

- ~1% of all thyroid malignancies
- F > M
- 7th - 8th decade

- All Anaplastic Thyroid Cancers are classified as Stage IV

IV A → limited to thyroid – 10%.
IV B → local invasion – 40%.
IV C → Distant metastasis – 50%

ATC occurs in synchrony ē other thyroid malignancies (PTC, FCC)

→ ? ATC occurs d/t de-differentiation of DTCs by accumulation of BRAF, RAS, p53 mutations

C/F
- long standing neck mass – rapidly enlarges, painful
  - Generally locally invasive
    - ulceration (+)
    - necrosis (+)
  - Dyspnea, Dysphonia, dysphagia - common

EVALUATION

- USG
- FNAC – characteristic giant & multinucleated cells – marked heterogeneity
  Core & incisional biopsies may be needed for confirmation

IHC – helps r/o other possibilities – Lymphoma
MTC
primary/ secondary sarcomas

Imaging to assess resectability
CT/MRI

Rx
- En bloc resection to achieve atleast R1
- Adjuvant RT
- Cytotoxic chemo – Taxane + Anthracycline + Platinum-based

Median Survival ≤ 6m
1y survival – 25%.
5y survival – 5%

THYROIDITIS

ACUTE THYROIDITIS

SUPPURATIVE THYROIDITIS

- very rare
  - thyroid gland is inherently resistant to infection d/t
    - ↑ Iodide content
    - Rich blood & lymphatic supply
    - Fibrous capsule
- usually a/i severe pyogenic infection of upper airway / otitis media
- direct spread via PYRIFORM FISTULA / thyroglossal duct cyst
- Penetrating trauma to thyroid
- Immunosuppression

m/c organisms -

Staphylococcus aureus
Streptococcus

Signs of acute infection

℞ - Parenteral antibiotics

Drainage of abscess

℞ of Pyriform sinus fistula

SUBACUTE THYROIDITIS

GRANULOMATOUS THYROIDITIS
DE QUERVAIN'S THYROIDITIS

- may occur in a painful / painless form
- usually follows a viral infection (URTI)

F : M :: 2 : 1

40y

Painful / Painless

Painful:
30-40y ♀
↓
Hyperthyroid
↓
Euthyroid
↓
Hypothyroid
↓ 90%
Resolution
↓
EUTHYROID

Painless:
occurs sporadically in the post partum period ~6 weeks after delivery
a/i ↑ TPO titres in early pregnancy

a/i HLA-B 35
↓ I^{123} uptake
FNA - Granulomatous

℞ - Pain - Aspirin / NSAIDs
severe - prednisone
Thyroid hormone replacement when necessary
B blockers in toxic state

DISABLING THYROIDITIS
- Thyroidectomy
- RAI ablation

CHRONIC THYROIDITIS

LYMPHOCYTIC / HASHIMOTO THYROIDITIS
STRUMA LYMPHOMATOSA

↓

leading cause of hypothyroidism today

30-50y ♀
HLA-B8 / DR-3 / DR-5

ANTIBODIES AGAINST
- Thyroglobulin - 60%
- TPO (95%)
- TSH-R (60%)
- NaI symporter (15%)

May be a/i
- ↑ Iodine uptake
- Lithium
- Amiodarone
- INF α

Diffuse thyroid enlargement
↓
granular / nodular & firm

Microscopy
- Diffuse lymphocytic infiltration
↓
small follicles ± well developed germinal centres

follicles lined by HURTHLE / ASKANAZY CELLS (eosinophilic granular cytoplasm)

Complication - LYMPHOMA

℞ - Thyroid hormone replacement

RIEDEL'S THYROIDITIS
RIEDEL'S STRUMA / INVASIVE FIBROUS THYROIDITIS

Replacement of all / part of thyroid parenchyma ± FIBROUS TISSUE
↓
May invade adjacent tissue

- a/i other sclerosing disorders like:
  - PSC
  - IRF

? Primary fibrotic disorder

IgG-4 related systemic disease

Painless, hard (WOODY) neck mass
- progression
- compression symptoms

FNAC - inadequate

℞ - surgery
↓
Tracheal decompression by ISTHMUSECTOMY

Thyroxine replacement
? Steroids ? Tamoxifen
? Mycophenolate Mofetil
? Rituximab

THYROID STORM

Life threatening condition characterised by severe clinical manifestations of thyrotoxicosis

RISK FACTOR : long standing / untreated hyperthyroidism

PRECIPITATING FACTORS

- Surgery - thyroid / non-thyroid
- Trauma
- Infection
- Parturition
- Acute iodine load - Contrast agents / RAI / amiodarone
- Abrupt cessation of antithyroid drugs

} Stress

a/c high mortality rate; needs ICU care

PATHOMECHANISM

1. Rapid rate of ↑ in S. thyroid hormones
2. ↑ responsiveness to catecholamines
3. ↑ cellular response to thyroid hormones

DIAGNOSTIC FEATURES

HYPERPYREXIA + SYSTEMIC FEATURES + ALTERED MENTATION ∴ Abnormal TFT (↑ T_3, T_4, ↓ TSH)

SYSTEMIC FEATURES:
CVS DYSFUNCTION
GI DYSFUNCTION, HEPATIC FAILURE

TREATMENT OF THYROID STORM

① General Measures

- O_2 supplementation
- Antipyretics
- Hemodynamic support
  ↓
  Correction of dehydration
- Treating precipitating factors such as infection
- Intensive monitoring

② β blockers

to control the manifestations of ↑ adrenergic tone

PROPRANOLOL
- 60-80mg PO Q6-8h
- 0.5-1mg slow IV over 10min repeated every few hrs

ESMOLOL
LD: 200-500μg/kg
+
Inf 50-100μg/kg/min

Dose titrated to HR

③ Antithyroid drugs

To block de-novo synthesis (no reduction in preformed hormone)

PTU - also blocks peripheral $T_4 \rightarrow T_3$

PTU - 200mg Q4h
or
Methimazole 20mg Q4-6h
[PO / NG tube / PR suppository]

④ Lugol's Iodine

↓
blocks T_3, T_4 release

5% Iodine in 10% KI
10 drops Q8h
or
SSKI
5 drops Q6h

⑤ Steroid (Glucocorticoid)

- ↓ Peripheral conversion (esp in liver)
- Hemodynamic stabilization
- Prevent adrenal exhaustion
- Improve hemodynamics

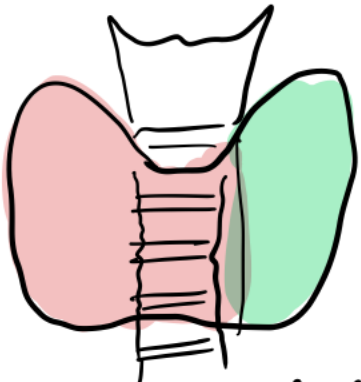
Hydrocortisone 100mg IV TID

⑥ Bile acid Sequestrants

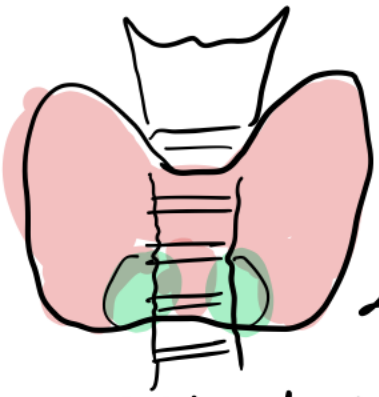
↓
Prevent reabsorption of free thyroid hormones in the gut (secreted in bile)

CHOLESTYRAMINE 4g PO QID

THYROID SURGERY

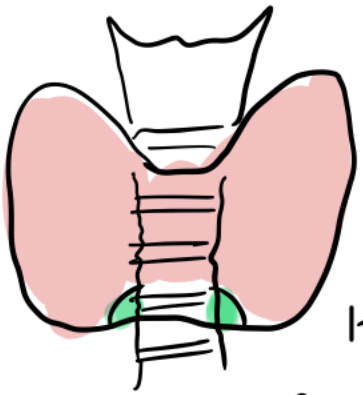


Hemithyroidectomy



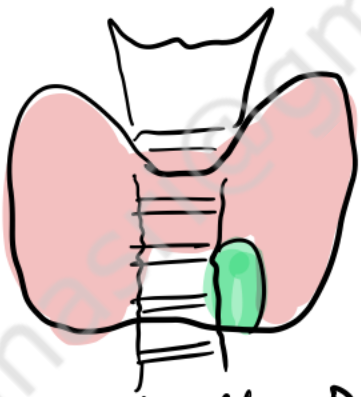
4-8g

Subtotal thyroidectomy

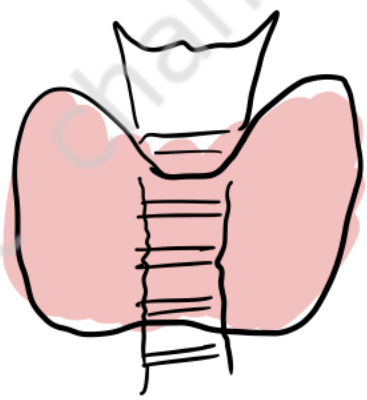


1-4g

Near total thyroidectomy



Hartley Dunhill



Total thyroidectomy

THYROGLOSSAL DUCT (+ CYST/ SINUS/ FISTULA)

Embryology

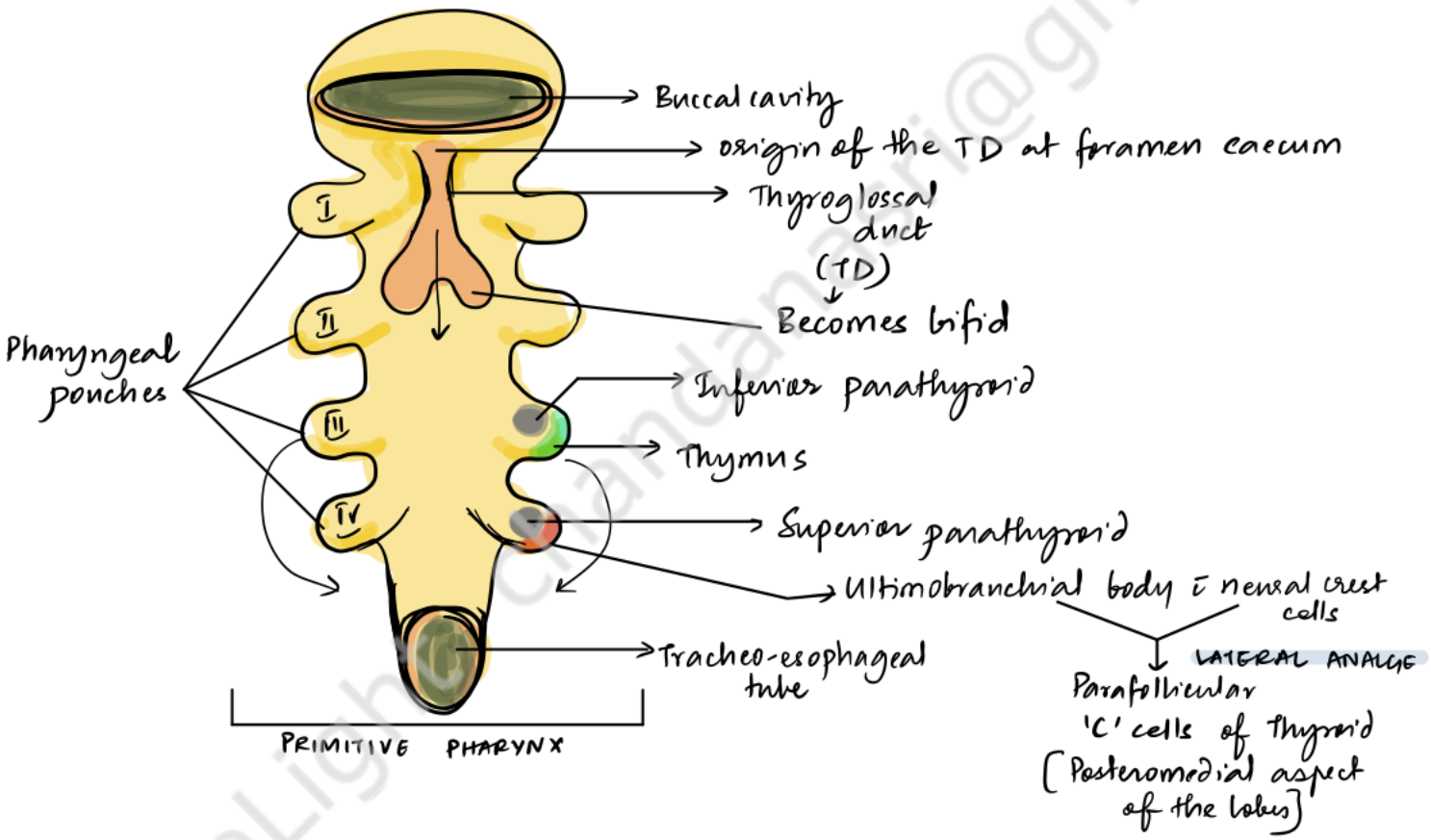
Thyroglossal duct is the vestigeal tract of descent of the thyroid gland from the foramen caecum of the tongue to the location of the thyroid

The tissue bud that becomes the thyroid gland initially arises as a MIDLINE DIVERTICULUM in the floor of the PHARYNX → ~3 weeks of gestation

PHARYNGEAL ANALGE (MEDIAN THYROID ANALGE) ↓

This point of origin represents the foramen caecum

Consists of cells of endodermal origin



- TD migrates caudally in close continuity with / through the developing hyoid bone (anterior / posterior)

- Thyroglossal duct is initially hollow
- The TD begins to obliterate around 5th week of gestation
- Thyroglossal duct DISAPPEARS ~8th week of gestation
- Median & Lateral thyroid analges fuse ~5th week

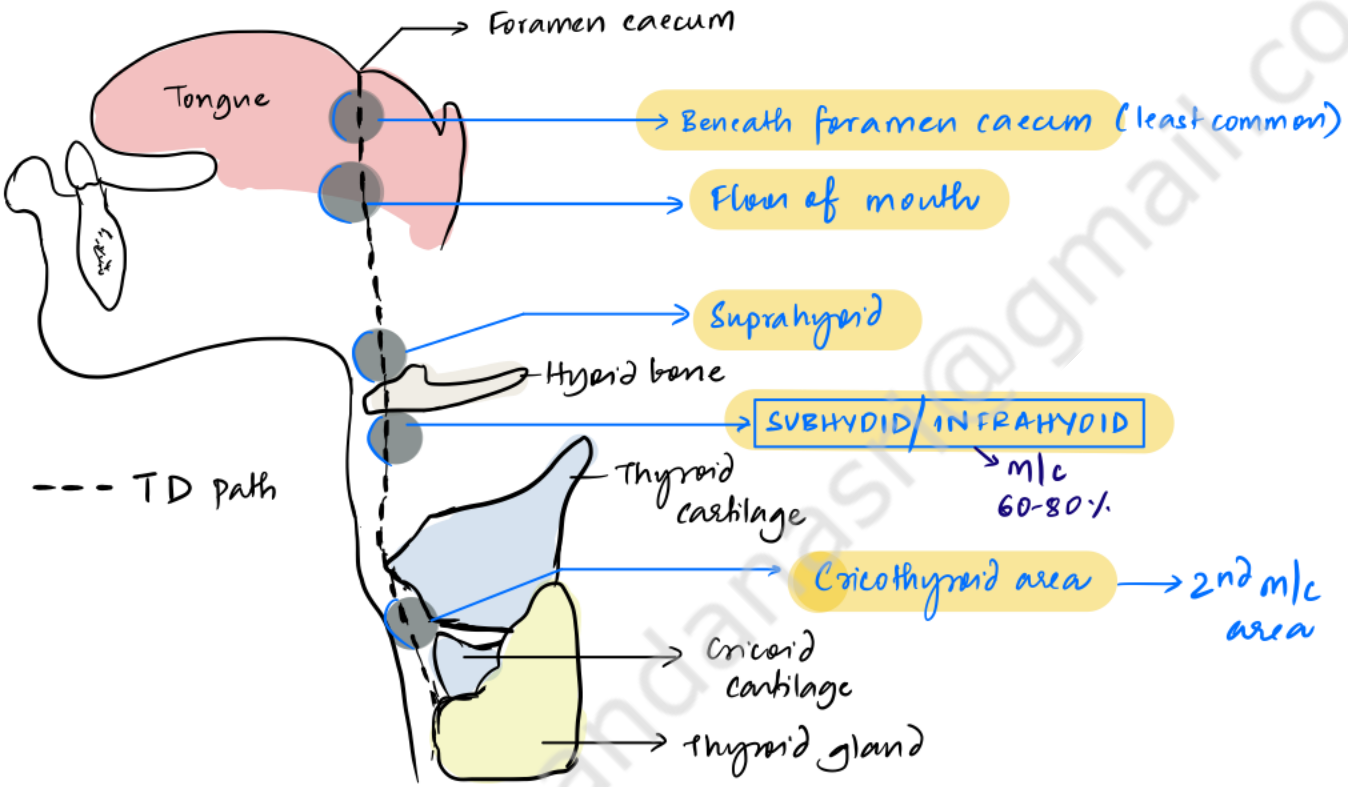
Follicular cells (derived from lining of TD): ~8 wks | Colloid formation ~11 weeks

Distal aspect of the TD may be retained as PYRAMIDAL LOBE IN ADULT THYROID

THYROGLOSSAL CYST

- Congenital cervical anomaly resulting from the persistence of a part of the thyroglossal duct (Considered a 'tubulodermoid')
- can occur anywhere along the migratory path of the thyroid

TYPES (Based on location)



Histologically, thyroglossal cysts are lined by PSEUDOSTRATIFIED CILIATED COLUMNAR EPITHELIUM AND SQUAMOUS EPITHELIUM ± heterotopic thyroid tissue present in ~20% cases (may be the only functional thyroid tissue)
- CYST FLUID IS FILLED ± CHOLESTEROL CRYSTALS / MUCOID MATERIAL / EPITHELIAL DEBRIS

Clinical features

- childhood - m/c ; can appear in adulthood - as late as 6th - 7th decade
- Midline neck cysts (0.5-5cm → fluctuant) - very very rarely, when they arise adjacent to the thyroid cartilage, they may lie slightly to one side of the midline
  Transillumination ± ; only sideways mobility.
- Generally asymptomatic
  - occasionally may become infected by oral bacteria
- Moves ± deglutition + Protrusion of tongue
  ↳ may be absent in cysts well below hyoid bone as they may lose attachment with the tongue

Ddx: Subhyoid bursitis, Sublingual dermoid

COMPLICATIONS

1) - Recurrent infection

2) - Carcinoma (1%) - Papillary carcinoma thyroid (85%), SCC, Hurthle cell, Anaplastic Ca
MTC - Not seen in thyroglossal cyst (for obvious reasons!)
Role of total thyroidectomy controversial - indicated i/c/o - large tumor
- additional thyroid nod
- e/o cyst wall invasion
- LN mets

3) THYROGLOSSAL SINUS/ FISTULA:
Due to - spontaneous / iatrogenic (I&D) rupture of thyroglossal cyst (usually infected)
- Incomplete removal of thyroglossal cyst

Clinical features:
- Midline sinus / fistula
- Hood / semilunar fold of skin just above fistula - d/t overgrowth of the neck tissue
- Pronounced dimpling of the sinus on protrusion of tongue

Investigations

Thyroid imaging may be done to confirm presence of normal thyroid tissue in the neck - USG, Thyroid scintigraphy, TFT

MANAGEMENT

Surgery - SISTRUNK PROCEDURE - EN-BLOC CYSTECTOMY + EXCISION OF CENTRAL HYOID BONE

- Transverse neck incision over the cyst
- Subplatysmal flaps
- Cyst dissected upto the hyoid bone
- Sternohyoid, Sternothyroid, Geniohyoid, Mylohyoid divided
- central 1cm of hyoid bone resected along i tract
- Tract identified & dissected upto the foramen caecum & ligated & divided

Thyroglossal fistula → Rx - Sistrunk operation

LINGUAL THYROID

- arises d/t failure of the median thyroid analge to descend normally

Embryology

Thyroglossal duct is the vestigeal tract of descent of the thyroid gland from the foramen caecum of the tongue to the location of the thyroid

The tissue bud that becomes the thyroid gland initially arises as a MIDLINE DIVERTICULUM in the floor of the PHARYNX → ~3 weeks of gestation

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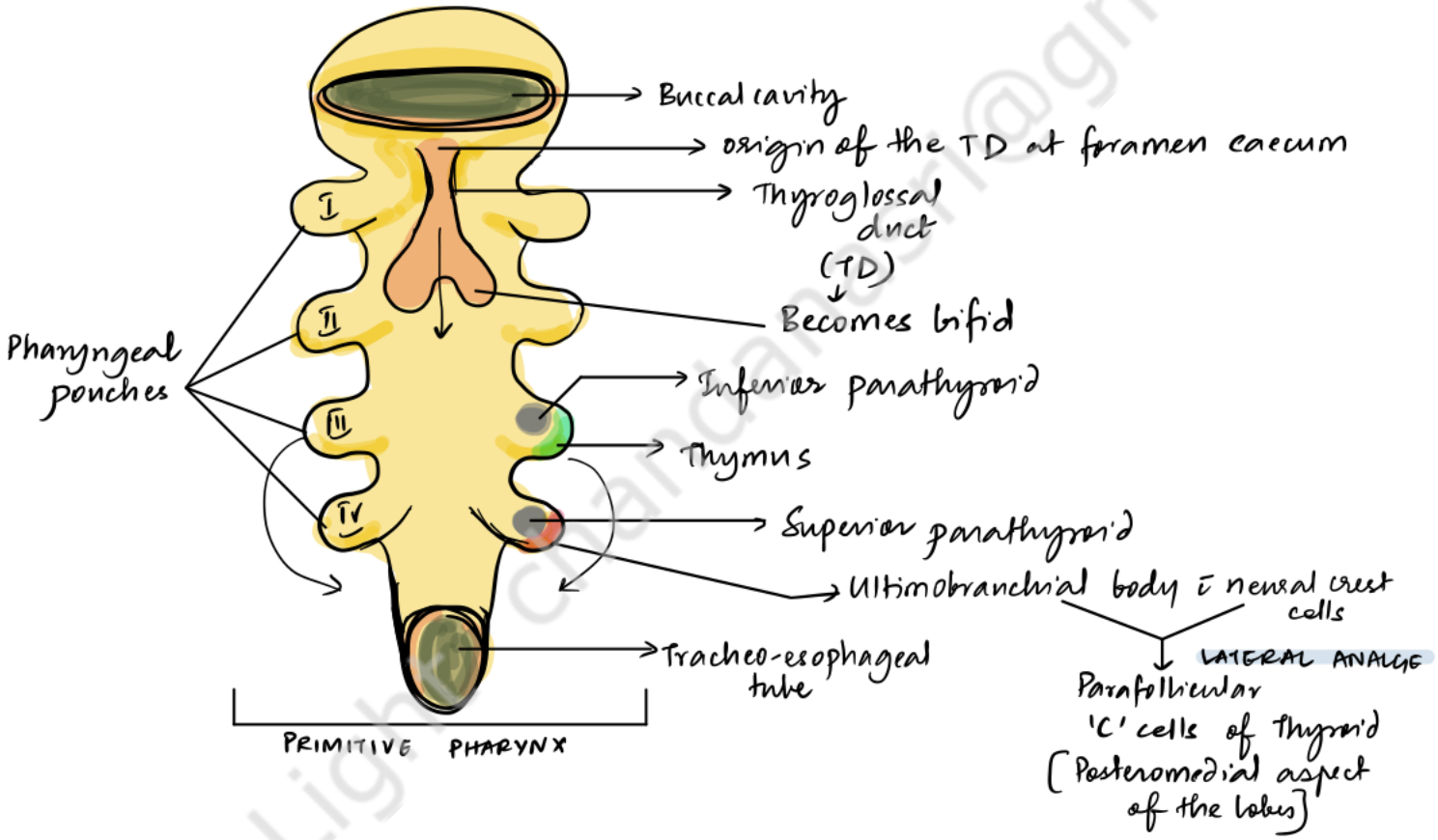
This point of origin represents the foramen caecum

Consists of cells of endodermal origin



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Follicular cells (derived from lining of TD): ~8 wks | Colloid formation ~11 weeks

Distal aspect of the TD may be retained as PYRAMIDAL LOBE IN ADULT THYROID

The lingual thyroid may be the ONLY THYROID TISSUE PRESENT

- Presents as a swelling at the foramen caecum near the base of tongue
- Many patients are hypothyroid
- Intervention is necessary i/c/o OBSTRUCTIVE SYMPTOMS
  - choking
  - dysphagia
  - airway obstruction
  - hemorrhage

Imaging to ascertain thyroid location & status

MEDICAL Rx i TSH suppression using exogenous thyroid hormone

RAI ablation → HORMONE REPLACEMENT

Surgical excision → Rarely necessary

NUCLEAR MEDICINE IN THYROID DISORDERS

RADIOACTIVE IODINE

I^{131}

- $t_{1/2}$ - 7-8 days
- Decays by emission of
  - β rays → CYTOTOXIC EFFECTS ON FOLLICULAR CELLS → ABLATION
  - γ rays → picked up by γ camera → IMAGING
- long $t_{1/2}$ - suitable for ablation detection of occult mets

I^{127}

- $t_{1/2}$ - 13 hours
- Decays by emission of γ rays
  - used for imaging
  - Radiation burden to thyroid - < 1% of that of I^{-131}
- Shorter $t_{1/2}$ → more convenient for 24 hr studies

INDICATIONS FOR RADIOACTIVE IODINE

Table 1 : Indications and contraindications for RAI therapy

The main indications for RAI therapy include the following conditions
1. Hyperthyroidism due to: a. Grave's disease b. Toxic multinodular giotre or c. Hyperfunctioning thyroid nodules 2. Non-toxic multinodular goitre 3. Thyroid cancer (DTC except Hurthle cell Ca)
Contra-indications for RAI therapy
1. Pregnancy 2. Breast feeding 3. Severe uncontrolled thyrotoxicosis

Hurthle cell Ca
Medullary TC
} Do not take up RAI

RADIO-IODINE IN THYROID CANCER

• PRINCIPLES OF RAI ABLATION

GOALS — Radioiodine is administered after thyroidectomy in patients with differentiated thyroid cancer to ablate residual normal thyroid tissue (remnant ablation), to provide adjuvant therapy of subclinical micrometastatic disease, and/or to provide treatment of clinically apparent residual or metastatic thyroid cancer.

- **Residual normal thyroid tissue** – The rationale for treatment of residual normal thyroid tissue with iodine-131 (131-I) is to destroy any remnant normal thyroid tissue remaining after total thyroidectomy (remnant ablation). This will, in turn:
  - Destroy subclinical, microscopic foci of disease remaining after surgery (adjuvant therapy)
  - Minimize the risk of development of de novo papillary thyroid cancers in at-risk patients (eg, history of head and neck irradiation, genetic predisposition syndromes)
  - Improve the specificity of measurements of serum thyroglobulin (Tg) as a tumor marker
  - Increase the specificity of 131-I scanning for detection of recurrent or metastatic disease by eliminating uptake by residual normal tissue
- **Residual macroscopic or metastatic disease** – The major goal of radioiodine therapy is to destroy clinically apparent macroscopic disease that is not amenable to surgical therapy. Radioiodine treatment of residual disease and metastatic disease may reduce the risk of recurrence and mortality, especially in small-volume disease that is radioiodine avid.

Table 3: Medications and other substances such as radiographic contrast materials that can interfere with RAI uptake and should be stopped before treatment

Type of medication or Substance	Duration of stopping treatment before RAI
Antithyroid medication (e.g., propylthiouracil, methimazole, carbimazole) and multivitamins	1-2 weeks for antithyroid drugs. Note: Beta Blockers can be continued 7 d for multivitamins
Expectorants, agar, Lugol's iodine, potassium iodide ("SSKI")	2-3 weeks, depending on iodide content
Radiographic contrast agents Intravenous (water soluble)	3-4 weeks (assuming normal renal function)
Amiodarone	3-6 monts or longer

Adapted from:
The Society of nuclear Medicine Guidelines (18), Martin A Walter, Matthias Briel, et al. BMJ 2007(26);334;514

PREPARING THE PATIENT FOR RAI

Thyroid hormone withdrawal — In the setting of 131-I treatment of residual tumor or metastatic disease, thyroid hormone withdrawal remains the standard approach to raising TSH levels for adequate radioiodine uptake. Thyroid hormone should be withdrawn three to four weeks prior to radioiodine therapy [2]. After thyroidectomy or cessation of T4 (levothyroxine) therapy, the patient's serum thyroxine (T4) concentration must decline sufficiently to allow the serum TSH concentration to rise to above 25 to 30 mU/L [26].

To minimize hypothyroid symptoms for patients withdrawing from thyroid hormone, our approach is to reduce the dose of oral T4 by 50 percent for four weeks and then discontinue the T4 for one week prior to administration of radioiodine. Serum TSH should be measured immediately before any 131-I is given to confirm that the concentration is high. One study found that with this approach, the majority of patients taking half-dose T4 achieved a serum TSH concentration of 25 to 30 mU/L by five weeks [27]. In addition, their hypothyroid symptoms were milder than a group of patients undergoing T3 (liothyronine) withdrawal.

Another strategy is to give the shorter-acting hormone T3 in doses of 25 mcg two to three times per day for the first two weeks after stopping T4 [28]. Lower doses (eg, 10 to 12.5 mcg two or three times per day) should be used in older patients and those with ischemic heart disease. After cessation of T3, the serum TSH concentration should rise to 25 to 30 mU/L within one to two weeks. Thus, the interval during which the patient receives no thyroid hormone is shortened.

Recombinant human TSH — For patients treated with radioiodine for thyroid remnant ablation, hypothyroidism can be avoided altogether by administering rhTSH before administration of 131-I.

With this method, the patient continues their usual dose of T4; rhTSH (0.9 mg) is administered by intramuscular injection on two consecutive days, followed by administration of radioiodine on the day following the second injection (ie, the third day). Serum thyroglobulin (Tg) levels are obtained 72 hours after the second rhTSH injection (the fifth day) and a post-treatment whole-body scan is performed two to seven days after the radioiodine administration.

- rhTSH 0.9 mg IM × 2 days
- 3rd day ↓ Scan

In patients in whom pretreatment (diagnostic) scanning is performed, the scanning dose is administered on the afternoon of the second rhTSH dose, and the diagnostic scan and therapy, if needed, are performed the next day. (See 'Pretreatment scanning' below.)

Rarely, the high serum TSH concentrations that occur after withdrawal of thyroid hormone stimulate rapid growth of persistent or metastatic thyroid cancer. Such rapid growth has also been described in patients given rhTSH [30]. (See 'Tumor swelling' below.)

rhTSH has no adverse cardiovascular effects [31]. If it is used, a two-dose regimen is preferable to a three-dose regimen for ease of administration and lower cost.

Low-iodine diet — To maximize uptake of radioiodine into thyroid cells, we suggest that patients follow a low-iodine diet for 7 to 10 days before and for one to two days after 131-I is administered (table 5) [32-34]. This suggestion is consistent with ATA guidelines [2].

In a systematic review of eight observational studies, dietary iodine restriction (<50 mcg daily) lasting anywhere from four days to four weeks prior to radioiodine administration compared with a normal diet reduced urinary iodine concentrations and increased 131-I uptake or lesional uptake [35]. In one retrospective study that assessed clinical outcomes, patients prescribed a low-iodine diet (24-hour urine iodine excretion 27±12 mcg) compared with controls (24-hour urine excretion 159±9 mcg) were more likely to have negative radioiodine uptake and Tg values <2 mcg/L when assessed six months after radioiodine treatment [36]. On the other hand, a subsequent retrospective study (not included in the meta-analysis) showed no relationship between urinary iodine excretion (range 25 to 1890 mcg/L, mean 132 mcg/L) and ablation success rates in a group of patients who were not routinely given a low-iodine diet [37]. Remnant ablation was unsuccessful in another retrospective study only when urinary iodine concentration was greater than 250 mcg iodine/g creatinine [38].

Other strategies to increase uptake — Other strategies can increase the efficiency of 131-I uptake by tumor, but at some risk. We suggest not using these strategies in the typical patient.

- Regimens to deplete body stores of iodine, such as the use of loop diuretics, or mannitol with strict low-iodine diets may increase uptake by tumor; however, there may also be a concomitant increase in total body irradiation [41].
- Lithium can prolong 131-I retention by thyroid tissue. In a small study of patients who had diagnostic 131-I scans before and then again after receiving lithium for one to two days, 131-I retention was higher and more prolonged during lithium administration in metastatic lesions and the thyroid remnants in most patients, so that the estimated 131-I dose to the metastases was higher [42]. Whether these findings will result in improved eradication of metastases remains to be determined.
- Inhibition of the mitogen-activated protein kinase (MEK) pathway with a MEK inhibitor (selumetinib) has been reported to restore radioiodine sensitivity in 12 of 20 patients with radioiodine refractory distant metastases [43]. Additional clinical trials are evaluating a variety of inhibitors of the MEK pathway (BRAF inhibitors, MEK inhibitors) with regard to their ability to restore radioiodine avidity in patients with locoregional and distant metastases [44].

Instructions to reduce exposure to others after I-131 RAI treatment

Action	Duration (Days)
Sleep in a separate bed (~6 feet of separation) from another adult	1-11*
Delay return to work	1-5*
Maximize distance from children and pregnant women (6 feet)	1-5*
Limit time in public places	1-3*
Do not travel by airplane or public transportation	1-3*
Do not travel on a prolonged automobile trip with others	2-3
Maintain prudent distances from others (~6 feet)	2-3
Drink plenty of fluids	2-3
Do not prepare food for others	2-3
Do not share utensils with others	2-3
Sit to urinate and flush the toilet 2-3 times after use	2-3
Sleep in a separate bed (~6 feet of separation) from pregnant partner, child or infant	6-23*

*duration depends on dose of I-131 given

Dealing ī recent iodine exposure

Recent iodine exposure — Radioiodine uptake by the thyroid remnant is reduced by the presence of excess circulating stable iodide. Thus, patients who have been exposed to high iodine loads (eg, iodinated contrast materials or medications high in iodine content, such as amiodarone) cannot have diagnostic radioiodine scans or receive radioiodine treatment until the iodine load is excreted.

(not really so in practice)

Iodinated contrast is cleared from the blood after one month [39], but radioiodine treatment is usually delayed for two to three months to be certain that there is no interference with iodine-avid cancer. Twenty-four-hour urinary iodine measurements (or estimated 24-hour measurements based on spot urine iodine measurements corrected for urine creatinine) can be used to document depletion of excess iodine loads in such patients. Once the 24-hour urine iodine content falls to about 100 mcg/24 hours, patients can proceed with diagnostic radioiodine scans and radioiodine therapies.

The iodine load associated with amiodarone administration can persist for months to years after discontinuation of the drug. Plasma exchange has been used to decrease whole-body iodine content in select patients who have persistent iodine contamination for months to years after discontinuation of amiodarone [40]. Patients with distant metastases in whom the amiodarone cannot be discontinued should be treated as if they have radioiodine refractory metastatic disease. (See "Differentiated thyroid cancer: Overview of management", section on 'Management of persistent or recurrent disease'.)

RAI scan / ablation → done around 6 weeks post surgery

PRETREATMENT SCAN : TO DO OR NOT TO DO...

- Allows avoiding RAI ablation in pts ī
  - very complete surgical clearance
- If significant distant mets are detected, higher ablation dose used

vs POST-TREATMENT SCAN after standard fixed dose

DOSAGE

SCANNING DOSE

I_{131} : 2-5 mCi = 75-185 MBq

If pre-treatment scan is planned

Whole Body scan done 48-72h later (upto 7d)

I_{123} : 1-5mCi = 45-185MBq

Whole Body scan done after 6h (within 24h)

ABLATION DOSE

1) Remnant Ablation : for residual (N) thyroid tissue

30mCi = 1.1 GBq

2) Metastasis

- SUBCLINICAL MICROMETASTASIS → 75-150 mCi
- CLINICALLY APPARENT GROSS RESIDUAL METS → 100-200mCi

→ Post treatment scan is done 2-8d later

Follow-up - 6-12m later - RAI scan

- Activity < 1% → Surveillance
- > 1% - Completion of ABLATION → 100-150mCi

RADIOIODINE FOR HYPERTHYROIDISM

Indications

Dx { Toxicity ± nodularity
Nodule ± ↓ TSH }

Rx { • Grave's Disease
• Toxic adenoma / MNG }

THYROID SCINTIGRAPHY < I_{123}
Tc 99m

Thyroid scintigraphy — Thyroid scintigraphy is used to determine the functional status of a nodule. A subnormal serum TSH, indicating overt or subclinical hyperthyroidism, increases the possibility that a thyroid nodule is hyperfunctioning. Since hyperfunctioning nodules rarely are cancer, a nodule that is hyperfunctioning on radioiodine imaging does not require FNA. In addition, thyroid scintigraphy may be useful in patients with multiple thyroid nodules to select those that are hypofunctional and therefore may require FNA. Although thyroid scintigraphy can be used to select nodules for FNA, it cannot be used to select patients for surgical resection.

Radionuclide scanning is contraindicated during pregnancy. If a women is breastfeeding, breastfeeding should be held if a radionuclide scan is obtained. The amount of time will depend on which isotope is used (breastfeeding needs to be held longer if radioiodine is used). (See "Overview of thyroid disease in pregnancy", section on 'Thyroid nodules'.)

Scintigraphy utilizes one of the radioisotopes of iodine (usually 123-I) or technetium-99m pertechnetate. If available, radioiodine scanning is preferred. These radioisotopes are handled differently by thyroid follicular cells. Normal thyroid follicular cells take up both technetium and radioiodine, but only radioiodine is organified and stored (as thyroglobulin) in the lumen of thyroid follicles [20]. Most benign and virtually all malignant thyroid nodules concentrate both radioisotopes less avidly than adjacent normal thyroid tissue (image 1). However, 5 percent of thyroid cancers concentrate pertechnetate but not radioiodine [20]. These nodules may appear hot or indeterminate ("warm") on pertechnetate scans and cold on radioiodine scans. Although most are benign nodules [21-23], a few are thyroid cancers [22,24,25]. As a result, patients with nodules that are functioning on pertechnetate imaging should undergo radioiodine imaging to confirm that they are actually functioning [22,26]. However, if the pertechnetate scan shows unequivocal increased uptake in a nodule with suppression of uptake elsewhere in the thyroid and an undetectable TSH, a radioiodine scan may not be necessary.

- **Nonfunctioning** – Nonfunctioning nodules appear cold (uptake less than surrounding thyroid tissue) (image 1), and they may require further evaluation by FNA. (See 'Sonographic criteria for FNA' below.)

- **Autonomous** – Autonomous nodules may appear hot (uptake is greater than surrounding thyroid tissue) (image 2) if they are hyperfunctioning. Autonomous nodules that do not make sufficient thyroid hormone to suppress serum TSH concentrations will appear indeterminate on thyroid scintigraphy. Autonomous nodules account for only 5 to 10 percent of palpable nodules. Only a few patients with autonomous nodules have been found to have thyroid cancer [27-29], and only a few of these cancers were aggressive [30]. Furthermore, in some of these patients, the cancer was adjacent to the autonomous nodule rather than within it. Since hyperfunctioning nodules rarely are cancer, a nodule that is hyperfunctioning on radioiodine imaging does not require FNA. (See 'Autonomous nodules' below.)

- **Indeterminate** – Because scintigraphy is two dimensional, its limitations result from the superimposition of abnormal nodular tissue and normally functioning thyroid tissue (image 3). Thus, while over 80 percent of nonautonomous nodules greater than 2 cm appear cold, smaller nodules present as a filling defect in less than one-third of cases [27]. The remaining majority of smaller nodules are indeterminate on thyroid scintigraphy [31]. They could represent either small, nonfunctioning nodules anterior or posterior to normally functioning thyroid tissue, or autonomous nodules that do not produce sufficient thyroid hormone to suppress TSH (image 4).

  These indeterminate nodules should **not** be referred to as warm or functioning, since the majority are, in fact, nonfunctioning nodules. Most nodules that are indeterminate on scintigraphy should be evaluated by FNA. (See 'Sonographic criteria for FNA' below.)

RAI therapy in Hyperthyroidism

Strategy

Hyperthyroid
↓
Start THIONAMIDES + β blockers
↓
Approach euthyroidism
↓
ABLATIVE THERAPY
↳ SURGERY
↳ RAI

SURGERY ↳ preferred if
- opthalmopathy is severe
- Pregnancy

PRETREATMENT PRECAUTIONS

1) R/O PREGNANCY
2) Antithyroid drugs (Methimazole) for 4-6 wks
3) Low iodine diet
4) Glucocosticoids in Opthal-mopathy
5) Use cautiously in retrosternal goiter

↓
Stop for 3d - 1wk
↓
RAI
↓
Resume after 3d
↓
Continue for 4-18 wk (based on TFT)

DOSE: 150-200 μCi/g of thyroid tissue
(8-12 mCi)

Fixed doses available - 5, 10, 15 mCi

$$\text{Dose} = \frac{[\text{Wt of thyroid gland (g)}]\,[\text{Dose to be delivered in } \mu\text{Ci/g}]}{\%\ 24 \text{ uptake}}$$

COMPLICATIONS OF RADIO-IODINE

Complications of radioactive iodine therapy (^{131}I) and doses at which they are observed

ACUTE	LONG-TERM
Neck pain, swelling, and tenderness	Hematologic
Thyroiditis (if remnant present)	Bone marrow suppression (>500 mCi)
Sialadenitis (50–450 mCi), taste dysfunction	Leukemia (>1000 mCi)
Hemorrhage (brain metastases)	Fertility
Cerebral edema (brain metastases, 200 mCi)	Ovarian/testicular damage, infertility
Vocal cord paralysis	Increased spontaneous abortion rate
Nausea and vomiting (50–450 mCi)	Pulmonary fibrosis
Bone marrow suppression (200 mCi)	Chronic sialadenitis, nodules, taste dysfunction
	Increased risk of cancer
	Anaplastic thyroid cancer
	Gastric cancer
	Hepatocellular cancer
	Lung cancer
	Breast cancer (>1000 mCi)
	Bladder cancer
	Hypoparathyroidism

1) Sialadenitis – Rx – NSAIDs ; Prevention: Amifostine (Radioprotectant)
2) 2nd malignancy – Salivary gland, breast, GI, Bladder, Leukemia
3) Gonadal dysfunction
4) Nasolacrimal duct obstruction
5) Gland swelling – Edema, TSH effect

PARATHYROID GLANDS

Embryology - arise from endodermal epithelial cells

SUPERIOR PARATHYROIDS - 4th Branchial pouch - closely ali Thyroid
INFERIOR PARATHYROIDS - 3rd Branchial pouch - closely ali Thymus
→ more variable location - upper carotid sheath to pericardium
- generally located in the inferior pole of thyroid

Secrete - Parathormone

SURGICAL ANATOMY

30 - 50mg

Superior parathyroids - posteromedial surface of middle - superior pole
(Symmetry - 80%) - near tracheo-esophageal groove
- posteromedial to tubercle of Zuckerkandl of Thyroid

Inferior parathyroids - behind inferior pole
(Symmetry 70%) - anterior to RLN

Blood supply - Branches of inferior thyroid artery (80%) to all 4
~20% - to superior glands from superior thyroid artery

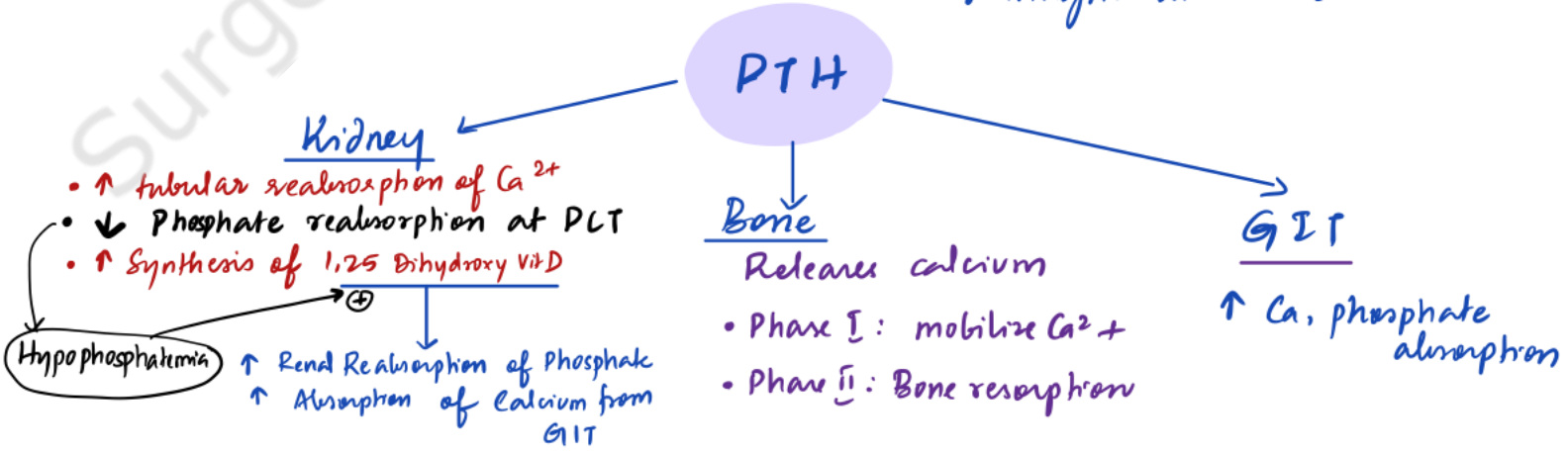
Venous drainage ← Superior thyroid - Internal jugular
middle thyroid - Innominate vein
Inferior thyroid - Brachiocephalic vein

Cells : Chief cells, oxyphil cells, adipose tissue, stroma

PHYSIOLOGY - Calcium Homeostasis, along with Vitamin D, Calcitonin → ↓ Serum Calcium by decreasing bone turnover

Parathormone (PTH) - peptide hormone
- secreted by chief cells
- $t_{1/2}$ - 4-5 min

→ Released in response to ↓ Serum calcium
↑ Magnesium levels



HYPERPARATHYROIDISM

1) Primary Hyperparathyroidism

- intrinsic abnormality of parathyroid glands
↓
Gland enlarges & secretes ↑ PTH
↓
↑ Ca^{2+}

(New setpoint - Sustained ↑ Ca^{2+})
Ⓝ Renal function

85% PHPT → SINGLE PARATHYROID ENLARGEMENT (Sporadic)
↓
- Parathyroid adenoma

Rarely - Multigland involvement

Risk factor: Irradiation of H&N in childhood

Multigland → MEN I, MEN 2A

- Parathyroid carcinoma

CAUSES

- Sporadic – Adenoma
- MEN-1 } – Hyperplasia
- MEN-2A }
- Parathyroid carcinoma (PTCA)
- Hyperparathyroid Jaw Tumor Syndrome

Gene: HRPT-2 (Chromosome-1) → Parafibromin
- PHPT - Adenoma / Hyperplasia - Cystic
↑ risk of PTCA
- Ossifying fibromas of Maxilla & Mandible

SYMPTOMS OF PHPT

'BONES'

Aches & pains	Osteitis fibrosis cystica
Osteopenia	Brown tumor / cyst
Osteoporosis	Pathological #

'STONES'
- Polyuria
- Nephrolithiasis
- Nephrocalcinosis

'GROANS' - Nausea / vomiting
- constipation

'OVERTONES'
- Fatigue
- Poor concentration / memory
- Insomnia
- Mood swings

Pancreatitis
Band Keratopathy } Metastatic calcification
Hypercalcemic Crisis } 2ry hypercalcemia

DIAGNOSIS

Primary Hyperparathyroidism
(Biochemical Diagnosis)

– BIOCHEMICAL – ↑ PTH,
↑ Ca,
↓ Phosphate,
Ⓝ Creat,
Ⓝ Vit D

Urinary Ca – N / ↑ (↓ ⇒ Familial Hypocalciuric Hypercalcemia)
↑ ALP (may cause post-op Hungry Bone SO)
Mild hypochloremic metabolic acidosis

MANAGEMENT → Surgery

Medical Management – in unfit pt / inoperable / recurrent / PTCA
↳ Aim – to ↓ skeletal complications & stabilise Ca^{2+} levels

- Bisphosphonates
- HRT / SERMs
- Calcimimetics – Alter set point of CaR on Parathyroid cell (CINACALCET)

2) Secondary Hyperparathyroidism

Deranged Calcium Homeostasis → Compensatory ↑ PTH → HYPERPLASIA OF ALL 4 GLANDS

↑ Rate of Bone resorption
- Cortical bone loss
- Markers of ↑ Bone turnover

HALLMARK - HYPOCALCEMIA / Normocalcemia ± Hyperparathyroidism (↑PTH)

Biochemical features: ↑ Phosphate, ↓ Vitamin D

X Ray - Osteitis Fibrosis Cystica
DEXA - Osteopenia

CAUSES
- Renal Failure
  - ↑ Phosphatemia
  - ↓ Vit D receptor expression
  - ↓ Metabolic clearance of PTH
  - Mutations in Ca-sensing receptors
- Vit D deficiency
- GI malabsorption
  - Celiac disease
  - Cystic Fibrosis
  - Short Bowel Sd°
  - Bariatric Surgeries
- Liver disease
- Chronic Lithium use
- Diuretics - thiazide, furosemide
- Hypermagnesemia
- DiGeorge syndrome

Rx - medical management → Calcimimetic drugs - CINACALCET (alter set point), Replace Ca^{2+}, Vit D, - phosphate Binders; Renal transplant

PTH Surgery - only if refractory - subtotal parathyroidectomy (NODULAR HYPERPLASIA predicts refractoriness)

3) Tertiary Hyperparathyroidism

Long standing renal failure, 2° HPT → Loss of response to serum calcium levels → Persistent AUTONOMOUS secretion of PTH → 4-Gland hyperplasia (even after renal transplant) → Hypercalcemia

Lab: ↑ PTH (unsuppressed), ↑ Calcium, ↓ Phosphate

Imaging: 4 Gland nodular hyperplasia

Rx - Surgery → Subtotal Parathyroidectomy

CALCIPHYLAXIS - Calcific uremic arteriolopathy - seen in ESRD on HD

disseminated calcification → Vascular calcification; Skin necrosis - painful purpura → gangrene

LOCALIZATION OF PARATHYROID GLAND

NON INVASIVE

① Tc 99m Sestamibi
Lipophilic
accumulates in mitochondria
↳ selective affinity for parathyroid glands d/t ↑ mitochondria

Methods to differentiate parathyroid & thyroid uptake

DUAL RADIONUCLIDE
Use both Sestamibi + I 123
↓
Subtraction imaging

SPECT
(for smaller lesions)

DUAL PHASE
Sestamibi alone
↓
Early & delayed phase

Advantage: Helps localise ECTOPIC GLANDS better
otherwise similar to USG

② USG - cheap
PARATHYROID ADENOMAS - oval, elongated, lobed, hypoechoic
- solitary feeding vessel
> 3cm - Giant adenoma

Advantage: Helps detect concurrent thyroid abnormalities
Drawback: Not so good for Ectopic / mediastinal glands

③ 4D-CT - Multiphase CT (4th dimension = time)
pre-contrast, post-contrast, delayed

Gland → rapid uptake & washout
LN → progressive enhancement

Drawback: ↑ radiation exposure

④ MRI
- Parathyroid → ↑ Intensity on T_2 weighted images

⑤ PET/CT

STRATEGY

Sestamibi + USG

Discordant → 4D-CT → 4 Gland exploration

Concordant → Pre-op marking c USG → Minimally invasive parathyroidectomy

(Single adenoma)

INVASIVE

Role -
In reoperative setting

Indications

1) Persistent / Recurrent hyperparathyroidism
2) Prior cervical surgery (Thyroidectomy)

Methods

① SVS - Selective Venous Sampling
- Catheterisation of common femoral vein → BASELINE PTH
- SVS from small venous branches from neck & mediastinum

↓
2x PTH value in SVS
⇓
POSITIVE LOCALISATION STUDY

② Parathyroid angiography
- vascular adenomas
→ persistent round/oval stain on imaging the Bl. Thyrocervical, internal mammary & carotids

③ USG guided FNAC
& testing aspirates for PTH
↓
Not routinely indicated d/t seeding risk

PARATHYROIDECTOMY

(MIP) Minimally Invasive Parathyroidectomy

- Open
- Endoscopic, Video-assisted

Principle - most pts have single adenoma

PRE-OPERATIVE LOCALISATION IS VERY IMPORTANT

Advantages

- ↓ Operative morbidity
- Comparable outcomes
- ↓ post-op hypocalcemia

(BNE) Bilateral Neck Exploration

Gold standard

Direct visualisation of all parathyroid tissue

Requires thorough knowledge of embryology & anatomy

ADENOMA

- Identify & remove diseased glands ± cervical thymectomy
- Spare normal glands

HYPERPLASIA

- Total parathyroidectomy + autotransplantation (SCM, Brachioradialis)
- Subtotal parathyroidectomy (preserve inferior if ⓝ)

Avoid routine biopsy

INTRA-OP LOCALISATION / ADJUNCTS

- γ-probe localisation - pre-op inj. 10-20 mCi Tc^{99m} Sestamibi
- Intraoperative PTH assessment - Miami criteria - PTH levels should fall by ≥ 50%, 10 min after excision

ECTOPIC PARATHYROID GLANDS

1) Superior -
   - Tracheo-esophageal groove
   - Retro-esophageal
   - Parapharyngeal
   - Posterior mediastinum

2) Inferior -
   - Thymothymic ligament
   - Thymus
   - Perithymic fat
   - Carotid sheath
   - Anterior mediastinum
   - Intrathyroidal

Cure Rate:

Cure = Normocalcemia after parathyroid surgery for atleast 6m

∴ Recurrent Hyperparathyroidism = HPT beyond 6m of ⓢ

Persistent Hyperparathyroidism = HPT within 6m of ⓢ

COMPLICATIONS OF PARATHYROIDECTOMY

① Nerve Injury

Recurrent Laryngeal Nerve Injury — U/L / B/L

External branch of Superior Laryngeal N injury
→ Subtle voice changes
Compromise in voice projection

② POST-OPERATIVE HYPOCALCEMIA

Circumoral tingling, Chvostek sign, Trousseau sign, Carpopedal spasm
Tetany

Causes:

- **TRANSIENT HYPOCALCEMIA**
  - d/t functional / relative hypoparathyroidism
  - ↓ in bone resorption, ↑ in bone formation
  - ↑ calcium excretion

  Resolves once normal parathyroid tissue resumes function (within 1 wk)

- **HYPOPARATHYROIDISM**
  - Atrophy of residual parathyroid glands [D/t prolonged hypercalcemia]
  - Inadvertant removal of (N) parathyroid glands
  - Devascularisation

  m/c after BNE Reoperation

- **HUNGRY BONE SYNDROME**
  - Prolonged & severe post-operative hypocalcemia
  - occurs in pts c pre-operative BONE DISEASE d/t chronic HPT
  - DUE TO ABRUPT FALL IN PTH
  - Due to acute reversal of parathyroid mediated BONE-RESORPTION
  - ↓
  - SUDDEN SWITCH OVER TO OSTEOBLAST-MEDIATED BONE FORMATION
  - ↓
  - ↑ in Bony uptake of Calcium, phosphate & Magnesium

  [More common in older pts, ↑ volume of resected adenoma, ↑ Pre-op BUN, ↑ Pre-op ALP]

  Features: Hypocalcemia + Hypophosphatemia + Hypomagnesemia ± Hyperkalemia
  ↓ touches Nadir 2-4 d post op

  Rx - Calcium supplementation — 10 amp Ca Gluconate in 1L NS at 30ml/hr in symptomatic severe Hypocalcemia
  Vitamin D

(can also occur following thyroidectomy for thyrotoxicosis)

③ Bleeding / Hematoma

④ Persistent / Recurrent Hyperparathyroidism

HYPERCALCEMIA

(S. Calcium ≥ 11mg/dL) → Total Ca Levels affected by albumin

Causes: 1) PRIMARY HYPERPARATHYROIDISM → m/c

2) NON PARATHYROIDAL HYPERCALCEMIA

ENDOCRINE
1) Thyrotoxicosis
2) Adrenal insufficiency
3) Pheochromocytoma
4) VIPoma
5) Familial hypocalciuric hypercalcemia

GRANULOMATOUS DISEASES
1) Sarcoidosis
2) Tuberculosis
3) Histoplasmosis
4) Coccidioidomycosis

DRUGS
1) Lithium
2) Diuretics
3) Hypervitaminosis D
4) Hormone Therapy
   - Estrogen
   - Testosterone
5) Milk alkali s.o

MALIGNANCY
- Solid tumors (Lung, Breast, Bone) Penis (PTHrP)
- Hematological Cancers
  Lymphoma - Calcitriol
  Leukemia
- Lytic Bone mets (cytokines)

SYMPTOMS - "NO BONES", "Stones" - Nephrolithiasis / Nephrocalcinosis / "Groans" / "Overtones"

Hypercalcemic crisis - generally occurs when S. Ca ≥ 14mg/dL + End Organ Dysfunction

m/c cause - Malignancy ** Untreated primary hyperparathyroidism

Clinical Features:

ACUTE CONFUSION
ABDOMINAL PAIN
VOMITING, DEHYDRATION
RENAL INSUFFICIENCY
Hyperkalemia

Rx - Aggressive Resuscitation - ECG monitoring

ADJUNCTS
1) Glucocorticoids - ↑ Renal excretion, ↓ GI absorption
2) Calcitonin - rapidly ↓ Ca^{2+} (24-48h) → ⊖ Osteoclasts, ↑ Renal excretion — 4IU/kg sc/im
3) BISPHOSPHONATES (in Malignancy) → ↓⊖ Osteoclast activity

- Hydration ; NS (>200ml/hr) promotes renal excretion of Ca
- ↓ after restoration of volume
- Diuretic - (FUROSEMIDE) to promote calcium excretion
- ↓
- Dialysis

Other Rx for Hypercalcemia

1) Calcimimetics - Cinacalcet 90mg TID
2) Gallium nitrate ⊖ Bone Resorption → ↓ Ca levels → useful in malignancy; ⊖ Renal Excretion
3) Mithramycin / Plicamycin

PARATHYROID CARCINOMA

Very rare
≤ 1 % of PHPT
Risk factors
- H & N Irradiation in childhood
- Renal failure
- MEN - 1
- Hyperparathyroid Jaw tumor so (Parafibromin)

Clinical features
PHPT + ++
Earlier presentation
Neck mass ++

Dx - Imaging

Conf - post-op

Mets - Lung, Liver, Bone

Rx - Surgery - when possible
Complete resection
} BNE & enbloc resection of tumor
ipsilateral thyroid lobe
lymphnodes - MRND if ⊕
Tracheoesophageal
Paratracheal
Mediastinal

Post op - HPE - IHC - Parafibromin
PGP (Protein Gene Product) 9.5

Control hypercalcemia - Cinacalcet, Bisphonates

RT for inoperable primary
bone mets

Immunotherapy

HYPOPARATHYROIDISM

Causes :

- Post surgical - most common → See in complications of Parathyroidectomy
- Congenital Hypoparathyroidism
  - Inadequate gland tissue → DiGeorge Syndrome
  - In-utero effects of hypercalcemia d/t Maternal HPT → transient neonatal Hypo-parathyroidism

- Pseudohypoparathyroidism – End organ unresponsiveness to PTH
  - HYPOCALCEMIA, HYPERPHOSPHATEMIA → Appropriate ↑ of PTH
  - → Albright hereditary Osteodystrophy

℞ - Calcium
Vitamin D
Recombinant Parathormone

ADRENAL GLAND

Embryology:

Cortex - 5th week of gestation from **mesodermal** tissue on the adrenogenital ridge

(∴ Ectopic adrenal tissue may be found in gonade / spermatic cord)

Zona
Glomerulosa - Mineralocorticoids
Fasciculata - Glucocorticoids
Reticularis - Sex steroids

Medulla - ectodermal origin - Neural crest cells

- Para-aortic → organ of Zuckerkandl (to left of aortic bifurcation near IMA)
- Paravertebral → Paraganglia
- Adrenal Medulla

Medulla - Catecholamines
Polyhedral chromaffin cells

Anatomy - Retroperitoneal
Superomedial to kidneys
5 × 3 × 1 cm, 4-5 g

Arterial supply
- Superior Adrenal A - Inferior phrenic
- Middle Adrenal A - Aorta
- Inferior Adrenal A - Renal A

→ Arterioles → Subcapsular plexus

Venous drainage
- R Adrenal V → IVC
- L Adrenal V → L renal A

Phenylalanine N methyl transferase - only found in adrenal medulla & organ of Zuckerkandl

DDX ADRENAL INCIDENTALOMAS

FUNCTIONING

BENIGN
- Aldosteronoma
- Cortisol producing adenoma
- Sex-steroid producing adenoma
- Pheochromocytoma

MALIGNANT
- Adrenocortical Carcinoma
- Malignant Pheochromocytoma

NON-FUNCTIONING

BENIGN
- Cortical adenoma
- Myelolipoma
- Cyst
- Ganglioneuroma

MALIGNANT
Metastasis
Adrenocortical cancer

CUSHING'S SYNDROME

Complex of symptoms resulting from hypersecretion of cortisol (F>M - 8:1)

- **Clinical Features:**
  1. Obesity ← weight gain - fat deposition in abnormal sites - Supraclav fossa, Nape of neck
     - Central obesity
  2. Facial plethora
  3. Rounded / Moon face
  4. Thin skin
  5. Menstrual disturbances, ↓ Libido
  6. Hypertension
  7. Hirsutism
  8. Depression
  9. Glucose intolerance
  10. Osteopenia / Fractures

If due to pituitary tumor
↓
Headache
Visual field defects
H/s/o panhypopituitarism
↑ ACTH - Hyperpigmentation

- **ETIOLOGY**

CAUSES

EXOGENOUS
↓
Prolonged administration of Glucocorticoids
Steroid abuse
MOST COMMON

ENDOGENOUS

ACTH DEPENDENT (↑ ACTH) (80%)
- Cushing's Disease (Pituitary origin)
- Ectopic ACTH Syndrome
- Unknown source of ACTH

ACTH INDEPENDENT (N/↓ ACTH)
- Adrenal hyperplasia
- Adrenal adenoma
- Adrenal carcinoma
- Others

- **INVESTIGATIONS**

1) Dx of Cushing's S° → ↑ Glucocorticoid levels
   - ↓ no diurnal variation
   - ↓ no suppression by exogenous hormone

SCREENING — Overnight Dexamethasone suppression test
1mg Dexamethasone at 11 pm
↓
Plasma Cortisol at 8.00am next morning

- Suppression (<2 mcg/dL) → (N)
- Not suppressed (≥ 2mcg/dL) → Cushing's Syndrome

CONFIRMATORY - LDDT - Low Dose Dexamethasone Suppression test
0.5mg Dexamethasone Q6h x 48h (10mcg/kg/dose)
↓
Plasma Cortisol 6h after last dose

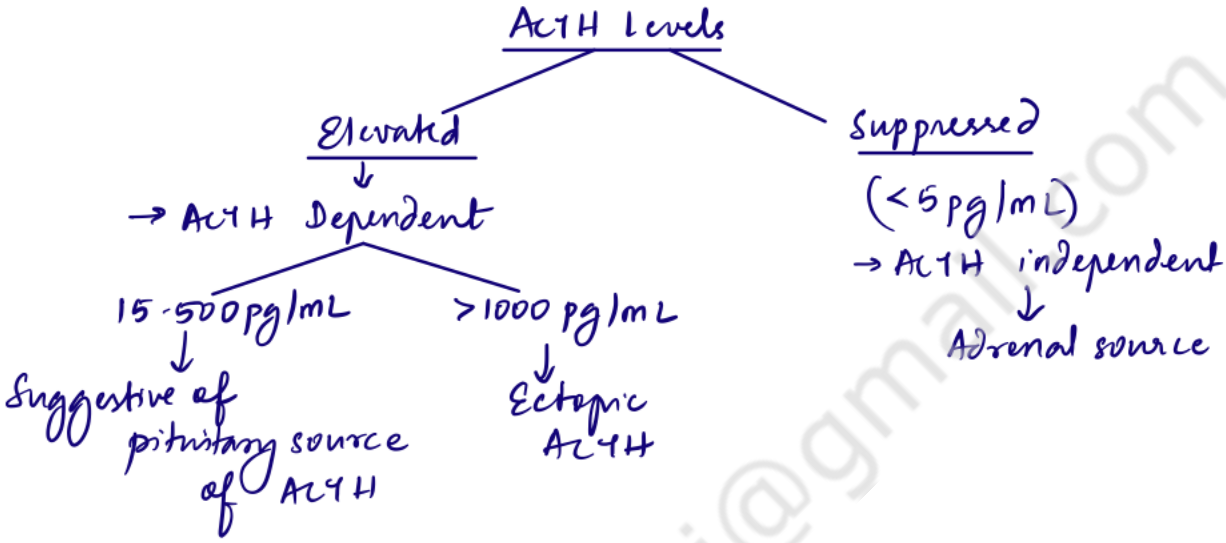
- <5mcg/dL → (N)
- ≥ 5mcg/dL → Hypercortisolism

- 24 hr urinary cortisol : < 135nmol/d (N); 3x ↑ = Cushing's S°
- Late night Salivary cortisol : ↑ in Cushing's

2) Evaluating cause of Cushing's S° – ACTH dependent vs independent

- **Measurement of Baseline ACTH levels**

(N) : 10–100 pg/mL



- **High dose dexamethasone suppression test (HDDST)**

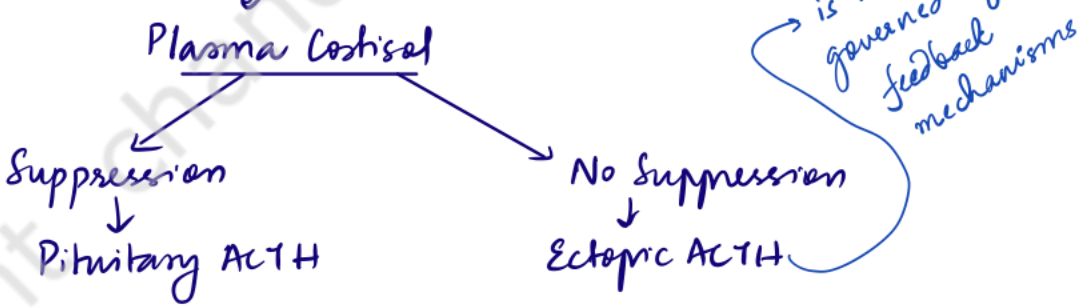
2mg Dexamethasone Q6h × 48h (40 mcg/kg/dose)

↓

6 hours after last dose

↓

Plasma Cortisol



- **CRH Stimulation test** – In pts ↑ equivocal ACTH levels & HDDST

↑ ACTH / Cortisol after CRH bolus → Pituitary origin

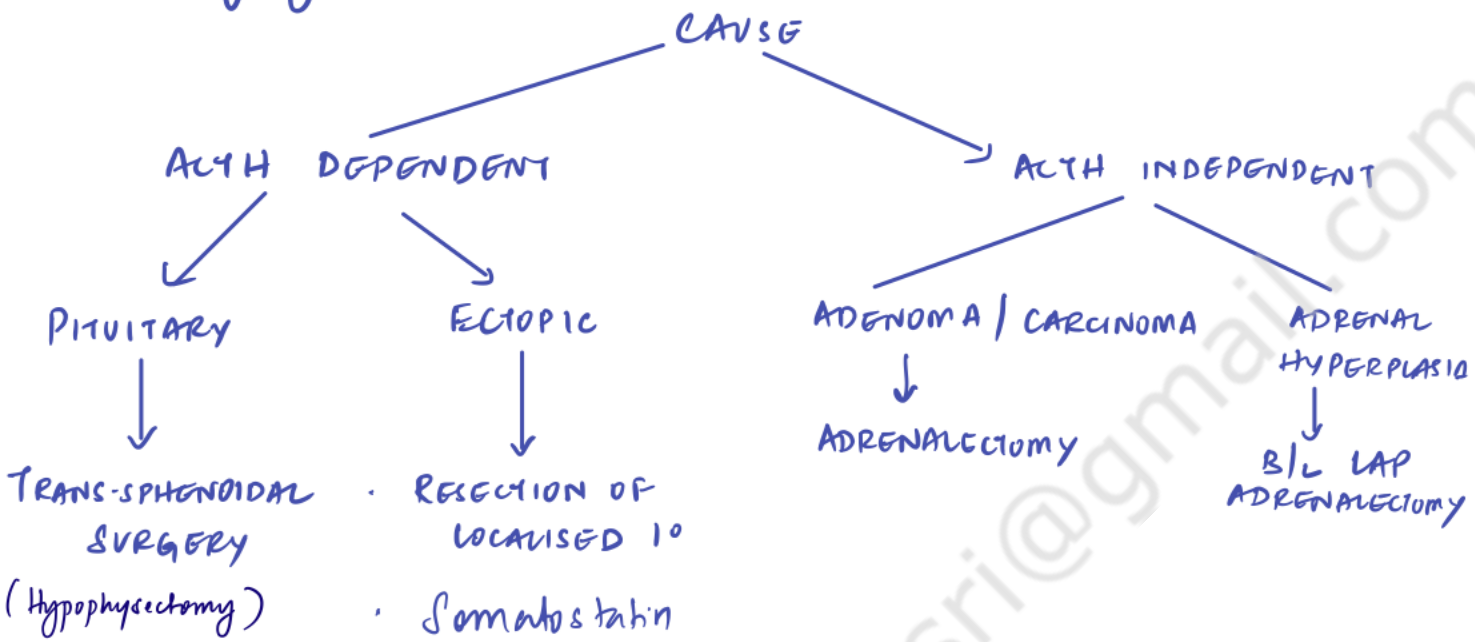
1) Pituitary source suspected → Pituitary MRI → no lesion → Inferior petrosal venous sampling

2) Ectopic ACTH – CT thorax/abdomen/H&N or FDG PET / ^{11}C-5 OH Tryptophan PET
lung cancer, NET pancreas, Medullary Ca thyroid, Carcinoid, Thymic Ca

3) ACTH independent → Adrenal source → CT/MRI

MANAGEMENT

- Surgery:



- Medical Management

Unfit for Sx - Medical Adrenalectomy - Metyrapone
Mitotane
Ketoconazole

PRIMARY HYPERALDOSTERONISM

(CONN'S SYNDROME)

- Bilateral adrenal hyperplasia
- Adenoma
- U/L Adrenal Hyperplasia
- Carcinoma
- Ectopic Aldosterone secreting tumor

In primary hyperaldosteronism, Aldosterone secretion is RAAS independent

Clinical features

HYPERTENSION & HYPOKALEMIA → may not always be present

LAB INVESTIGATIONS

- ↑ S. Aldosterone
- ↓ Serum Renin ← Negative feedback
- Failure to suppress aldosterone levels & sodium loading

IMAGING

CT/MRI

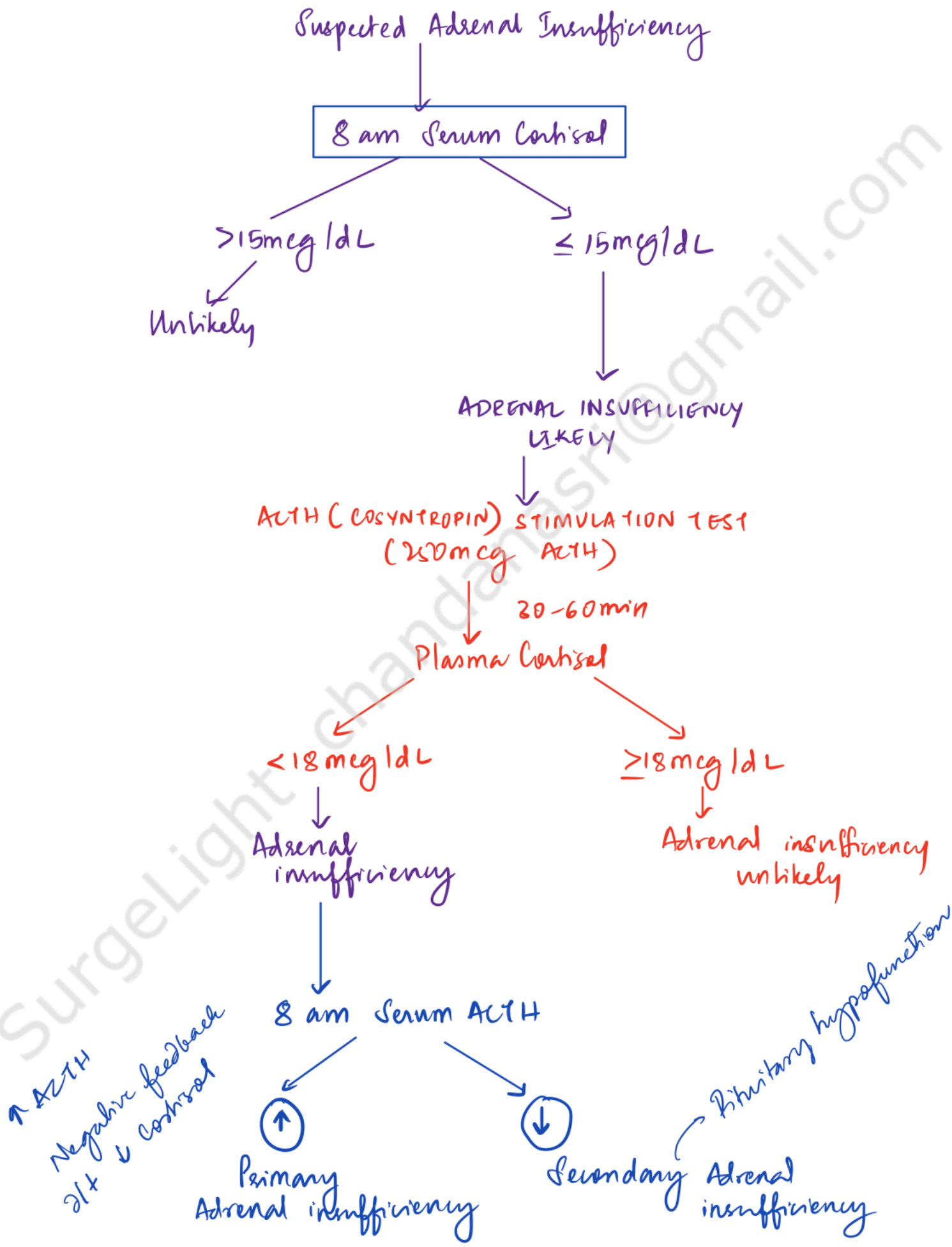
- Unilateral adrenal tumor → Adrenalectomy
- Bilaterally abnormal / (N) adrenals → Radioscintigraphy & NP-59 (I^{131} Iodomethyl nor-iodocholesterol)

or

B/L Adrenal venous sampling for aldosterone

- U/L ↑ → Adrenalectomy
- B/L → Medical Management
  - Spironolactone (aldosterone receptor antagonist)
  - Amiloride
  - Triamterene
  - ACE inhibitors

TESTS FOR ADRENAL INSUFFICIENCY



PHEOCHROMOCYTOMA

Catecholamine secreting tumor arising from the chromaffin cells of adrenal medulla

Rule of 10 :
- 10% are multiple / bilateral
- 10 % familial
- 10 % extra-adrenal
- 10 % malignant
- 10 % recur after surgery
- 10 % Benign sporadic tumors are incidentalomas

(R) Adrenal > (L) Adrenal

SYNDROMIC FORMS

1) MEN 2A & 2B - RET Gene mutation — 50%
   - MEN 2A — Associated : MTC, HPT, Amyloidosis, Cutaneous lichen planus
   - MEN 2B — MTC, Neuromas, Marfanoid habitus

2) VHL Type 2 — VHL Gene — 10-20%
   - RCC
   - CNS & Retinal hemangioblastomas
   - Pancreatic cysts
   - Renal Cysts

3) NF 1 — 1%
   - Cafe au lait spots
   - Neurofibromas

4) Familial Paraganglioma syndromes — ~20% — Carotid body tumors
   - SDHB mutations

- Clinical Features

TRIAD
1) HEADACHE
2) PALPITATIONS
3) DIAPHORESIS

Hypertension - paroxysmal / sustained
intervening normotension / orthostatic

Myocardial Infarctions

Glucose intolerance

EVALUATION

1) Biochemical Investigations

URINE:

→ 24 hour urine Metanephrines (98% Sensitivity & specificity)
(VMA - less sensitivity / specificity - false +ve from caffiene, raw fruits, α methyl dopa)

→ Fractionated urinary catecholamines

BLOOD:

→ Plasma free metanephrines ← ∵ phenylalanine N methyl transferase

→ Plasma catecholamines - Epinephrine + Norepinephrine
↳ adrenal / organ of Zuckerkandl

EQUIVOCAL → Clonidine suppression test - suppresses neurogenically mediated Catecholamine release but not from pheochromocytoma
(after 3hr of 0.3mg clonidine PO)

→ Chromogranin A - monomeric protein in adrenal medulla

2) Imaging - CT (Sensitivity 85-95%, 100% specificity)

Diaphragm to Bifurcation of aorta

MRI - 95% Sensitivity; 100% Specificity
characteristic appearance on T2 weighted images / Gadolinium

^{123}I MIBG - META IODO BENZYL GUANIDINE - taken up by pheochromocytomas
helps in localising extraadrenal
→ helpful in malignant pheochromocytoma - helps localise mets

Thyroid Prokchin Give Lugols iodine from D-1 to 5D before giving tracer

TREATMENT

Medical Management - to stabilize hypertension

Phenoxybenzamine - α blocker - started 7-10d pre-op 10mg OD-BD
↑ by 10mg - 20mg every 2-3d
Final dose 20-30mg TID

Fluid optimisation
Na liberal diet (>5g/d)

β blockade - to control tachycardia ; 2-3d pre op
Always after α-blockade (∵ β_2 blockade - worsens HTN)
PROPRANOLOL 10mg TID - BID

Catecholamine synthesis Inhibitor – Metyrosine → ⊖ Tyrosine Hydrolase

Anaesthesia – Avoid { Ketamine, Fentanyl, Morphine } can stimulate Catecholamine release

{ Halothane, Desflurane } avoid → sensitize myocardium to arrhythmogenic effects of catecholamines

INTRAOP HTN – SNP / Phentolamine / Nicardipine

SURGERY

- Lap – Transperitoneal / Retroperitoneal approach – solitary <8cm adrenal pheochromocytomas
- Open – Large / Malignant – anterior approach

✓ Cortical sparing adrenalectomy in B/L syndromic pheochromocytomas

follow-up – 1-2 wk post op 24 hr urine metanephrines & catecholamines
↓
yearly

Malignant → especially SDHB mutations
↓
^{131}I MIBG ablation

Chemo – Dacarbazine
Cyclophosphamide
Vincristine

SURGICAL APPROACHES

Laparoscopic
- Lateral jackknife
- Retroperitoneoscopic
- Prone

Open
- Midline
  - Thoracoabdominal
- Posterior Lumbotomy
- Subcostal