PG Quest Ca Rectum

H/o Pain → Lat Pelvic wall spread
→ spread to nerve
→ Obstruction
→ Spread to Perineal regions.

Diagnosis → Describe as Cancer of "anorectal" region if it is lower ⅓ rectum.

If lesion is mobile, it would be T_1/T_2
Restricted Mobility → T3
Fixed → T4

For lower rectal cancer, Proctoscopic biopsy is better than Colonoscopic biopsy.

Anorectal ultrasound is better for early lesions.
For larger lesions, MRI should be done.

CECT (A+P+T) Vs PET CT → PET CT does not change management significantly compared to CT scan.

★ In lower rectal cancers, the risk of lung mets is higher ★.

Endorectal USG has poor accuracy for nodal picture & CRM. So, it is not done in T2 & above.

other disadvantage - 1) Technical expertise need
2) not done in obstructing lesions.

Tumor Marker — CEA

Role of Pre OP CEA → Baseline levels
→ Tumor burden
→ If CEA is high, we can go for PETCT [ESMO Guideline]

Objective of NACT-RT → Downstaging
→ Sphincter saving
→ Achieve R0

Preop RT does not improve OS.

~~Non Surgical EMD~~ → A Posteriorly placed lesion, low rectal cancer, can be done up front APR.

In case of anteriorly placed lesion in a female, there is no mesorectum bet^n rectum & vagina so there is chance of positive margins.

PREPARE CA RECTUM MANAGEMENT Pre-op/Intra op/P
headings with studies.

In a low rectal cancer, the long course RT will irradiate inguinal fields too. It is not done in short course.
So, it is better to give long course in low rectal cancer

Chemo with Short course RT → Cannot combine at same time.
But Chemo can be given after RT.

Site of colostomy -
Importance of Pathology -

Post RT - Complete response → Can Surgery be avoided?
- Clinical exam, Endoscopy.
- Biopsy → Report is not often reliable
→ as tumor may be present in submucosal space.

Endoscopy - look for absence of ulcer, telangiectasia.

Total neoadjuvant treatment → All cycles of FOLFOX + RT before surgery.
Compliance is better.

yp T0 N0 M0 → No adjuvant Rx
yp T(1-4) N0 → Capecitabine
yp T0 N1 → FOLFOX

Stockholm trial → Short course RT + Delayed Surgery is as good as long course RT.

Trials of Breast

NSABP trials

① NSABP B-04 → 2 trials running in parallel

Node neg. Node positive.

Node negative trial – 3 arms → RM
→ Mastectomy + Axillary RT
→ Mastectomy alone.

Result – No significant difference in long term outcome bet^n the three arms
Hazard ratio for death bet^n Mastectomy + Axillary RT & RM → 1.08
HR bet^n ~~RM~~ Mastectomy alone & RM → 1.03

Pathologic evaluation of RM specimens in these trial demonstrated pathological nodal disease in 40%. So, we can assume that 40% in other arms were also cN0 but pN+. However, axillary failure rate in Mastectomy alone arm was only 19%.

∴ Microscopic disease in axilla doesn't affect survival.

Node positive trial → 2 arms → RM
Mastectomy + Axillary RT

No significant diff. in long term outcome

The overall outcome was that less radical Procedures could be done.

(2) NSABP B 06 – Concept of BCS.

Compared lumpectomy + ALND ± Breast RT with MRM.

No significant differences in OS, DFS or distant disease free survival b/t MRM & BCS ± RT.

However in breast recurrence in BCS only group is 39.2 % & BCS + RT is 14.2 %.

Other trials for BCS → Milan I, II, III.

(2) ~~NSABP~~

(3) NSABP B 21 – Whether Tamoxifen is as good as Breast RT in preventing recurrence in breast cancer upto 1cm.

Three arms → Lumpectomy + ALND + RT
" + Tamoxifen
" + Tamoxifen + RT
} × 5 yr.

RT alone resulted in 4q % lower hazard rate compared to tamoxifen.

RT + Tamoxifen → 63 % lower HR compared to RT.

" → 81 % lower HR " " Tamoxifen

So, if node negative pt < 1cm also, RT is needed. & Tamoxifen + RT is best.

(4) NSABP B 32 → SLNB alone Vs SLNB+ → ALND

2 arms ↔ SLNB + ALND
↳ SLNB + ALND if node (+)

In 2/3rd cases, sentinel nodes were the only metastatic nodes.

(5) NSABP B 39 → Evaluating APBI
RTOG 0413
Criteria for inclusion → DCIS / stage I/II Ca Breast
→ < 3cm
→ < 3 nodes positive
→ Lumpectomy with free margins.

Result → IBTRs were marginally higher in APBI group
10 yr Recurrence free survival was higher in Whole Breast RT group but the difference was < 1 %.

(6) NSABP B 37 → Is additional chemo needed for breast recurrences following index surgery?

Two arms → Chemo ± RT
Two arms → Observation ± RT

(7) NSABP-B17 → Lumpectomy alone Vs Lumpectomy + RT in DCIS.

Result → Adjuvant RT decreases rate of recurrence

No difference in OS, but over 2/3 deaths in this trial were not cancer related.

(8) NSABP B24 → Role of tamoxifen in DCIS

Addition of tamoxifen improved DFS from 77.1 to 83%.

Cumulative incidence of all IBTR & C/L Recurrences was reduced from 16% to 10%
[31% Reduction in ipsilateral &
47% reduction in C/L breast cancers]

In subset analysis acc to ER status, the benefit of Tamoxifen was much higher in ER+ve tumors.
While benefit observed in ER-ve.

(9) NSABP B35 - ATAC trial demonstrated efficacy of anastrozole in ER+ve, Post menopausal women.
Risk of C/L breast disease is significantly reduced.

NSABP B35 designed to compare Tamoxifen & Anastroz

Result →

(10) NSABP B43 - Trastuzumab in Her 2+ve DCIS.

(11) NSABP B13, B14, B23, B36
:2→ Adjuvant Rx in No. ER-ve disease.

1) B 13 → Surgery alone Vs Surgery + MF
(Methotrexate + 5 FU)

→ Improved DFS & OS in MF group.
Statistically significant DFS for
Women < 50 yr and > 50 yr.
BUT
Significant OS only in > 50 yr.

2) B19 → MF Vs CMF

→ DFS & OS advantage ≥ CMF
Advantage seen more in women < 50 yr.

3) B23 → 4 x AC / 6 x CMF ± Tamoxifen.

It was hypothesized that Tamoxifen also acts by modulating growth factors such as TGF α or TGF β by increasing levels of SHBG in serum.

Result → No Significant prolongation of DFS or OS was seen by Tamoxifen in ER-ve disease.

It does not even prevent Contralateral disease, proving that majority of second primary in breast is having same hormonal profile as 1st.

Also showed that 4 ⊙ AC is equivalent to 6 ⊙ CMF

4) B 36 → 4 ⊙ AC Vs 6 ⊙ FEC with a Secondary Randomization with celecoxib. But after Coxibs were withdrawn from Market, the latter stopped.

Result →

(12) ER +ve, node negative trials

[B 14, 20, 33, 42]

1) B 14 → 5 yr of Tamoxifen Vs 5 yr Placebo
Improved PFS & OS
↓ rate of contralateral breast Ca.

On Prolonged observation, no benefit seen with > 5 yr Tamoxifen.

2) B20 → Value of adding chemo to Tamox.

Three arms → Tamoxifen only
→ Tamox + MF
→ Tamox + CMF

Addition of chemo showed improved DFS & OS over tamoxifen alone.
Greatest reduction in recurrence in pt < 49 yrs.

Most recent update at 12 yrs also shows improved DFS & OS.

2) The Paraffin blocks from B14 & B20 were used to validate Oncotype DX.

3) B33 → Use of Aromatase Inhibitors [Exemestane] after 5 yrs of Tamoxifen.
Primary aim is Prolongation of DFS.
Secondary aim is Prolongation of OS.

Study Population chosen were those pt who completed 5 yr of Tamoxifen & remained disease free.
This trial was closed early because MA.17 trial showed results with letrozole.

4) B42 → Whether Prolonged Letrozole will benefit & improve DFS in ER+ve and/or PR+ women who have completed 5 yrs of hormonal therapy with either 5 yrs AI or 3 yrs tamoxifen f/b AI.

Also to see if Prolonged letrozole improved survival, Cancer-free survival, time to recurrence.

Also to see if it increased incidence of osteoporotic or thrombotic events.

Result → Did not significantly improve DFS
7 yrs DFS → Placebo - 81%
Letrozole - 83%

Most common grade 3 adverse event - Arthralgia
- Back Pain

" " grade 4 → Thromboembolism [Placebo
UTI, IHD, LV systolic [letrozole
dysfn

Studies for Node Positive disease

Studies for Taxanes

1) NSABP B28 → Use of Paclitaxel following AC

Significant improvement in DFS
No Significant improvement in OS.

It confirmed the findings from CALGB 9344

2) NSABP B30 → Comparision betn AC → T
AT [Doxorubicin - Taxol]
TAC

Result → Sequential AC → T improved DFS

compared with AT or TAC.
Amenorrhea was associated with improved survival regardless of treatment ER status.

AT & TAC are non inferior wrt OS.

3) NSABP B38 → CALGB 9741 examined the efficacy of dose dense therapy [Chemo at 2 week interval instead of 3 week] and whether A → C → T is equivalent or better than AC → T.

Dose dense therapy had improved DFS & OS.

BCIRG 001 trial showed efficacy of TAC over CAF regimen.

So, NSABP B38 compared dose dense AC→T and TAC and to determine whether dose dense AC→T can further improve outcome.

Results → Adding gemcitabine did not improve outcome.

No significant difference in efficacy b/w dose dense AC→T & TAC.

Studies for Trastuzumab

1) NSABP B31 → To evaluate the role of Trastuzumab in adjuvant setting.

Two arms → AC→T
→ AC→T + Paclitaxel

Other Herceptin based trial → HERA
BCIRG 006

At 2yr follow up, it reduced risk of treatment failure by 52% & risk of death by 33%.

Cardiac morbidity is higher.

2) NSABP B44 / CIRG (TRIO) 011

Adding Trastuzumab + Bevacizumab Vs
Trastuzumab only.

Aim is to see whether it improves invasive DFS.

Studies evaluating Bisphosphanates

NSABP B34 - Oral clodronate as adjuvant Rx

IV Zolendronate role in reducing Ca Breast recurrence → Austrian Breast & Colorectal group. in pre menopausal pt with were randomized to receive anastrozole or tamoxifen.

Result of B34 → Might have anticancer benefit in older, post menopausal women.

Trials of NACT

1) B18 → Preoperative Vs Postoperative NAC.

Primary aim → Prolongation of DFS & OS
Secondary aim → Evaluation of clinical & Pathological response of Primary tumor.

Determination of effect of chemo on nodes

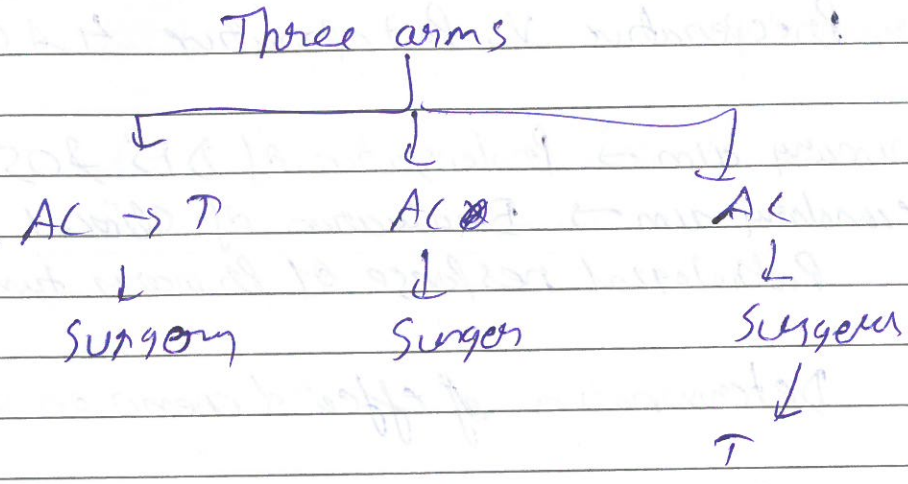
Whether NACT increases rate of BCS.

Result – 36% pt had cCR, 43% had cPR
13% had pCR.
Axillary LN downstaging in 37%

No difference in DFS, OS, distant DFS
BUT Pt achieving pCR had significant improvement in DFS & OS compared to those who had cCR or cPR.

At 9 yr follow up, same findings present
Rate of IBTR is slightly higher (not significant)

2) B27 → Addition of Taxol TO 4 CAC in NACT



AC → T – Increased rates of pCR
– Decreased rate of involved nodes
– Did not increase breast conservation

3) NSABP B40 → Adding Bevacizumab to Taxol alone / Taxol + Capecitabine / Taxol + Gem

Primary aims → TO determine whether adding capecitabine or gemcitabine to Taxol in NACT will improve pCR in Her2 -ve case.

~~4) NSABP B40~~

Secondary aims – Determination of whether addition of bevacizumab will improve DFS and/or increase toxicity.

Result → Addition of Gem. or Cape does not improve survival.

Overall improved OS with Bevacizumab but it contradicts other studies

3) B 41 → AC → Weekly Pacli + Trastuzumab
(Dual Her 2 targetting) vs
AC → weekly Pacli + Trastu + Lapatinib
vs
AC → Weekly Pacli + Lapatinib

Result → Addition of Lapatinib results in numerically higher, but non significant improvement in pCR

Prevention Trials

① NSABP - P1 → To test efficacy of Tamoxifen in Prevention of Ca Breast

Eligibility - All women >60 yrs
- If 35-60 yrs, then they should have ↑ risk
- LCIS

Result → 49% reduced risk of Ca Breast
→ Reduced rate of # hip, spine
→ ↑ risk of Ca endometrium, DVT, PE

2) NSABP-P2 (STARR Trial)

Multiple Outcome of Raloxifene Evaluation (MORE) study had Ca Breast as secondary endpoint & it reduced risk by 72%.

This trial was Tamoxifen Vs Raloxifen.

There was 47% reduction in incidence of Ca Breast, as estimated by Gail model

- Raloxifene is not as effective as Tamoxifen in preventing, though the difference was not statistically significant.

- More Uterine malignancies in Tamoxifen group (not statistical significant)

- Fewer thromboembolic events in Raloxifen

- Raloxifene is an attractive alternative to Tamox in post menopausal women

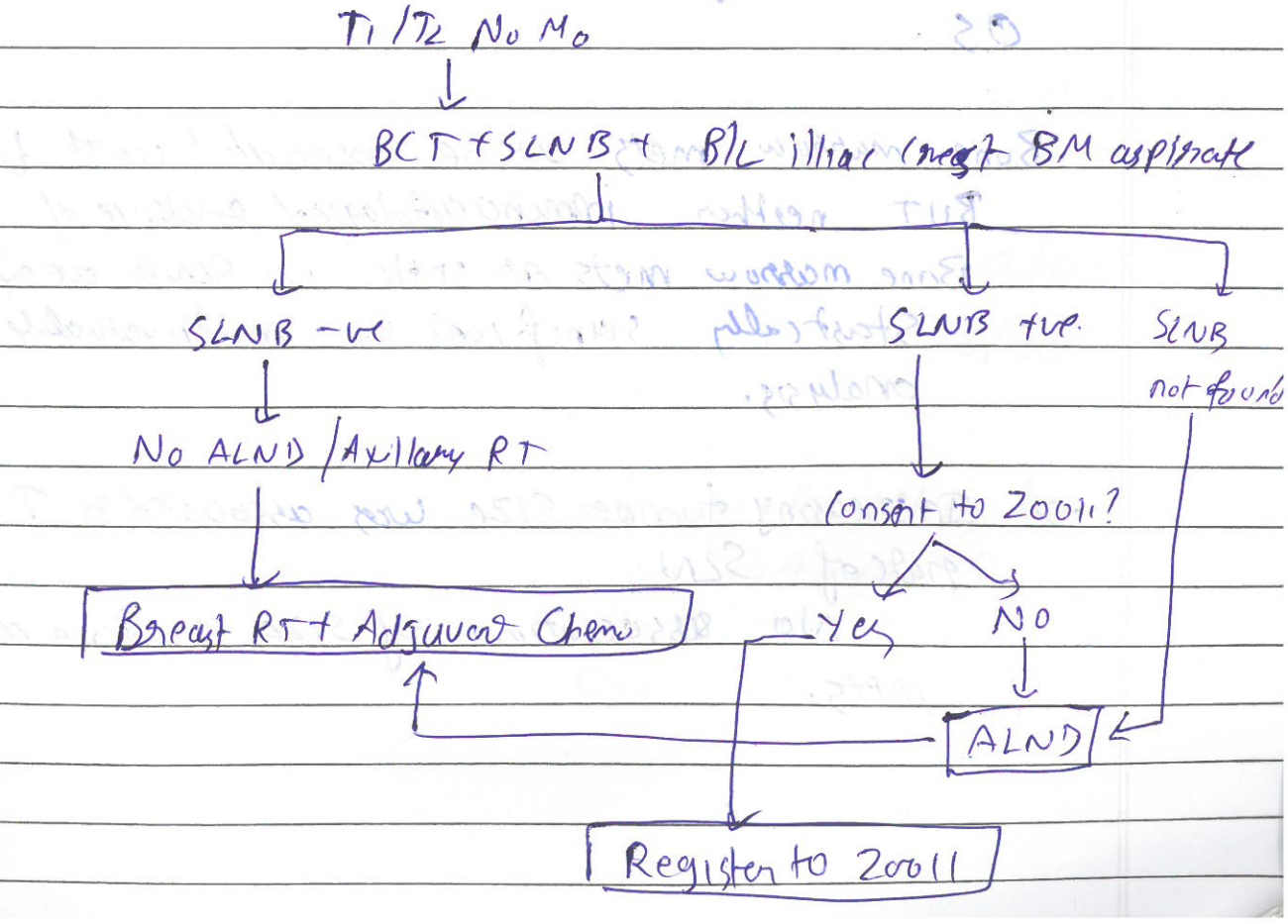
ACOSOG trials

(1) Z0010 – Prognostic study of Sentinel node & Bone marrow micromets in women with clinical T_1/T_2

Pt treated with BCS + RT.

Objectives – TO estimate Prevalence & evaluate Prognostic Significance of sentinel node micromets detected by IHC.

- TO estimate – – – of bone marrow micromets. detected by immunocytochemistry.
- TO evaluate for hazard rate for regional recurrence in women with negative sentinel nodes.



SLN identification rate → 98.6 %
Avg number of SLN → 2.3

Evaluation of occult mets of bone marrow provided evidence of 1st ever cancer stem cells.
Mean Prevalence of Putative cancer stem cells (CD 44+ / CD24 - low) in pt + positive bone marrow was 72 %.

Results → Out of 5119 SLN specimens, 3904 were tumor negative by H&E stain.
Out of 3326 SLN specimens examined on IHC, 349 were tumor positive.
Out of 3413 bone marrow specimens, 104 were positive.

IHC evidence of SLN mets was not associated with OS.

Bone marrow mets were associated with ↓ OS BUT neither immunocytological evidence of Bone marrow mets or IHC in SLNB were Stastically significant on multivariable analysis.

→ Increasing tumor size was associated ∈ ↑ Positive rate of SLN.
No association of size ∈ Bone marrow mets.

Occult Bone marrow mets were significantly associated ↑ Mortality but NOT increased recurrence.

(2) Z0011 – SLNB Positive – ALND or not?

T_1/T_2 No Mo → BCS + Positive SLNB [1-2 nodes]

ALND No ALND

↓

Breast RT + Adjuvant chemo

Results – No statistically significant difference in local or regional recurrence bet" SLNB & ALND.

Median number of sentinel nodes removed → 2
" " " +ve nodes in SLNB arm → 1

Locoregional recurrence in SLNB arm → 12/425
" " " ALND → 16/388
No significant difference.

On multivariate analysis, factors predicting locoregional failure → Modified Bloom Richardson Score
→ Age

(3) Z1031 – Neoadjuvant exemestane (25 mg) letrozole (2.5) Anastrozole (1 mg) for 16-18 weeks for Post Menopausal women

These Patients had All Red score 6-8.

Result → Neoadjuvant AI therapy improved surgical outcome

(4) Z1072 – Cryoablation in invasive Ca Breast

Result → Further studies with modifications recommended.

(5) Tailorx trial – TO study the use of adjuvant therapy in patients with midrange score in Oncotype DX.

Total 10,253 pt were eligible for participation,
9719 pt were eligible in follow up
6711 had recurrence score of 11-25

Median duration of adjuvant endocrine Rx in 11-25 range was 5.4 years.

In this population, endocrine therapy was non inferior to chemo in the analysis of DFS, OS or loco regional recurrence.

(6) NSABP B39/RTOG → Trial to evaluate feasibility of APBI.

EORTC ~~10000~~ Trials

(1) EORTC 10853 - Role of Breast RT after local excision of DCIS.

Result → Significant decrease in the rate of local recurrence after addition of RT

(2) EORTC 10801 - BCS Vs Mastectomy in tumors <5 cm

↓

At 10 years, no significant difference betn two groups. no OS or distant mets.
Loco regional recurrence was higher in BCS group.

(3) EORTC 22881-10882 — Boost Vs No Boost irradiation after WBI in stage I & stage II Ca Breast.

Extra boost of 16 Gy to be given or not, on the site of tumor.

Result → Improved local control, but no difference in survival.

Def^n of Median follow up?

(4) EORTC 10792 - Treatment of locally advanced Ca Breast with RT alone or in combination with hormonal / chemo therapy.

→ Best results seen with both Chemo + HT.

(5) AMAROS trial → ALND vs Axillary RT in SLNB +ve cases.

Inclusion → T_{1-2} / N_0 breast Ca with no NACT.

Primary endpoint was non-inferiority of 5yr axillary recurrence.

Result → Axillary RT & ALND are both excellent methods for axillary control.

Axillary RT has lower morbidity.

In ALND group, 220/672 Pt had additional +ve nodes.

. Axillary recurrence in ALND group → 4/744

" " in RT group → 7/681

Lymphedema was significantly higher in ALND group.

NCCN discussions Breast

Definition of Her 2 +ve result

- 3+ by an IHC method defined as uniform membrane staining for Her2 in 10% or more of tumor cells
- Her 2 gene amplification by ISH method (single probe), average Her 2 copy number ≥ 6.0 signals/cell

  Dual Probe Her 2/CEP 17 ratio ≥ 2.0 with an average Her 2 copy number ≥ 4.0

  Dual Probe Her 2/CEP 17 ratio ≥ 2.0 with avg. Her 2 copy number < 4

  Her 2/CEP 2, with avg. Her 2 copy number ≥ 6 signals/cell.

- High average number of Her 2 (≥ 6 signal/cell) is considered +ve, regardless of Her 2/CEP ratio

DCIS * ER/PR status is to known so that endocrine therapy can be started

* Her 2 status has prognostic significance but does not alter treatment strategy, and is hence, not required.

* MRI has sensitivity of 98% in DCIS.
But it can overestimate extent of disease.
So, surgical decisions should not be based on MRI.
NO reduction in re-excision rates seen in women undergoing lumpectomy following MRI vs those who did not undergo MRI.

DCIS Management
i) Mastectomy → SLNB is to be done with it.
Also, if lumpectomy is done in a region which will hamper lymphatic drainage, like in axillary tail, SLNB should be done.

ii) Lumpectomy + Whole breast RT →
long term follow up of RTOG at 7yr, LRR was 0.9% in RT arm & 6.7% in non RT arm

However, it does NOT affect OS.

RT boost - Provides a small, but statistically significant reduction in IBTR risk.

3) Lumpectomy alone without

Selected pt have a low risk of recurrence when treated with excision alone.
But in long term, there is risk of IBTR

- Minimum margins for DCIS → 2mm.
- Post op → Adjuvant Tamoxifen (NSABP B24)

IBIS II trial compared anastrozole Vs Tamoxifen showed non inferiority of anastrozole.
Side effect profiles of both drugs were different

NSABP B35 compared Tamoxifen with Anastrozole

Trials of NACT for Ca Esophagus

(1) Boonstra et al → Included only SCC

→ Regimen – Cisplatin + Etoposide

20 NACT given → Response assessment

- No response → Immediate Surgery
- Partial Response → 2 more cycle of NACT → Surgery

Median OS: Surg only arm – 12 months; NACT → surg – 16 mon.

5 yr survival: Surg only – 17%; NACT → 26%

(2) INT 0113 → SCC + Adeno Ca taken in Study.

30 NACT Cisplatin + 5 FU → Surg → 2 Adj. Chemo of C + 5 FU.

* Compared to surgery alone, it has no survival advantage, curative resection rate or treatment mortality.

Median survival is also same.

No long term survival advantage of NACT

* [60% Vs 54%]

* Those pt who underwent Ro resection had long term survival, compared to those with R1 resection.

* Another conclusion, that there is no difference in curative rates between diff. histological types.

- Ro resection confers survival advantage of >2 yr.

3) MRC Oesophageal Cancer Working group trial by Allum et al

* Pre Op 2 o NACT Cisplatin + 5-FU

* Curative (Ro) Resection Rate was similar, though it reached statistical significance.
* Improved median Survival [16.8 Vs 13.3 months
" 2yr Survival [43% Vs 34%]
" OS ↓
In NACT group

* Post op mortality → 10% in both

* At follow up of 6yr, survival benefit ~~decreased~~ diminished to 6% [23% Vs 17%]

* No difference in Pattern of failure.

MAGIC trial → Stomach - 75%.
EG 5th - 11%.
lower eso - 14%.

4) MAGIC trial → Distal esophagus, Gastric & GEJ Adeno Ca.
Medical Research council Adjuvant Gastric Infusional Chemotherapy by Cunningham et al

- 503 pt were assigned to 3 ○ NACT [ECF] f/b surgery f/b 3 ○ Adjuvant chemo.
- 6 month improvement in PFS
  4 month " in median survival
  13% improvement in OS [36% Vs 23%] } - Significant
- No improvement in R0 resection rates [69% vs 66%]
- Downstaging was observed in NACT group.

5) Ychou et al → Distal, GEJ, Gastric adeno Ca
→ Cisplatin + 5-FU NACT
→ Improved R0 resection [84% Vs 74%]
→ " 5yr survival [38% Vs 24%]

6) Schumacher et al → NEGATIVE TRIAL.
→ Performed all modern pre surgical staging like - EUS
- CT scan
- Laparoscopic

Only endoscopic T3 & T4 were eligible

* Ro resection rate was improved from 67% to 88%.

Median Survival → 65 month (NACT)
63 month (Surgery)

2yr OS was equivalent (70% Surgery
73% chemo)

7) OEOS – All pt staged T3 & above on EUS
N+ disease
– pt underwent staging lap & PET

410 Pre OP E+C+ Capecitabine Vs 20 C+5FU
[ECX]
– No difference in OS
" " " 3yr survival
Higher rate of Ro resection
More ECX pt were T0-1 & No pos2 NACT.

Concluded that ECX is NOT better than C+F
∴ Removed the Role of Epirubicin

8) STO3 – Cunningham et al
Pre OP ECX + Bevacizumab Vs ECX

No improvement in OS
↑ Rate of leak!!

Ongoing Trial → INNOVATION
↳ Addition of Trastuzumab/Bevacizumab in Neoadjuvant Setting in GE5° Adeno Ca.

9) FLOT Trial - Al-Batran et al.

ECF Vs FLOT Regimen

FLOT → 5FU (2600 mg/m² over 24 hr) + leucovorin (200 mg/m²)
+ Oxaliplatin (85 mg/m²)
+ Docetaxel (50 mg/m²)

FLOT Showed - Improved PFS (30 vs 18 month)
- Median OS (50 vs 35 month)
- Projected 5yr OS
- Rate of R0 resection higher

More Patients treated with FLOT had ↓ T, disease & node negative at surgery.

* Only 52-60% completed Post op Chemo
Only 37-46% completed all Planned Chemo.

10) JCOG 9907 trial (Ando et al)
- Only S1C cases
- Resectable Stage II & III

Pre OP CTF Vs Post OP CTF.

× Pathological N0 Pt in Post op did not receive Chemo. So, only 65% in this arm received Chemo.
× No significant difference in PFS, but 5 yr OS Improved.

Trials for NACT-RT esophagus

(1) Ajani et al → Phase II trial comparing induction Chemotherapy + Preop CT-RT to CT-RT alone

Regimen → Induction - Oxaliplatin 100mg/m²
+
5-FU 2400mg/m² over 48hrs

CT-RT → 50.4 Gy + weekly Oxaliplatin
+ weekly 5 FU.

Majority pts were Adeno Ca of GEJ

pCR higher in induction arm
No difference of OS
Along with OE05 trial, thus reduced the trend of giving additional Chemo beyond 2 cycles

(2) Urba et al → Pre Op Cisplatin + Vinblastine + 5-FU + RT Vs Surgery alone

Survival improvement not significant (30 vs 16%)
Locoregional recurrence significantly reduced
Pt who achieved pCR had better outcomes
But trial was underpowered, So conclusions could not be made

(3) Walsh et al → 113 pt of Adeno Ca GEJ & Cardia

Pre OP → Cisplatin + 5FU + 40Gy Vs Surgery alone

Operative mortality higher in trimodality arm (9% Vs 4%)

Significant improvement in median survival time & 3yr survival rate.

Conclusion → low survival in surgery alone arm, indicating more lethal disease

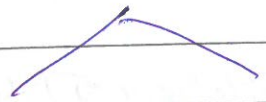
(4) Bosset trial → EORTC conducted
→ SCC patients taken.
→ Stage I & II SCC pt were taken

Pre OP regimen → Single agent cisplatin + 5 # of 3.75 Gy X

Higher rates of curative resection
Better 3yr DFS
NO improvement in OS or medial survival time.
3X higher Post OP mortality for combined modality.

(5) Burmeister et al → Pre OP Cisplatin + 5FU + RT
→ Both SCC & Adeno Ca.
→ No difference in surgical Cx
→ No difference in median OS or 3yr survival
→ Higher rate of curative resection in CRT arm
→ pCR was more in SCC (27%) than Adeno (9%)
→ Better PFS & OS in SCC than Adeno Ca.

(6) Tepper et al → CALGB 9781



Surgery 2 CP + 5 FU + 50.4 Gy.

Failed to meet accrual target
Significant improvement in 5 yr survival (34 Vs 16%)
But confounded by 0% of low accrual

(7) Marvette et al → Utilized modern staging techniques
D-Lap, EUS, CT, PET

→ Stage I & II cancers, mainly SCC.

✓ 2 CT + 5FU + 45 Gy RT Vs Surgery

No increase in Ro resection (94% Vs 92%)
" " " OS (31.8 Vs 49.2 months)
" " " 5 yr OS (41% Vs 53.8%)

P/R of 33.3% found in CT RT arm
Relatively high rate of operative mortality was observed on CT RT arm (17% Vs 3.4%)

Conclusion → Early stage I & II Ca esophagus should Not undergo line of CT-RT.

(8) Cross trial → Van Hagen et al

Majority pt had Stage III adeno Ca. [T_2/T_3 N+]
GE jn & ~~distal~~ distal 1/3 Ca.

Rx of Carboplatin @ Area under curve of 2 mg/ml/min
+ Paclitaxel 50 mg/m² once weekly for 5 weeks
+
Concurrent RT 41.4 Gy (1.8 Gy/23#)

Majority pt were node (+)

Median survival increase (44 month Vs 24 month)
Improvement in 2yr & 5yr OS (67 Vs 47% & 50 Vs 34%)
Ro resection rate improved (92% Vs 69%)
pCR seen in 23% adeno Ca & 49% SCC.
Survival benefit greater with SCC (HR = 0.453)
compared to adeno Ca (HR = 0.741)

PFS also improved [Adeno - 29.9 month Vs 17.7 month
SCC - 74.7 month Vs 11.6 month]

75.7% pt had adeno Ca
58% pt had distal 1/3 esophagus tumor
65.1% pt were NT

(9) Stahl et al → Adeno Ca only
Cisplatin + 5-FU Vs CF + Cisplatin based RT (15#/25)
- Similar pRo rates
- pCR higher in CRT arm (15.6% Vs 2.1%)
- 3 yr survival higher in CRT arm (47.4 Vs 27.7%)

Ongoing Trials

1) ESOPEC → CROSS Vs FLOT

2) NeoAEGIS → CROSS Vs MAGIC

3) TOPGEAR → Perioperative ECF done
Vs
2 cycles of ECF f/b Chemoradiation f/b Post op ECF

Other trials

Post OP Chemoradiation → INT-0116 [MacDonald Regime]
→ T2 & above adenoca of GEJ on Stomach

Observation Vs 4 cycles 5FU + Leucovorin + 45 Gy 4 Rt

Improved PFS, OS, decreased local failure

It has been criticized for poor quality of surgery & low rate of LN retrieval.
Hence, adjuvant Rx only had impact on local recurrence, not systemic relapse

Decrease in local failure (19% Vs 29%)
Increased Median Survival (36 Vs 27 months)
3 yrs relapse free survival (48% Vs 31%)
OS (50% Vs 41%)

It established Chemoradiation as standard of care for GEJ ca

CRITICS trial → Post op Chemo RT for pt treated with NACT
→ No improvement in survival.

Definitive Chemoradiation

RTOG 85-01 trial
→ Mainly SCC
5 FU (1000 mg/m² × 4 days) + Cisplatin (75 mg/m²)
RT 50 Gy @ 2 Gy/day. Vs RT alone

Cycles 3 & 4 were given every 3 weeks instead of 4 weekly.
Control arm had higher RT dose (64 Gy)

CT-RT → Improved median survival [14 Vs 9 months]
" 5 yr survival [27% Vs 0]
Histologic type: not significant

Higher acute grade 3+ toxicities seen.
Late grade 3+ toxicity was same in both arms.

As a result of this trial, Curative CT-RT became an accepted treatment for those pt who are not resection candidate.

INT 0123 → Trial for higher RT dose in curative RT
↳ No benefit.

Intensification of Chemoradiation

INT 0122 → Intensification of treatment described in RTOG 85-01

Both chemo & RT were intensified by 20%

Median survival time - 20 month

5 yr survival ~ 20%

~~INT 0123 — 50.4 Gy RT~~

INT 0123 → 4 05 FU + Cisplatin [Same as RTOG 85-01]

+

/ —

50.4 Gy 64.8 Gy.

Modification from RTOG 85-01

- Using 1.8 Gy # to 50.4 Gy
- Treating proximal & distal 5cm to 50.4 Gy directly instead of whole esophagus with 30 Gy & cone down 5cm margins to 50 Gy
- 4 weekly cycles 3 # 4, instead of 3 weekly.

NO significant improvement of OS, median survival.

∴ Standard RT dose → 50.4 Gy.

Trials for observation vs surgery in post NACT-RT pt ☐

cCR → SANO
→ ESOTRATE } - Both ongoing.

✓ PRODIGE 5 / ACCORD 17 trial → FOLFOX vs 5FU+Cis

No significant diff. in PFS or OS
Hence, for pt unable to tolerate Cisplatin, FOLFOX can be given.

Targeted Agents

① Cetuximab → SCOPE 1 trial - lower survival
[50 Gy / cap / Cisplatin - lower OS
± - Higher toxicity.
cetuximab]

→ RTOG 0436 trial → No difference in outcome
[50.4 Gy / Paclit ± Cetuximab]

② Trastuzumab → RTOG 1010

50.4 Gy / Carbo / Paclit ± Herceptin.

No significant improvement in DFS, or OS.

Update of Neo AEGIS trial - 377 pt ☐ T2-3 N0-3 were randomly assigned to receive CROSS or MAGIC/FLOT (latterly, FLOT was used)

	CROSS - 178	MAGIC/FLOT - 184 (154/2
3yr survival (1° end Point)	56%	57% (N.S)
R0 resection	95%	82%
TRG 1&2	41.7%	12.1%
pCR	16%	5%

Similar incidence of post op Cx.

Obstructive Jaundice Case

- Which "bilirubin" leads to clothing in urine?
- Reason for color difference in unconjugated & conjugated hyperbilirubinemia.

- Primary & secondary biliary cirrhosis.

Unconjugated bilirubin is more toxic than conjugated, since it can cross BBB.

Performance Score for Pediatric Patients?

Generalized Weakness + OS → Portal compression due to enlarged node.

Mechanism for Sister Mary Joseph nodule?
→ Dissemination along the obliterated umbilical artery.

mechanism for Virchow's node
→ Pathway along ~~osteochondral~~ Thoracic duct

Mechanism for Krukenberg node
↳

CA 19-9, CEA etc ~~of~~ ~~for~~ AFP

- Origin
- Secretion
- Ⓜ value
- Causes of ↑

CEUS – Uses & Principle?

USG features of malignant liver mass?
(↑ " " " " ")

LI-RADS

Liver Protocol CT scan →
Pancreatic " " " →

Tests for FLR determination

(1) Child Pugh Score

Parameter	1	2	3
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	Absent	Moderate	Severe
Encephalopathy	Absent	Moderate	Severe
PT Prolongation(s)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

(2) Volumetric methods by 3D reconstruction based on CT Scan

For a healthy liver, FLR of 25% is sufficient
For chronic liver disease (or chemo) without cirrhosis, it should be 30%.
For Cirrhosis without Portal HT, it should be 50%.

(3) ICG dye excretion → Indocyanin green dye is a water soluble inert tricarbocyanin with hepatic extraction rate of 70% & is almost completely excreted in its unchanged form.

Test results are expressed as % of ICG returned after 15 min (ICG R-15). Normal value is <20%.

Use of ICG is limited in the presence of hyperbilirubinemia since uptake is by the same hepatic transporters and it will cause false decrease in ICG clearance.

(4) ^{99m}Tc Mebrofenin → Mebrofenin is iminodiacetic acid (IDA) analogue with highest specificity for hepatocyte. It is absorbed & excreted unchanged by hepatocyte. The rate of uptake of Tc^{99} labelled Mebrofenin can be quantitatively assessed during scintigraphy.

(5) ^{99m}Tc GSA → ^{99m}Tc DTPA - galactosyl serum albumin is taken up only by liver. The uptake of this agent is not affected by hyperbilirubinemia & hence, can be used in a cholestatic patient.

(6) ^{13}C - Methacetin breath test is based on the activity of CyP450 1A2. It is metabolized by the enzyme to paracetamol & $^{13}CO_2$. The test is performed by measuring $^{13}CO_2$ / $^{12}CO_2$ in expired breath, before & after administration of the agent. The result is expressed in µg/kg/hr. & it gives total liver function.

* ICG + CT volumetry Predicted Post hepatectomy liver failure quantitatively [Hwang et al].

* Chemotherapy > 12 weeks should have FLR > 30%.
Drugs → Irinotecan, Oxaliplatin

Augmentation of FLR

① Portal vein embolization

- Developed to improve size & function of FLR by occluding ipsilateral portal vein. As a result, the opposite liver hypertrophies. PVE results in increased FLR volume in roughly 60% pt, average increase being 12%.

Degree of hypertrophy following PVE is inversely proportional to the FLR ratio before PVE.
∴ A smaller FLR will have a larger hypertrophy.

Procedure is commonly used to occlude the Rt portal vein & induce left lobe hypertrophy. There are two approaches
- Ipsilateral → Gain access to Rt PV directly
- Contralateral → Gain access to left PV, then pass to right.

Different agents → Gelatin sponge
PVA + coils or plugs
N-butyl cyanoacrylate
Filtering glue.

Non cirrhotic liver grows @ 12-21 cm^3/day & cirrhotic liver @ 9 cm^3/day.

Post PVE, CT scan to look for increase in FLR should be done at 4-6 weeks & surgery planned.

(2) ALPPS → Associated liver partition & Portal vein ligation.

Typically used for large Rt sided masses, where Rt Portal vein is ligated, & liver is divided along falciform ligament. Best described use is for colorectal mets.

Advantage is, post procedure waiting time is lower than PVE, but it is a physiologically demanding procedure.

(3) ALIVE → Assessment of Liver function Intra-operatively using ICG clearance during Vascular Exclusion.

Newly reported intra-op technique, which may have advantage of some planned ALPPS (single stage) as well as identifying the need for ALPPS where one hasn't been performed. It involves measurement of ICG Plasma Disappearance Rate (ICG-PDR) at 5 points

1) Before anesthetic induction
2) Following mobilization of FLR
3) During inflow occlusion of lobe to be resected
4) During parenchymal transection
5) During inflow as well as outflow occlusion.

Aim is to replicate post resection state intra-op

(4) Associating Portal embolization & artery ligation (ALPEAL)

Right portal vein is ligated, FLR mobilized & Rt sectoral artery ligated.

The second stage is undertaken 1–2 months later.

Pancreatic Cystic Neoplasms

(1) Serous Cystic Neoplasm

- Most commonly observed in women (3:1 ratio)
- Avg age of diagnosis 63 years

4 subtypes
- Serous microcystic
- Serous macrocystic (oligocystic)
- VHL associated Pancreatic cysts
- Serous cystadenocarcinoma

- Fluid filled cysts. lined by a single layer of cuboidal epithelial cells.
  Lack of atypia / ~~necrosis~~ mitotic features

- Grossly → Honey comb appearance around central scar.
  → Calcifications in the proximity of the scar.

Oligocystic variant DOES NOT have central scar.
Predominantly found in Pancreatic head.

VHL associated Pancreatic cyst → Loss of heterozygosity on 3p25 & mutation in VHL gene. They have multifocal disease
Behave similar to non VHL serous cystadenoma.

Serous cystadenocarcinoma → Only 25 cases described till 2010. Very rare.

The central "scar" is due to fibrous nature of the disease.
When SCA >10cm, it may cause compressive symptoms such as early satiety, OJ & Pain.

Radiology Three different imaging patterns

1) Polycystic — most common, multiple small cysts, all <2cm central fibrous scar with radial calcification appearing as a "starburst".

2) Honeycomb Variant → multiple subcentimetric cysts that appear as a single mass. The honeycomb appearance is produced by septal wall enhancement due to contrast administration.

3) Oligocystic → Seen in <2% cases. Small cystic areas with stromal hypervascularity.

Radiographic Criteria → 1) Location in pancreatic head
2) Lobulated contours
3) Lack of wall enhancement
4) Wall thickness equal to or less than 2mm.

SCN is diagnosed @ 100% specificity in any 3 out of 4 are present

MRCP → Appears like a cluster of grapes on T_2 weighted images. Main disadvantage is the inability to detect central calcifications commonly seen in SCN.

EUS → SCN typically appear as microcystic compartments without fluid.

Fluid cytology & Biochemistry → Bland cuboidal cells containing glycogen, clear cytoplasm with cellular atypia or necrosis.

Mucin → Absent
CEA → low
Amylase → low.

Operative management → Smaller lesions can be observed.

Indications for surgery → Presence of symptoms
→ Size 7.4cm [Study by Tseng et al]
→ Uncertain radiographic picture.

Either Whipple's or Central Pancreatectomy. No role of enucleation.

(2) Mucinous Cystic Neoplasm

→ Avg age of presentation 40-50 yrs.
Female : Male ratio → 20:1

→ Mainly found in body & tail
Avg size at diagnosis 6-10 cm

Grossly → Spherical
→ Infrequently encapsulated by a calcified fibrous wall
→ Almost all MCN are multilocculated
→ Fluid is thicker & more viscous than in SCN.
→ MCN does not communicate with pancreatic ductal system.

Microscopy → Tall, mucin producing columnar cells
→ Ovarian like stroma is pathognomic
→ Immunoreactivity for CK 7, 8, 18, 19, Epithelial Membrane Antigen, CEA, MUC5AC, CA 19-9.
→ Stroma cells stain for estrogen, progesterone & α-inhibin.

3 categories of MCN based on highest degree of cellular atypia
1) low grade
2) Intermediate grade
3) High grade

< 20% MCN progress to invasive cancer, and hence it is a precursor to cancer.

- Any presence of mural nodule in these lesions is a concern for invasion.

- These may have peripheral eggshell-calcification.

Factors associated ~ malignancy on imaging [Allen et al, Zamboni et al]
1) Presence of septations
2) Larger size
3) Mural nodule

Radiology

CT scan → Usually macrocystic & unilocular
→ May be multilocular
→ MCN may lead to Pancreatic duct dilatation but does not communicate with the duct
→ Cyst walls are thick & with papillary excrescences
→ Calcification is often peripheral (eggshell).
→ Direct correlation bet^n intracystic mural nodules & risk of malignant degeneration.

MRI → Better identify contents in the cyst
→ Mucin leads to high signal intensity on T1 & T2

Fluid Cytology & Biochemistry → Honeycomb sheets & clusters of columnar cells containing mucin.

Mucin → High

CEA → High. Cut off to differentiate from SCN → 192 ng/ml (Brugge et al)

If CEA < 5, MCN can be excluded

Amylase → Normal / low

Operative management → Resection always.

→ Whipple's or distal pancreatectomy

→ If there is no evidence of malignancy, Spleen preservation can be considered

→ Adjacent organs may need to be removed due to involvement.

Observation can be considered if

1) Asymptomatic
2) < 3cm size
3) Absence of pancreatic or CBD dilation
4) Absence of lymphadenopathy.

IPMN → Intraductal Papillary Mucinous Neoplasm

→ More common in head > Diffuse > body/tail

Three types

1) Main Duct (25%) IPMN → > 5mm dilation of main Pancreatic duct in the absence of other causes of ductal obstruction.

2) Branch duct (57%) IPMN → Pancreatic cyst >5mm communicating with MPD

3) Mixed type (18%) → Meets criteria of both.

→ Slightly more prevalent in males
Peak incidence 60-70yrs.

Main Duct → MPD >5mm,
→ Mucin filled
→ Tortuous
→ Fish mouth appearance on endoscopy
→ Found near head of pancreas
→ Mucin seen in duodenum in both major & minor papillae involved.

Branch Duct → Uncinate Process
→ Grape like structures that are multicystic & fluid filled cysts.
→ Adjacent pancreas is normal.

IPMN based epithelial lining

① Gastric subtype (Most common)	Intestinal type	Pancreaticobiliary
- Basal small nuclei	- Finger like	- Cuboidal cells &
- Apical cytoplasmic mucin	Projections with	atypical nuclei
- low grade	Cigar shaped nuclei	- Higher grade
- MUC5AC, MUC6	- MUC5AC, MUC2	- Invasive carcinoma
-	CDX2	
	- Asso & Colloid Ca.	

(4) Oncocytic → Abundant eosinophilic cytoplasm
→ large amount of mitochondria
→ High grade
→ Express MUC 1 & MUC 6

IPMN may represent a "field defect" or genomic instability of entire pancreas.

Radiology → Cystic dilation of MPD or side branch

Imaging characteristic ∴ higher risk of malignancy

1) Main duct IPMN
2) Mural nodule
3) Dilation of biliary tree

MRI → MRCP has largely replaced CT as the choice of imaging work up

Main duct IPMN → Either segment of the pancreatic duct or entire duct are dilated & filled ∴ low density material

→ Overlying pancreatic parenchyma thinned
→ Solid mural nodules seen
→ Occasionally, mucinous material can be seen to bulge out of a dilated ampulla of Vater.

ERCP → Ohashi triad → Bulging Ampulla of Vater
→ Mucin secretion
→ Dilated MPD

Management

Sendai Consensus guidelines (2006)

"Sendai Positive" → Tumor size ≥ 3cm
→ Symptomatic
→ Mural nodules
→ Thickened wall
→ MPD ≥ 6m.

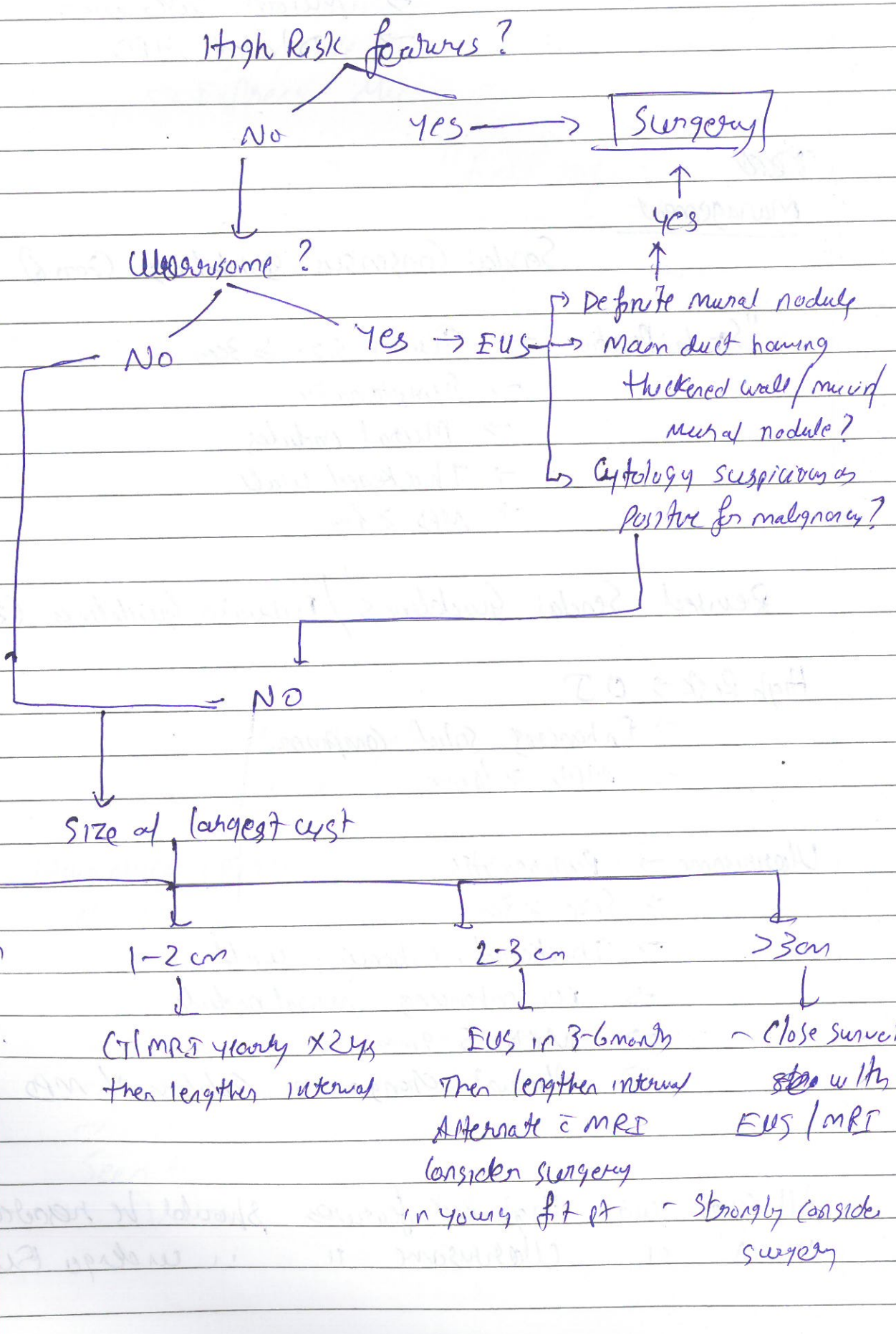
Revised Sendai Guidelines / Fukuoka Guidelines (2012)

High Risk → OJ
→ Enhancing solid component
→ MPD ≥ 10mm

Worrysome → Pancreatitis
→ Size ≥ 3cm
→ Thickened, enhancing wall
→ non enhancing mural nodule
→ MPD 5-9mm
→ Abrupt change in caliber of MPD

All cysts with High Risk features should be resected
" " " Worrysome " " undergo EUS.

Flow chart of management



Survival - Survival for MCN with invasion is 26%.
- Survival of localized MCN is much better than similarly staged IPMN

- factors associated ↓ Survival - Tubular subtype
  - Lymph node mets
  - Vascular invasion
  - Positive margins.

JSPAC → Gemcitabine Vs S-1 [Tegafur + Gimeracile Oteracil]
1 yr survival → 53% vs 70%.

Trials of Ca Pancreas

Adjuvant trials

(1) GITSG trial → First adjuvant trial.
→ small study population
→ 40 Gy radiation + Bolus 5FU during first 3 days of RT f/b maintenance × 2 yrs.

Superior survival compared to observation only (20 Vs 11 month)

(2) EORTC trial → 218 pt ↑ pertumor or PDAC randomized to chemoradiation or observation.

Regime → 40 Gy RT + 5FU as continuous infusion (not Bolus) on day 1–5 of RT.
No maintenance chemo.

Survival → 21.6 months Vs 19.2.

(3) ESPAC 1 → 2×2 study design.
4 groups → 1 → Chemo RT (GITSG protocol) f/b Chemo (leucovorin + 5FU infusion) every 28 days × 6 cycles

2 → Chemo only
3 → Chemo RT only
4 → observation.

Group 1+2 had superior survival (20.1 Vs 15.5 months) compared to 3+4.

ESPAC 2 trial → Surgery + Intra-arterial Chemo + RT Vs Surgery alone

→ Survival of chemoradiation groups (1+3) was LOWER than 2+4 [15.9 Vs 17.9]
Even if group 2 was removed from above, the survival of 1+3 < 4.

→ This trial established Chemo standalone as mode of Rx

(4) CONKO-001 (Charité Onkologie) → German trial
→ 368 pt. Gemcitabine Vs observation alone
Gemcitabine
→ DFS was improved (13.4 Vs 6.9) but not OS (at initial analyses)
At subsequent analysis later, OS is also improved.

→ 5yr survival difference is 10%. & 10 yr survival diff. is 5%

→ Data Prove that gemcitabine monotherapy is effective in 10% pts.

(5) ESPAC 3 trial → Gemcitabine Vs 5 FU
→ No chemo RT
→ OS were similar but toxicity less with Gem.

(6) RTOG 9704 → 5FU + (50.4 Gy + infusional 5FU)
Vs
Gem "

OS was similar both subgroups.

RTOG 0848 → Gem Vs Gem + Erlotinib

No survival diff

In patients with Pancreatic head tumors, Gemcitabine has superior survival.
Role of Post op CA 19-9 was defined.

(7) ESPAC 4 → For "high performing" patients

Gem Vs Gem + Cap
OS was improved with combination therapy, as was 5yr survival rate.

(8) HEAT trial → Adjuvant Gem/Cap ± Hypofractionation

Trials of locally advanced Ca Pancreas

(1) FFCD/SFRO trial → 60Gy + 5FU + Cisplatin f/b Gem
VS
Gem alone.
Multimodality therapy had LOWER survival.

(2) ECOG 4201 → Gem based RT f/b Gem did better than pt receiving Gem alone (11.1 vs 9.2)
This trial had only 71 patients.

(3) SCALOP trial → Gem + 50Gy f/b Gem + Cap
VS
Cap + 50Gy f/b Gem + Cap

Mildly increased efficacy & ↓ toxicity for Cap + RT.

→ 2×2 trial, Pt assigned to Gem Vs Gem+Er Cetuximab at 4 months, Pt assigned to 2 month chemo on CRT [Top based — If no Progre

(4) LAP07 trial → No benefit of ChemoRT after Chemo, as compared to additional chemo.
As most patients cannot tolerate additional chemo, consolidation ChemoRT ± Capecitabine as radiosensitizer is an acceptable option.

(5) ✓ ESPAC 5F → 4-arm, Prospective randomized phase II trial of
Surgery Up front Vs Chem-Rad
OR
4× FOLFIRINOX
OR
[50.4 Gy RT + Cap] Chemo-RT
in Pt ± Borderline resectable or Potentially

[Pg 1039 of Blumgart for flowchart]

Resection rate was 62% for up front Surgery
55% for NACT

R0 rate → 15%
23%

1 yr Survival → 40%
77%

∴ No difference in resection rate but higher rate of R0 & Survival benefit.

Trial was not powered to compare different Neoadjuvant Strategies.

Alliance A021501 → Treat mFOLFIRINOX ± RT for borderline resectable Carcinoma

18 months survival → 68% Vs 47%. [with or without RT]

(6) PREOPANC-1 → 64 resectable + 58 Borderline resectable pt randomized to immediate surgery or Pre-op Gemcitabine based chemo RT, with f/u adjuvant Gem based chemo.

OS < NACT → 17.1 month
Upfront → 13.5 month.

low surgical quality ∴ poor trial design.

(7) NEONAX trial →

NEOLAP trial → 2 courses of initial Nab-Paclit/Gemcitabine

↓

130 pt had no Progression/adverse effect

↓

2× Gem + Nab-Paclit 4× FOLFIRINOX

No significant diff^n Rt resection rates b/t two groups, but improved histopathological downstaging seen in FOLFIRINOX group (but its impact on OS not clear).

Shows that nab-Paclit + Gem is as good as FOLFIRINOX.

JASPAC 05 ⇒ Neoadjuvant S1 + Concurrent RT for Borderline resectable Pancreas

Ro rate → 63%

Median Survival → 30.8 mon

NEOPAC – 4 cycle of Gem OX f/b Surgery f/b 20 Gem

vs

40 Gem f/b Surgery f/b 20 Gem.

[Adjuvant vs Neoadjuvant Gem]

MD anderson Series → Retrospective analysis of 485 consecutive Pt, who received Nab-Paclitaxel/Gem (200) and FOLFIRINOX (285).

More response seen in FOLFIRINOX as per RECIST criteria (19% Vs 8%), more Pancreatectomy done (27 Vs 16%), but similar OS. (21 month Vs 20).

★ PRODIGE 24 (FOLFIRINOX ~~adjuvant~~)

493 pt, 21-84 days after Ro/R1 resection

PS 0-1, no hematological/cardiac/renal dysfn

↙ ↘

6 month Gem. alone | FOLFIRINOX

↓

34 month median follow up

DFS →	12.8 month	21.6 month.
OS →	35 month	54.4 month
Grade 3/4 adverse effect →		More.

~~Ro rate~~

Dose of FOLFIRINOX ⇒ Oxaliplatin 85mg/m² +

5 FU 2400mg/m² + leucovorin 400mg/m² +

Irinotecan 180mg/m²

Trials for metastatic Ca Pancreas

(1) Burris et al → Landmark study that depicted role of Gemcitabine
- → Gemcitabine Vs Bolus 5 FU
- → Most pt had metastatic disease, although 26% had locally advanced disease
- → Grade 3/Grade 4 toxicity like TCPenia, neutropenia, anemia, nausea was more common ∈ Gem.
- → Clinical benefit, based on Pain score, PS, weight was seen ∈ 23.8% pt in Gemcitabine Vs 4.8% in 5FU.
- → OS ← 5.65 month (Gem)
  4.41 month (5 FU)

1 yr survival ← 18% (Gem)
2% (5-FU)

Partial tumor response ← 5% (Gem)
0% (5FU)

Stable disease ← 39% (Gem)
18% (5FU)

(2) EORTC E6201 trial → Gem Ox Vs Weekly 30 min Gem Vs fixed dose rate Gem

Improved OS for fixed dose rate arm compared to 30 min infusional arm, but had greater toxicity.

No survival advantage of Gem Ox

(3) SWOG S0205 → Gem + Cetuximab is not better than Gem alone.

(4) National Cancer Institute of Canada Clinical Trials Group Study
Gem + Erlotinib Vs Gem ~~alone~~

OS < 6.24 month (Gem + Erlo)
5.91 month

However, this therapy costs $10,000 a month, yielding just 10 days to survival

(5) MPACT Study → Gem + Nab-Paclitaxel Vs Gem alone.

Median OS < 8.5 month (Gem + Nab)
6.7 month

PFS < 5.5 month
3.7 month

1 yr OS < 35 %
22 %

2 yr OS < 9 %
4 %

So, Gem + Nab Paclitaxel became standard of care.

(6) PRODIGE 4/ ACCORD 11 Study

→ Pt to have PS 0-1
→ FOLFIRINOX Vs Gem.

OS < 11.1 months
6.8 months

PFS < 6.4
3.3

Objective response rate < 31.6 %.
9.4 %.

FOLFIRINOX had substantial higher toxicity, including grade 3/4 neutropenia, febrile neutropenia, diarrhea.
But only 31 % pt had deggradation in quality of life in FOLFIRINOX Vs 68% in Gem.

(7) GREST study → S1 Vs Gem Vs Gem + S1
S1 is a combination of Tegafur / Gimeracil / oteracil

Objective response rate < 21 % (S1)
28 (Gem + S1)
13 % (Gem)

Infectious diseases Mimicking (a Buccal Mucosa)

Oral premalignant conditions - 2006 Classification.

When free fibula flap cannot be done?
→ Pre-irradiated neck
→ Fibular #
→ Peroneal Magna (lower leg supplied by only one vessel)
→ Athlete

Other bone flaps - Scapular flap
- DCIA (iliac)

Study describing role of adjuvant RT?

If only PNI +ve and all other high risk feature negative, then adjuvant RT is TBD - based. except in Adenoid cystic & mucoepidermoid Ca.

PNI is when ≥ 33% of nerve sheath is involved by tumor cells.

LVI	+
PNI	+
WPOI	3/4/5
Grade	High
Differentiation	Mod/Poor

If three out of these five are positive, pt to be considered for PORT

Management of locally advanced Head & neck Cancers

Three combined modality approaches studied

- NACT f/b surgery/RT
- Concurrent CT-RT
- NACT f/b Concurrent CT-RT

Advantages of adding chemo to RT

1) Induction chemo may reduce tumor volume & improve function, thereby permitting more effective & less toxic local therapy

2) Treatment of subclinical metastatic disease without delay

3) Improve locoregional control & organ preservation

4) Provide prognostic information to select chemo-RT intensity

5) Sensitization to RT & ↓ radiation resistance.
Reduction of repopulation between radiation treatment fractions may contribute to benefit of concurrent CT-RT.

D) Disadvantage of NACT

1) Increased toxicity, which may limit patient compliance
2) If NACT is ineffective, it will delay definitive therapy
3) May induce cross-resistance to subsequent RT or chemo RT

MACH-NC ~~study~~ → Meta Analysis of Chemotherapy in Head & Neck cancer.
- Updated in ~~2009~~ 2020
- Data from 93 trials & 16,485 patients with resectable or unresectable disease.

- In all trials, pt were randomized to a definitive local therapy (surgery/RT) or definitive local therapy in combination with some form of chemotherapy.

- Included all head & neck cancers except Primary nasopharyngeal tumors.

- Primary end point was OS.

Results 1) Concurrent chemo → Assessed in ~~9~~ 71 trials, ~~6005 patients.~~ 10,680
→ ~~Med~~ Median follow up ~~8.6 years~~ 9.2 yr.

→ Significantly reduced risk of death compared to local therapy alone [HR 0.81 correlated to 6.5% absolute decrease in mortality in 5 years. & 3.6% at 10 yr.

→ For Event free survival, HR of 0.80 & absolute benefit of 5.8% at 5yr & 3.1% at 10yr.

→ No statistically significant difference in RT schedule (once daily Vs altered schedule)

→ Statistically significant ↓ in effect with pt age > 70 and no benefit observed in that population.

→ At the time of these studies, there was no routine identification of HPV.

2) Induction chemo → 45 trials, ~~3312 pts~~ 7054 pt
~~→ No benefit (pts who completed chemo/surgery/RT~~
→ When analyzed, based on regimen, Cisplatin + 5FU was significantly better in OS compared to surgery/RT alone.
→ HR for death - 0.96, absolute diff of 2.2% at 5yr
For EFS, absolute diff of 1.4% at 5yr.

3) Concurrent Vs Induction → 8 trials, 861 pt.

→ ~~No~~ difference in OS in favor of concomitant with absolute benefit of 6.2% at 5yr.
→ Concurrent more effective against locoregional failure
Induction " " " distant mets

4) Adjuvant chemo → 6 trials, 2567 pts.
→ No improvement in OS compared to definitive local therapy.

* Benefit of chemo was higher in concomitant group than induction.
Better effect of Chemo on women.

Trials for Sequential Chemo-RT [Induction f/b Concurren

1) Spanish Head Neck Cooperative Group - 439 patients, randomized to concurrent CT-RT alone (7 weeks RT + Cisplatin on Day 1, 22, 43) or Induction with TPF or PF f/b concurrent CT-RT

Result → No statistically significant differences in PFS, Time to Treatment failure (TTF) or OS in three arms.

Due to toxicity of cisplatin, almost half the pt DID NOT complete the entire course.
A secondary analysis of those who did, showed improvement in PFS in NACT group.

2) Italian trial → 421 pt, randomized to induction chemo with 3 cycle TPF f/b chemo RT Vs Chemo RT alone.

Within each group, pt were secondarily randomized to concurrent Chemo ± 2 cycle of PF or to concurrent Cetuximab.

So, FOUR groups overall
1) TPF + Chemo RT ± PF
2) TPF + Chemo RT ± Cetuximab
3) Chemo RT ± PF
4) Chemo RT ± Cetuximab.

Median follow up of 44.8 months.

* Induction f/b Chemo RT significantly improved OS (Median 34 month Vs 30, 3yr OS 58% Vs 47%)

Improved PFS (30 Vs 19 month)

Locoregional failure also reduced.
Distant mets NOT reduced.
Trend to more improvement ☐ Cetuximab + NACT
But study was not powered to make the conclusion.

3) DeCIDE trial → 280 treatment naive patients, with N2/N3 disease, assigned to NACT (2 DTPF) f/b Chemo RT or Chemo RT alone.

Chemo RT → Docetaxel + 5FU + Hydroxyurea, given as 5 cycles in combination ☐ RT at 150 cGy BD, repeated every other week.

Primary end point was Overall survival.
Original Plan was to have 500 pt, but due to slow accrual only 280 patients.

Follow up → 2.5 year.
No statistically significant difference in OS
Incidence of distant mets was reduced in Sequential arm, but no improvement in OS.

4) GORTEC 2007-02 trial → N2a, N2c, N3 patient, 370 patients.

Two arms { Chemo RT alone (7 weeks RT + carbo + 5 FU)
NACT (3 @ TPF) f/b chemo RT ± cetuximab

NACT group was given prophylactic ciprofloxacin & Growth factor support.
Induction was complicated by febrile neutropenia in 30 Patients & treatment related mortality in 12 Patients.
Of those assigned to TPF, 30 pt did not receive Planned RT.

Median follow up of 2·8 year, induction therapy resulted in lower rates of distant mets (HR - 0·54)

No difference in OS, PFS or loco regional control

* Spanish trial used intention to treat in concluding no benefit.

* Italian trial demonstrated higher induction & Chemo RT treatment completion rates than Spanish, and their PFS difference was similar to the per-protocol pt analysis in Italian trial.

* In the DeCIDE trial, there was 7 cycles of total chemo in the induction group which may have led to high survival in both groups.

- Use of sequential therapy should be reserved for very healthy pt at high risk of local or distant recurrence.
  Mostly used for Bulky N2b, N2c low nodes or N3, and T3/T4 as per DeCIDE & Italian trial.

- If a pt has poor performance status, consider definitive RT
  In age over 70, chemo has actually decreased survival.

Trials for NACT regimen

1) TAx 324 → TPF Vs PF, both followed by concurrent CT-RT using weekly carboplatin (AUC 1.5). 5FU dosed @ 1000 mg/m² over 4 day.
   OS is significantly better in TPF group.

   Acute toxicity is higher in TPF group.

2) TAx 323/ EORTC 24971 → TPF Vs PF
   5FU is dosed @ 750 mg/m² over 5 days here.

   OS improved in this regimen.

* pt ↓ progressive or stable dz after 2 cycle underwent surgery. Only those who showed response underwent third cycle.

Regime for NACT-RT [Single agent Chemo]

Good PS, ~~not~~ and not received NACT with platinum agent → Cisplatin

Good PS, contraindication to Cisplatin → Carboplatin (acceptable, less effective)

Good PS, CI to ~~Platinum~~ Platinum (hearing loss, dialysis, ~~neuropathy~~) → Cetuximab (acceptable, less effective)

Old pt (> 70yr), Poor PS, significant comorbidity → Definitive RT.

Trial by Lisa Licitra et al

198 pt [T_2-T_4, N_0-$_2M_0$]

Chemotherapy arm (99)
↓
3 cycles 5FU + cisplatin*
↓ then surgery
↓
Complete flu - 96 pt

Surgery alone (99)
↓
Complete flu - 95 pt

[Adjuvant RT for both]

- 27% had cCR,
- 82% objective response rate
- 27% had pCR

Similar DFS, OS, distant mets.

5yr OS 57% 46%

pt ↓ pCR had 5yr OS of 85%.

~~Segmental~~ Segmental mandibulectomy in 31% pt of chemo Vs 52% in surgery

So, NACT has role in organ preservation.

Landmark trials in Head Neck

An article, abstract or work in a scientific Journal regarded by workers as a seminal study or which has substantial impact on that area of knowledge. They form basis of Evidence Based study.

Papers on disease biology

1) Clinical update on head & neck cancer: molecular biology & ongoing challenges.

2) Field cancerization in oral stratified Squamous epithelium
Slaughter et al.
783 pt reviewed.
Finding → In every instance in which the tumor itself was 1cm or less in diameter, separate foci of in situ cancer or isolated islands of invasive SCC were found.

3) Genetic Progression model for head & neck cancer
- Joseph Califano et al
Molecular basis of field cancerization.

4) Global epidemiology of oral & oropharyngeal cancer
- Soman Warnakula suriya.
→ Oral cancer is the most common cancer in South East asia

→ Attributable risk to tobacco & alcohol > 80 %
→ Heavy drinkers & smokers have 38 times risk
→ Tongue more common in West
BM in Asia

Diagnosis

1) Detection of lymph node mets in head neck cancer
A meta analysis comparing US, USG FNAC, CT & MRI – RBJ de Bondt

→ Sensitivity highest for USG (87%) ✓
Specificity " " US-FNAC (98%) ✓

USG FNAC is most accurate modality.

2) Detection of cervical lymph node mets in head neck cancer patients with clinically No neck – a meta-analysis comparing different imaging modalities. – Liao et al.

Specificity of CT is highest ✓
Sensitivity slightly lower. ✓

So, CT is best imaging modality.

Surgery of neck

1) Neck dissection first described by Hayes Martin in 1951

"Any technique designed to preserve XI nerve should be condemned unequivocally.

2) Conservation technique in Radical neck dissection - Bocca et al.

Conservative neck dissection - Suarez et al

↓

Crucial point is that the whole cervical nerve system be removed in one piece together with the "packing material", i.e. the cellular & fat tissue contained therein.

Bocca described the types of MRND.

3) Elective vs Therapeutic neck dissection in early cancer tongue - Abdul R. Fakih, Raja Rao, Anita Borges

100 pts were entered

HG vs HG + RND

	HG	HG + RND	
DFS	52%	63%	[NOT significant]
T_1	64%	70%	[NOT significant]
T_2	46%	60%	

- Tumor depth > 4mm was found to have higher risk of nodal mets & for survival (83 Vs 46%). No diff in survival in the two treatment groups with DOI.

4) Byers et al → Skip metastasis in the neck in Ca tongue

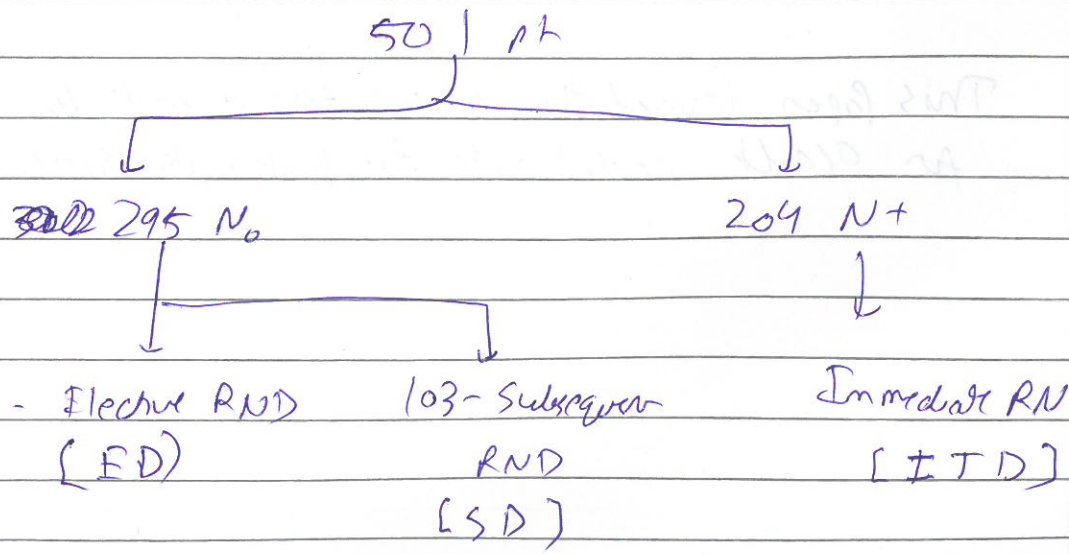
277 OSCC pt.

- 15.8% had level III mets as the only manifestation of disease in the neck, or level III was the only node present without disease in I-II.

So, Selective neck dissection [I-IV] is minimum surgery for tongue.

Flaws → Heterogenous inclusion of neck dissection
→ lack of sampling of other levels in those cases who had level III IV
→ Retrospective analysis, so lack of quality control.

5) Pattern of cervical lymph node mets from SCC oral cavity → Jatin Shah et al.



34% pt in elective RND
64% pt in ~~selected~~ ITD
90% in ~~selected~~ SD
} had LN mets.

Level II mets in 3% in ED group. Vs 17% in SD+ITD

Tongue, RMT, cheek → no mets in level IV

< 1% in FOM, GBS primary. for level V in ED Vs
6% in ITD+SD

☆ Basis for reduced neck dissection ☆, in both N_0 & N+ diseases.

(6) Weiss et al → Use of decision analysis in planning a management strategy of N_0 neck

Mathematical analysis performed to determine optimal threshold for neck treatment

Result → If probability of cervical mets > 20%, treatment of neck is warranted.
Treatment plan should be single modality therapy

This paper formed the basis of elective neck dissection for occult nodal mets for high risk site & stage.

7) Elective Vs Therapeutic neck dissection in N_0 oral cancers
- D'Cruz et al.

Absolute OS benefit of 12.5 % in elective neck dissection over Therapeutic. (80% in END Vs 68% in TND).
DFS benefit of 23.6 %.

Significant increase in LN yield with DoI
3mm → 5.6 %
4mm → 16.9 %

8) SEND trial → RCT of END Vs TND in T_1/T_2 N_0 pt.
Done in UK.

250 randomized + 346 observational cohort

Occult neck disease found in 19.1 % in T_1 & 34.7 % (T_2)
5yr OS → HR 0.71
DFS → HR 0.66

9

9) SENT trial → Sentinel European Node Trial

415 pt - T_1 // T_2N_0

SNB was undertaken, with an average of 3-2 nodes.

SN was found in 99.5 % cases.

Positive SN in 23%
False negative rate 15%
DFS was 94%
Sensitivity → 86%
Negative predictive value → 95%.
Reliable & Safe Oncological practice.

10)

Surgical aspect of oral cancer

1) Surgery + Post op RT Vs RT only - Robertson et al.

Only 35 accrued. Trial stopped prematurely

2) Routes of entry of SCC to the mandible
- MacGregor & MacDonald.

46 non irradiated. (10 partially dentate & 36 edentulous) mandibles invaded by tumor,
41 were invaded through occlusal surface
most involvement was thru alveolar crest.

1st rationale for conservation of Mandible.

BUT, in radiated mandible, routes were more varied, multifocal, loss of distinction betⁿ soft tissue & Mandible, with loss of Periosteal protection.

∴ In post RT mandibles, conservation should NOT be done.

Drawback → Site of Primary not mentioned
→ Did not answer question of HOW spread occured.

3) Patterns of invasions & routes of tumor entry - James Brown 100 mandibles.

Findings → Routs of tumor entry
Direct → 28%.
Direct through the Junction of attached & reflected mucosa → 4
occlusal surface → 23%.

Pattern of tumor invasion depended on DOI with in hard & soft tissues.

Dentate mandible → Route of tumor entry was at the point of abutment (Direct) in all 13 cases

Edentulous mandible → 50% spread through occlusal surface.

∴ In a dentate mandible, if Paramandibular spread is less, we can do a marginal ~~resection~~ Mandibulectomy

In edentulous, MM cannot be done.

4) T4a oral cavity cancer below the mandibular notch is resectable - Liao et al.

45 pt. ← 38 pt infra notch (below the sigmoid notch)
7 pt supra notch.

5 yr locoregional control Infra > Supra

Infra notch No-1 > N2
Nerve invasion is adverse prognostic.
So, surgery should be done for T4a infra notch pt.

5) Taiwanese study - Clinical outcome of Taiwanese pt with cT4 oral cavity SCC - Liao et al.

492 pt btn 2004-2010 ← 327 - surgery
165 - non surgical

Out of 165 non surgical, 78 underwent salvage Sx.

5 yr DFS ← Surgery - 51%
Non surgery - 38%.

OS ← Surgery - 43%
Non surgical - 27%.

Among T4a who initially received non surgical t/t, subjects who subsequently underwent surgery showed

better outcomes.

So, if possible, offer surgery to all T4a infiltrates.

6) Impact of medical treatments on survival of locally advanced T4a/T4b BM cancers. - Anil D'Cruz

T4a - 135
T4b - 75
Nodal mets in 11% pt
With adequate margins, Local recurrence rate is similar for T4a & T4b (19.3% Vs 22.7%)

Factor affecting DFS & OS → Nodal mets
→ PNI.

7) Orofacial & Mandibular reconstruction with Illiac crest free flap
→ First objective attempt to classify acc. to extent & reconstructive need.

Upper case alphabets denote bony defect
H - Hemimandibulectomy, lateral segment including condyle
C - Central defects, entire anterior segment (2 canine & 4 incisors)
L → lateral defect excluding condyle.

→ - a- ≤ midline of the hard palate
b- Bilateral alveolar Maxilla & hard palate
c- entire alveolar Maxilla & hard palate

So, 8 classes of bony defects are possible three letters
H, L, C, HC, LC, LCL, HCL/LCH, HCH.

Brown modification in 2016 → 4 corner principle

8) Reconstruction of maxilla & midface - James Brown

Classification of maxilla defect

Stressed importance of Free flap in Class III & beyond.
Class 1 → no oro-nasal or oro-antral fistula. Only Palatal bone removed
Class 2 → not including orbital floor or rim
Class 3 → Including orbital floor or rim, with or without skull base
Class 4 → Orbito-maxillectomy
Class 2-4 have horizontal component (a, b, c)*

9) Significance of Margins → Thomas R Loree et al

398 pts
129 with the margins
LR is 2x in pt with positive margins (36 Vs 18%)
Statistically significant difference in 5 yr OS
(60 Vs 52%)

10) Primary Tumor staging for oral cancer & Proposed Modification incorporating DOI
- ICOR study

Retrospective analysis of 3149 pt.
Follow up of 40 months.
DOI added to AJCC.

11) PNI in SCC - Fagan et al.

PNI was significantly associated with local recurrence & disease specific mortality.

Centrifugal & centripetal propagation of tumors around nerves.

PNI nerves < 1mm predicts local recurrence independent of tumor size, adjuvant, margins, LVI.

* 1st to suggest stratification of risk on the basis of PNI
1st to suggest use of Adjuvant Rx in case of PNI.

Adjuvant Rx

1) Post op RT + Surgery Vs Surgery alone
R.C. Mishra et al

Surg - 60 pt
Surg + RT - 80 pt

Significant POOR outcome without RT

2) Bonnen & Cooper trial
EORTC 2931, RTOG 9501

60 Gy 30# 6 week + 3 weekly cisplatin
Variable high risk factors taken - ECE
- R1 resection

EORTC 2931 5 yr estimate (if chemo given or not)
DFS 47% Vs 36%
OS 53% Vs 40%
Local failure → 17% Vs 31%

RTOG 2 yr estimate
DFS 54% Vs 45%
OS - 64% Vs 57%
Local failure → 18% Vs 28%

Basically, ECE & positive margins → Give Chemo..

2) Lisa Licitra - Primary Chemo in resectable oral cavity SCC

145 resectable, T_2/T_4, N_0-2 untreated SCC.

3Q cisplatin + 5 FU f/b surgery Vs surgery alone.

PCR rate → 27%.

But OS was equal in both arms

More mandibles preserved

less PORT requirement

3) Zhong et al → 2 OTPF f/b surgery Vs surgery

Rectal Cancer (Dr Madhu Muralee Sir)

Systemic therapy is more imp in colon cancer
Locoregional therapy (surgery + RT) is more imp in rectal cancer.

- Rectum is 15 cm from anal verge

Imaging

1) TRUS - Diff. betⁿ T_1 / T_2 from T_3 / T_4

Disadvantage - Highly operator dependent
- not useful in obstructing lesion.

2) MRI - nodal status
- CRM
- Adjacent organs
- MERCURY trial

3) CEA

4) Full colonoscopy → Synchronous lesion - 30%. [Polyp/adenoma]
Synchronous cancer - 3%.
If obstructed, full colonoscopy within 6 months.

5) CT Chest + abdomen to look for mets

6) PET CT no role in initial evaluation.

"Surgeon is an independent Prognostic factor for survival"
- Hohenberger et al.

Trials of TME → Dutch trial
German
CORRT
MRC

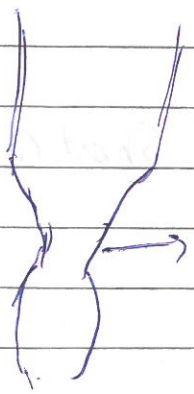
ELAPE → Extra levator APE

Data from Dutch trial showed that pt with AR has lower rates of CRM positivity, lower LR compared to pt with APR.

As distance from anal verge ~~decreases~~ increases, the CRM positivity rate goes down.

Similar finding from German trial.

Morson's Waist → The coning of specimen of ~~APR~~ Conventional APR has a narrowing just above perineal part. It is called morson's waist.



Philip Quincke, a pathologist gave the concept of ELAPE.

Ligation of IMA → Dutch review by Lange et al

↓

No need to do it for Oncological reasons.
But should be done for technical reasons

Extended resections → Multivisceral resection

Outcomes of exenteration → Overall survival - 30-35%.

Neoadjuvant therapy

Historical Trials of Post op Chemoradio therapy [1980s]

1) GITSG
2) NCCTG
3) NSABP R01
4) NSABP R02

Reduces LR by 30-35%. but no impact on OS.

Swedish Trial
Dutch Trial
Norway Trial
MRC Trial
— Short course RT Trial

German trial
NSABP trial
EORTC trial
} → long course ~~chemo~~ RT trial.

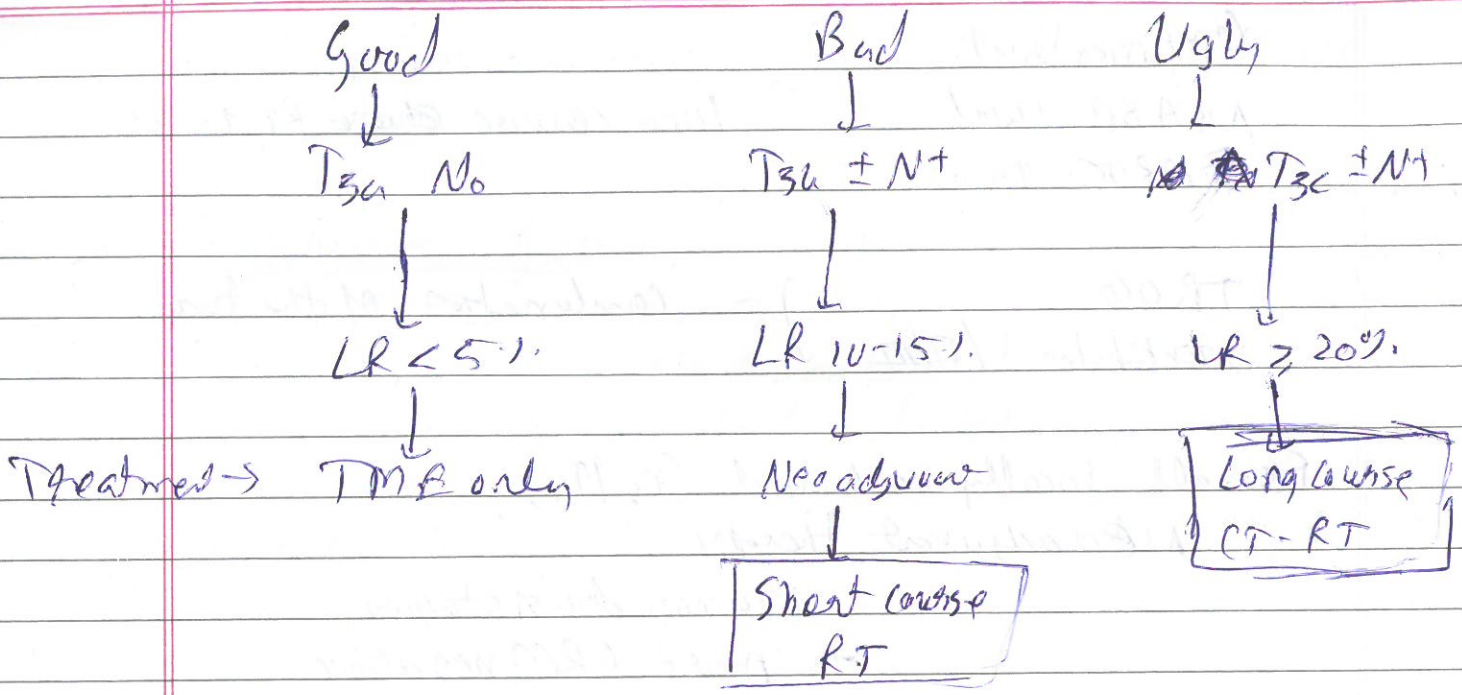
TROG
Stockholm I/II/III
} - combination of the two.

For all locally advanced (T_3 T_4)
NEO adjuvant therapy
→ Tumor down staging
→ More CRM negative.
→ ↓ LR
→ Enhanced Sphincter preservation
→ Lesser toxicity compared to PORT.
→ less long term toxicity.

Short course RT → 25 Gy in 5 #
→ Surgery within 7-10 days.

long course → 50.4 Gy in 25 #
→ Surgery after 6-8 week
→ Adjuvant chemo.

T_{3a} - 1-5 mm ~~of~~ of perirectal fat [Good]
T_{3b} 5-15 mm of perirectal fat [Bad]
T_{3c} >15mm " " , reaching upto 1 mm of CRM [Ugly]



Perioperative issues

Incidence of leak is much higher in a pt who has received Preop RT. Does not differ betn Short course & long course RT.

German trial
MRC
Dutch trial.

If a pt is Post RT, divert. Esp in short course RT.

In terms of anastomosis, there is no difference betn end to end & end to side anastomosis.

Sphincter Preservation rate increases by 20% in Pre op Chemo RT → German Trial.

MD Anderson data

Distance from verge	Sphincter Preservation rate
3 cm	1%
3-4 cm	10%.
4-5 cm	20%.
6 cm	42%.

Response to Chemo RT	Sphincter Preservation
Complete	72%.
Partial	67%.
No response	30%.

MIS in Rectal Cancers → COST, COLOR, CLASSIC Trial for colon.

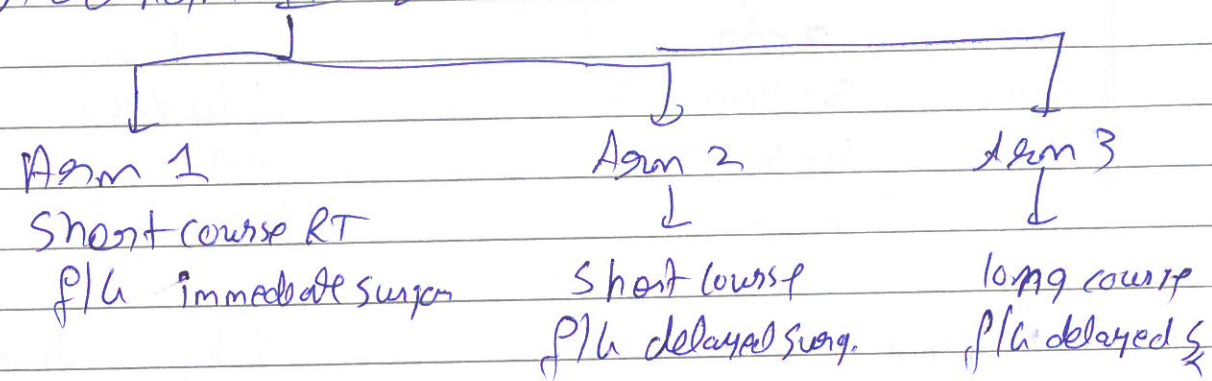
ACOSOG & ALaCaRT Trial showed MIS to be INFERIOR to open surgery in Rectum.

Margins in Rectal Cancers → In preoperatively radiated patients, just negative margins should suffice. Intra op frozen should be done. 1 cm is also not needed.

Oligomets

Rectum → Chemo RT + Surgery
Liver → Surgery + Chemo

Stockholm III trial



Arm 2 showed results as good as other two.
So, sequence in these pt is

Chemo RT (short course) → Liver resection → 6-8 weeks
→ Rectal resection → Adjuvant chemo.

This sequence came after Stockholm III trial.
Before that, long course RT was used.

Wait & Watch??

Halan Gema Protocol

In the Halan Gema institute data, LR rate was 3-4%. But in other institutes, the rate was 25-40%. (~ 33%)

Review article in Clinics of North America

→ Until long term durability of non-operative approach is proven, Surgery is standard of care.

Chemo Radiation in Ca Rectum

Recurrence in colon cancer is more common in distant organ, than local. Usually occurs in 2yr of surgery. So, in colon, main Rx affecting OS is systemic.

In rectum, local recurrence is a significant problem since it is in narrow pelvic cavity, so margins are not always found. Adjuvant chemo doesn't increase OS in rectum.

Issues in Tt of Ca Rectum

- Local control
  - Distal tumor free
  - CRM negative
- Quality of life
  - Stoma-free survival (sphincter preservation)

Improvement of local control → Surgical technique
→ Multimodality approach.

* In low or average grade tumors, spread beyond 2cm occurs in only 10% pt.
Even in poorly diff cancers, it is <10%.
So, distal margin can be <2cm.
But extra mural spread can be >4cm. So, TME is necessary.

A CRM ≤2mm is considered close or positive.

Multimodality approach needed for $T_3/T_4 \pm N_1$

Preoperative therapy

Timeline of development:

Pre op Short course RT + Surgery Vs Surgery alone

↓

Pre op short course RT + Surg Vs Long course RT + Sx

↓

Pre op RT + Sx Vs Chemo RT + Surg.

Short Course RT trials

1) Swedish Rectal Cancer trial

Respectable Rectal Cancer

	25 Gy/5 #	Surgery (TME not done)
LR →	~~9~~ 11%	27%
OS →	58%	48%

2) Dutch trial (CKVO 95-04) → Same design, but TME done.

LR →	5.6%	10.9%
OS →	82%	81.8%

~~Add~~

★ No other trial had significant improvement in OS, except Swedish trial. May be attributed to more number of absolute reduction of LR.

∴ Preop Short course RT → Reduces LR
→ No effect on OS if TME is performed
→ No effect on rate of sphincter preservation.

Is there a benefit in delaying surgery after NA SCRT?

Pach et al study → Preop RT (25 Gy/5#)

7-10 day → TME

4-5 weeks → TME

LR →	=	No difference
5 yr OS	→	"
Sphincter Preservation	→	"
Downstaging	→	44% 13%

Preop SCRT Vs Long course RT

Stockholm III trial → 3 arms

- SCRT f/b early S
- SCRT f/b delayed S
- Long course f/b surgery

Interim analysis (2010) → Sphincter preservation in higher number of pt in Long course.

Post op complications is lesser in long course.

Final data (2017) → No diff in LR
→ significant ↓ in complication in long course.

∴ long course is better.

Comma et al Meta-analysis
(Pre op RT)
→ Biggest impact on local control
→ slight improvement in OS.

Pre op RT Vs Chemo RT

1) Polish trial → 316 pt

RT (SCRT)	Chemo RT (long course)
↓	↓
Sx within 7 day	Sx after 4-6 wk.

LR →	14 %	9 % (not significant)
OS →	66.2 %	67.2 % (NS)
pCR rate	1 %	16 % (significant)

2) FFCD 9203 742 pt

RT (long course)	Chemo RT (long course)

LR →	16.5 %	9.1 % (significant)
OS →	55.6 %	58.4 % (NS)
pCR →	3.6 %	11.4 % (significant)

Toxicity higher in Chemo RT.

∴ Addition of chemoRT improves loco regional control
chemo DOES NOT improve Sphincter preservation rate
pCR improves significantly.

Pt with Tumor Regression Grade (TRG) 4 had better Prognosis. Multiple RCTs have correlated TRG with OS & DFS.

In German trial, 5yr DFS & Mets free survival increases with improving TRG, but has no effect in local recurrence.

So, pCR has little effect on local control but certain have effect on distant failure.
Suggest that pCR is an indicator for sensitivity of disease to chemo.
So, these pt are also benefitted more by adjuvant chemo

Pre OP CTRT Vs Post OP CTRT

German Trial → T3/T4 & N1

- Pre OP CTRT → TME → 4 05FU
- TME → Post OP RT + 5 FU (in wk 1, 5) → 4 05FU

Better compliance with Pre OP ✓ 90% Pt completed tt
Post OP → 50% only.

Grade 3/4 side effects were lower in Pre OP arm.

Local recurrence was significantly lower in pre op arm.
* More sphincter preservation in pre op arm *

↓

The only trial to report sphincter preservation in pre OP NACT-RT.

DFS & OS were similar.

→ Randomized Phase 3 trial using capecitabine Park et al
* No diff in DFS, OS, LR (same design as German trial)
* more sphincter preservation in pre OP NACT-RT group.

Summary

* Rectal tumors downstaged, ↑ pCR with NACT-RT
* Sphincter preservation may improves only in German trial. Not in other trials.
* Though all trials show ↑ OS, but it is not significant
* NACT RT ↓ risk of LR, but has no effect on mets.
* Increased Grade 3/4 toxicity in NACT-RT (except in german trial)
* Compliance is better.

classmate
Date
Page

Indication - T3/T4
- Node positive
- Distal rectal tumor close to sphincter where APR is only option
- Tumor free CRM is doubtful.

5FU Vs Cap

NSABP R04 → Similar efficacy with better tolerability

5FU + Oxaliplatin

STAR 01
ACCORD
NSABP R04
} - No advantage, ↑ toxicity.

RT dose 45 Gy Vs 50 Gy

STAR 01
ACCORD
} 50 Gy better result ∵ ↑ pCR

Timing of Surgery after RT

Gastro intestinal cancer Symposium data

When surgery is performed within 60 days, there is no diff in OS.
If delayed, it ↓ OS.

Can we avoid surgery ?

GI cancer Symposium - In Pt ∘ cCR
- 74% have no evidence of DZ at 4 yrs.
- Need to be followed up regularly
- Salvaged by surgery successfully

* Salvage surgery has LR rate of 1.5%.
- Similar OS
* Rectal preservation is also possible.

Neo adjuvant Rx for Ca Rectum [Up to Date]

Indications → The only definitive indication for neo adjuvant Rx is a cT3/T4 disease. These patients, if operated up-front, will need Post operative chemoradiotherapy, and as shown in German Rectal cancer Group study, Pre op CT-RT is better than Post op.

cT3N0 tumors → Due to limitation of current imaging, we consider all patients with cT3N0 as candidates for NACT-RT. Based on MRI, we can study the extra mural Penetration. Studies have shown the Extra mural Invasion [EMI] >5mm is associated with higher rate of nodal involvement & lower rates specific survival. ↳ Quircke etal

Updated ESMO guidelines state that < 5mm EMI can be taken for surgery directly.

Sub classification of T3 disease based on MRI →
[MERCURY study group]

→ T3a → <1mm EMI
T3b → 1-5 mm
T3c → 6-15 mm
T3d → >15 mm

Relative indications → ① T_1/T_2 with node positive
Determination of node positivity on MRI/EUS is difficult. 15-42% rectal cancers have <5 mm mesorectal nodes containing cancer.
[D worsak O].

New staging recommendations of node are as follows
- Any lymph node with short axis ≥ 9mm
- 5-8 mm node with atleast two morphologic criteria
- <5 mm and all three morphologic criteria.

Morphologic criteria → Round shape
→ Irregular borders
→ Heterogenous signal intensity

→ ② Mesorectal fascial involvement
Neoadjuvant CRT may be considered if pre-op staging suggests threatened CRM.
Anterior tumors → EUS or MRI can predict CRM
Posterior tumors → MRI

NACT-RT can be given in these patients to improve rates of negative CRM

→ ③ Distal tumors → Distal tumors need an APR.
So, T_3/T_4 distal tumors can be given NACT RT to attempt to preserve sphincters. However it has not been definitely proven in studies.

Approach to Neoadjuvant Rx

$T_3 N_{0-2}$ → If CRM is clear, short course RT can be considered. However, standard is fluoro Pyridine based long course RT.

Any bulky disease / T_4 → long course CRT on Total neoadjuvant therapy, esp if mesorectal fascia is involved, or clearly node positive or low lying rectal tumor.

TNT is associated with ↑ compliance to chemo, improved local control and ability to consider non operative Mx, should pt refuse surgery.

* $T_3 N_0$ pt who would require an APR or very low coloanal and anastomosis, the decision to pursue TNT for organ preservation is NOT a standard of care.

If TNT is chosen & chemo initiated first, follow up scan to be done in 2 months & look for response.
For non responders, long course CRT started immediately.
Oxaliplatin based chemo should be used i.e FOLFOX or FOLFIRINOX (as used in PRODIGE 23 trial)

Long course RT + Chemo → Trials for adding chemo
1) FFCD 9203 → ↑ DFS, ↓ LR, ↔ OS, ↑ toxicity
2) EORTC 22921 → Downstaging
3) EORTC GIT cancer cooperative group

Downstaging of tumor, better local control was observed.

Pre operative Vs Post operative therapy

German Rectal Cancer study group

	Pre OP →	Post OP	
5 yr Pelvic relapse	6%	13%	
10 yr "	7%	10%	
5 yr DFS	68%	65%	(not significant)
OS	76%	74%	
* Sphincter preservation	19%	39%	*

* Prognosis was related to final T stage & number of involved nodes. These were studies of German trial data.

- Rödel et al - Impact of TRG

TRG	DFS 5 yr
4	86%
2+3	75%
0 / 1	63%

- Fokas et al → TRG & ypN+ status are predictors of distant mets
  Local recurrence is affected by ypN status & lymphatic invasion.

Patients with ypN2 had poor outcomes & it makes them candidate for expanded post operative chemo.

Other trials

1) NSABP-R03 →

Pre OP → ~~weekly 5FU bolus~~ 5FU + Leucovorin on 1st & 5th week of RT
f/b TME f/b 4 Q Adjuvant

Post OP - Surgery + weekly bolus 5FU + leuco 1 cycle
+ 2 Q chemo + RT f/b 4 Q weekly adjuvant

	Pre OP	Post OP
PCR	15%	-
DFS	65%	53%
OS	75%	66% (Not significant)

No difference in LR rates.

2) Korean trial → Capecitabine was used (1650 mg/m²)
In 240 patients, cT3 or N+
pCR - 17%
DFS, LR, sphincter saving rates were similar.
In pt ↑ low lying tumors, sphincter preservation was higher (68 Vs 42%)

Timing of surgery → Traditionally, interval betn conventional fractionation RT & surgery is 6 weeks.

A tumor size of 54 cm³ would take 20 weeks to regress to 0.1 cm³ (Regression of rectal cancer with radiotherapy with or without concurrent capecitabine. Dhadda AS et al).

Trials for time interval

1) GRECCAR 6 → Two groups

	7 week	11 week
pCR →	15%	17.4%
Morbidity →		More
CRM negative →	90%	78.7%

∴ No benefit of waiting beyond 7 week.

2) ~~S~~ STARRCAT trial → Same conclusion

3) Lyon R90-01, 17 year follow up
   → Duration has no impact on survival
   → Radiation did not impact LR

Conclusions from meta-analysis

1) longer interval (>8 week) may have greater pCR rates, but no impact on survival, Ro rate or sphincter preservation

2) Reduced distant mets with improved pCR but no impact on LR

Complications

Pre operative CTRT does not increase complication rate (German Trial, Enker WE et al, Roh MS et al)

Data from GRECCAR6 trial suggest Perioperative complication rate may be higher in those who undergo delayed surgery at 11 weeks.

Late adverse effects of RT

1) Multimodality therapy negatively affects anorectal function after TME. Fecal incontinence occurred more in irradiated patients, and manometric results are worse compared to those undergoing TME alone

[Meta analysis - Effect of Pre Op Radio (chemo) therapy on long term functional outcome in rectal cancer patients Moos et al].

2) Risk of sexual dysfunction in patients undergoing treatment for rectal cancer, more in pt with APR compared to LAR. Individual role of surgical technique or RT is unknown.

3) Sacral insufficiency fractures are uncommon late complication of RT.

Choice of Chemo → Infusion 5FU, on days when RT is delivered, over 5 days, rather than bolus 5FU
Daily capecitabine is an acceptable alternative.

Addition of oxaliplatin is not yet of standard approach

Trial for capecitabine → German Phase III trial
5 yr OS is non inferior [76% Vs 67%]
3 yr DFS " [75% Vs 67%]
Similar local recurrence
Fewer pt had distant mets in capecitabine group
↳ Also, NSABP-R04

Trial for oxaliplatin → NSABP R04 - negative trial.
No difference in efficacy
Higher toxicity.

RT dose → 50.4 Gy in 25 # @ 1.8 Gy/day

Short Course RT

Trials → Swedish Rectal Cancer trial
- Showed improvement in DFS & OS
- But adequate surgery (TME) carry not done in "surgery only" arm.
- Higher rates of complications.

→ MRC trial - Decreased LR
Increased DFS
Similar OS
Those who received pre op RT had greater degree

of sexual dysfunction. This trial had a large number of Stage I patients (315) and inadequate TME was done.

→ Dutch trial → 1861 patients. < TME
SCRT f/b TME.

✓ ↓ 5yr local recurrence rate (5.6 Vs 10.9%)
Similar 5yr OS
more perineal wound problems following APR
" sexual dysf"
" anal incontinence
" anal blood loss.
" problem ē erection.

Short course Vs long course RT + Chemo

i) Polish trial → PCR rate higher in long course
Fewer rates of involved CRM
Similar rate of sphincter preservation
Early radiation toxicity higher in CRT
late toxicity, LR, DFS similar.

ii) Trans Tasman Radiation Oncology Group (TROG) 01.04 trial
326 pt to SCRT or CRT.
SCRT pt received Post op 60 Adjuvant chemo
CRT " 40 " "

CRT → lower recurrence, not significant
No diff in distant recurrence, OS, grade 3/4 toxicity

Timing of surgery after SCRT

Standard is 7 days, as used in Swedish trial, MRC trial, TROG trial

Dutch trial has 21 days.

Delay to 4-8 weeks?

⇒ Stockholm III trial

840 pt

	SCRT f/u	SCRT f/u	long course RT f/u
[129 pt]	1 week surgery	4-8 weeks (128) surgery	delayed surgery (128)
	~~(318)~~	~~(285)~~	~~(94)~~
PCR	0.3%	10.4%	2.2%

PCR is associated with superior OS.

No chemo in long course RT arm

~~Radical arm~~

~~Palliative arm~~

Median time to LR	33.4 month	19.3 month	33.3 month

Primary end points → local recurrence

Total Neoadjuvant therapy (TNT)

In pt with bulky tumor (T4), or where there is a high risk of margin positivity, or those who are clearly node positive and low lying rectal tumor. TNT can be given

TNT → Oxaliplatin based chemo f/b long course / short course CRT.

It is associated with increased compliance to chemo, improved local control and ability to consider non operative treatment.

For T3N0, that is low lying, and would require APR or low colorectal anastomosis, TNT for organ preservation is not yet standard.

If chemo is initiated first, then restage scan should be done in 2 months. If no response, proceed directly to CRT. This is esp imp in tumors with deficient mismatch repair/ High MSI, as they may be resistant to NACT [Cercek A et al]

Chemo → FOLFOX or FOLFIRINOX [used in PRODIGE 23]

Rationale is to add chemo to neoadjuvant RT to improve rates of resectability & pCR (Cercek A et al
Garcia-Aguilar J et al
Petrelli F et al)

Preliminary data from OPRA trial suggests that increasing duration btw RT & surgery may be a mechanism for benefit of TNT, esp when long course CRT is used

classmate
Date
Page

TNT with long course RT

PRODIGE 23 → 461 pt with T_3/T_4 < 15 cm from anal verge

3 months of FOLFIRINOX f/u Long course CRT + Capecitabine f/u 3 month adjuvant FOLFOX/CAP	long course CRT f/u 6 month adjuvant (FOLFOX/CAP)
42 % pt completed all therapy	69 % pt received & 75 % of those completed it.
pCR → 28 % 3 yr DFS → 76 % [Significant]	12 % 69 %.

OS results not yet matured.

Further support is given by MSKCC retrospective cohort analysis. Greater % pt who received TNT completed all courses. pCR rate was NOT significantly different but "complete response rate" (pCR & cCR in those who did not undergo surgery for 12 months) was higher in TNT group.

Rate of non operative treatment was higher.

TNT with Short Course RT

1) Polish II trial → Short RT f/b FOLFOX4 x 3 months
Vs
long course CRT + oxaliplatin + Bolus FU + LV

Pre OP toxicity rates are lower in short course arm, but no diff in pCR, complete resection rates.
long term survival also same.
But regimen in control arm is NOT standard.

2) RAPIDO trial → 920 pt with T4 b/l disease, Extra mural venous invasion, cN2 disease, involved meso rectal fascia or enlarged lateral nodes

Short course RT f/b CAPOX/FOLFOX [18 wk]
Vs
long course RT + cap f/b adjuvant FOLFOX/CAPOX

PCR rates higher in short course arm [28% Vs 14%]
3 yr DFS higher, 3 yr rate of mets lower.

If TNT is used, induction chemo should be limited to 4 months and adjuvant chemo omitted.

* Chemo given either before (induction) or after (consolidation) CRT.

Alternative Strategies

(i) Non operative management → 2020 NCCN guidelines state that those with cCR to TNT, no clu disease on DRE, MRI or colonoscopy, non operative management can be considered.

Modern induction chemo + CRT can offer pCR rates of 16-27%

i) OPRA trial → Organ preservation of Rectal Adenocarcinoma
324 pt, stage II/III
↓
* 4 month FOLFOX + long course CRT
↓
cCR after 8-12 weeks? [MRI, DRE, Sigmoidoscopy]

4 month FOLFOX may given either before or after CRT.

Yes → Watchful waiting

NO → TME.

Consolidation arm had more pt with cCR.
Organ preservation — Induction arm - 43%.
consolidation - 58%.

ii) meta analysis by Dossa F et al → Total 23 studies, none of them randomized trials, total 1967 pt

Overall, local recurrence rate for wait & watch is 15.7%

95.1% pt with local recurrence underwent salvage R.
Sphincter preservation observed in 49.3%.

8 studies in the meta analysis compared wait & watch with patients who underwent radical surgery with a cCR or pCR.

NO significant difference in Distant recurrence
cancer specific mortality
OS

But pts in W&W had poorer DFS

Two studies showed that pt with local recurrence, have a higher rate of distant mets & survival was inferior.

So careful examination will reveal the pt in whom W&W can be tried, but there is no randomized trial to prove.

* multiple trials are underway that use accurate pelvic MRI staging at baseline & predefined criteria for cCR.

Local excision after CRT - Transanal endoscopic surgery after NA-CRT will have low pooled recurrence rate (4%) in pCR is achieved [Hallam S et al] but LR rate >20% if any residual tumour is (+)

Trials 1) GRECCAR 2 trial - 186 pt, T2-3, N0-1 low rectal cancer (≤8cm from verge), size ≤4cm received NA-CRT

↓

148 pt had good response (residual tumor ≤2cm)

TME LE

LE < Trans anal excision – 72%.
TEM – 28%.

pt who had ypT2-3 / R1 resection after LE were offered TME.

Result → Morbidity & organ preservation in LE is same as TME. LE is oncologically safe

2) CARTS study → 55 pt ≥ T1-3 No rectal cancer underwent long course NA-CRT
↓
6-8 weeks
↓
Those with significant downsizing underwent TEM

3o patients (55%) pt were ypT0-1 & needed no further surgery. In 12 months, one pt out of thirty developed LR & underwent TME.

At 5 yrs, rectum was preserved in 64% of these 55.
5 yr LR rate → 7.7%
5 yr DFS rate → 81.6%
" OS " → 82.8%

In conclusion, local excision for ≥ T2 No should only be used for grossly unfit patients or in the setting of a clinical trial.

Tumor Response assessment → MSKCC classification

	Complete	Near complete	Incomplete
Endoscopy →	Flat, white scar	Irregular mucosa	Grossly visible tumor
	Telangiectasia	small mucosal nodules	
	No ulcer	Superficial ulceration	
	No nodularity	Mild erythema	
DRE →	Normal	Smooth induration	Palpable nodule
MRI →	Only dark T_2 signal	Mostly dark T_2	More intermediate
	No intermediate signal	Some intermediate	than dark T_2
	AND	AND/OR	No progressed LN
	no lymph node.	Partial LN regression	
	No visible tumor on	Significant regression	NO significant
	DW-MRI.	of signal on DW MRI	regression on DW

Only those pt with cCR in these criteria are eligible for W&W.

However in MSKCC data, 75% with cCR has residual tumor on HPE.

∴ No imaging modality (EUS, MRI, PET, DRE, Endoscopy) can accurately predict pCR

MRI + DRE + Endoscopy is used. When MRI is used, TRG is a part of evaluation

Definitive RT → Doses must be escalated to achieve complete tumor control.
EBRT + endocavitary RT + interstitial brachyRT is used.

Aumock A et al Study on 199 pt c localized tumors T1-3 N0-1 tumor treated.

Local control c RT alone → 71%.
" " RT + salvage S → 81%.
Tumor size & mobility were independently associated c outcome.
Mobile T1 → 100% local control, 100% 5yr DFS
" T2 → 85% " , 90%.
All other → 56% " , 67%.

Hakan Gunn Study for WSW

70 pt c distal rectal cancer
↓
69 concluded CRT (5FU/Leuco + 54 Gy)
↓
Reassessment at 10 weeks
↙ 22 (32%) incomplete response & early progression
↘ 47 (68%) cCR
↓
34 sustained cCR
↓
35 pt (51%) had no surgery!
↙ 4 late recurrence
Surgical.

Surgical Principles in Ca Rectum

Distance from anal verge	Part
0 – 4 cm	Anal canal
4 – 8 cm	Distal rectum
8 – 12 cm	Middle "
12 – 15 cm	Upper "

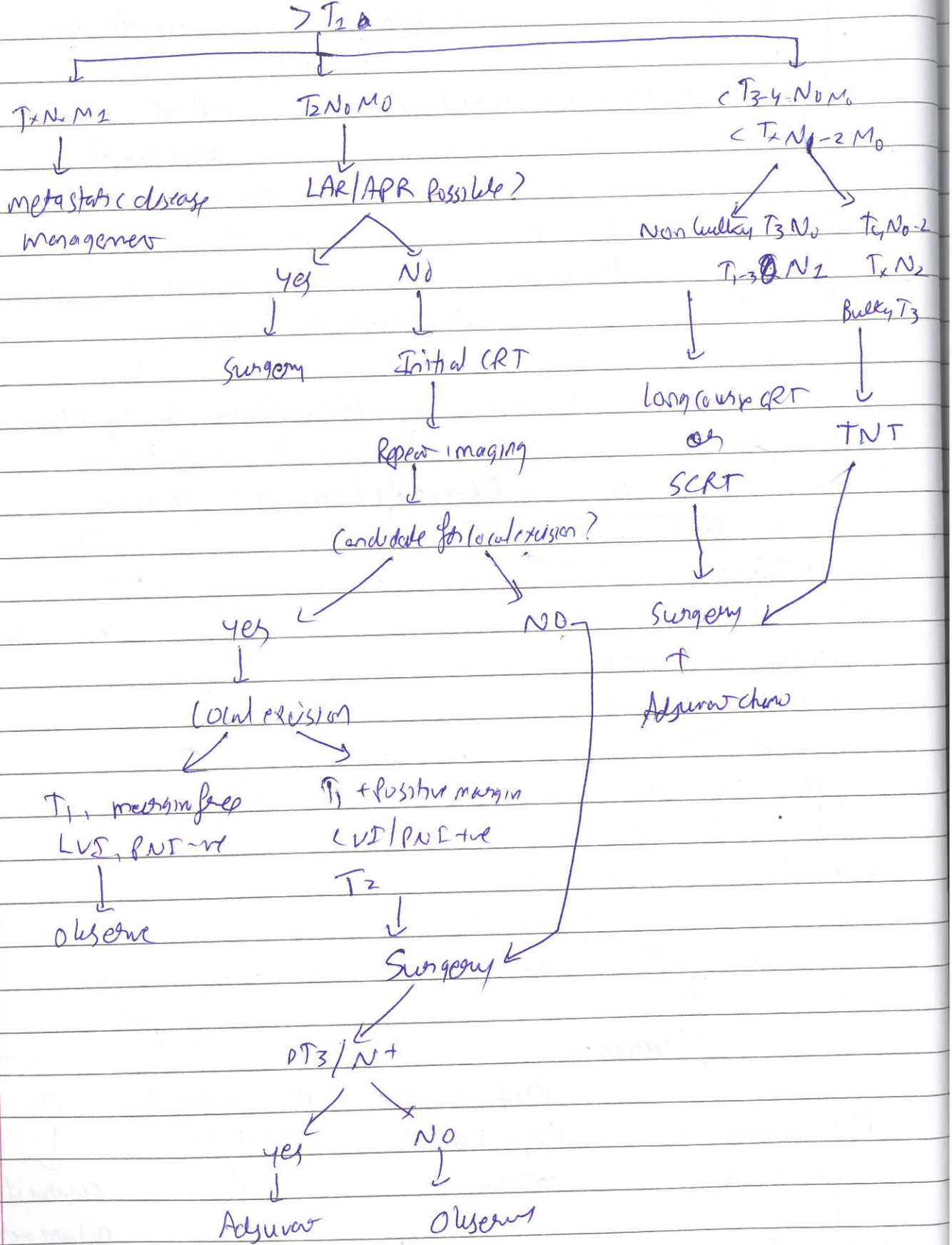
Approach to Ca Rectum

Endoscopic biopsy / Polypectomy showing adeno Ca

↓

Pelvic MRI / EUS + CT thorax

- cT1N0M0
  - Polyp meet criteria for Polypectomy alone?
    - Yes → Nothing else
    - NO → Amenable to local excision?
      - yes → Local excision
        - → pT1, margin -ve, no LVI or PNI → Follow up
        - → pT1 + margin ⊕ / pT2, LVI/PNI → CT thorax
          - → NO mets → Is pt candidate for trans abdominal surgery?
            - yes → Surgery
            - NO → Adjuvant RT/CRT
      - NO → Transabdominal Surgery
        - pT1, margins free, no LVI/PNI → observe
        - pT2 → Observe if no lung mets
        - N1 → Adjuvant Rx
- > T1 (next page)


> T2 a
T×N×M1
metastatic disease management
T2N0M0
LAR/APR Possible?
yes
No
Surgery
Initial CRT
Repeat imaging
Candidate for local excision?
yes
No
Local excision
T1, margin free LVS, PNI-ve
observe
T1 + positive margin LVI/PNI+ve T2
Surgery
pT3/N+
yes
No
Adjuvant
observe
< T3-4 N0 M0
< T× N1-2 M0
Non bulky T3 N0
T1-3 N1
T1 N0-2
T× N2
Bulky T3
long course CRT
or
SCRT
TNT
Surgery
+
Adjuvant chemo

Criteria for endoscopic Management of Polyp

* If it is excised completely & submitted (pT1)
* It is possible to determine depth of invasion, grade, completeness of excision
* Not poorly differentiated
* NO LVI/PNI
* Margins are free
* No invasion beyond submucosa
* Not a sessile polyp.

Criteria for local excision

* Within 8cm of verge
* Superficial T1, limited to submucosa
* No mets to regional nodes
* Tumor <3cm in diameter
* Well differentiated, no LVI or PNI
* <30% lumen circumference
* Mobile, non fixed
* Clear margins
* Compliance & Part of surveillance

* Those who receive full TNT (4 months induction chemo) do not receive adjuvant chemo.

Resection margins

* Proximal margin of 5 cm is required to remove draining lymphatics and assure anastomosis to a well vascularized bowel.

* Distal margins should be histologically negative. Positive distal margin is associated with 40% LR rate and ↓ 5 yr OS, even c TME ± RT

* Minimum distal resection margin

For cancer located above distal mesorectal margin, the minimum negative distal margin is 2 cm for most sphincter sparing procedures.

For cancers at or below the distal mesorectal margin, 1 cm is acceptable, esp after NA-CRT.

Meta analysis of pt who underwent sphincter saving surgery c TME and/or RT, ≤ 1 cm distal margin DID NOT have LR rates greater than those c greater margins [Fitzgerald et al]

Pt who did not receive TME/RT had higher LR if margins were < 1 cm.

Inherited Colorectal Cancer Syndromes

There are three classes of genes involved in cancer
1) Proto-oncogenes
2) Tumor suppressor genes
3) Genes maintaining genomic stability.

(1) Classic Chromosomal instability.
* Inactivation of Wnt signalling pathway *.

Biallelic inactivation of APC gene.
↓
Removal of protein that binds to β catenin.
↓
Increased β catenin intracellularly
↓
Increased growth of cell.

Similar effect can also occur with stabilizing mutation of β catenin, making it resistant to degradation.

Normal cell → APC/β catenin mutation → Small Adenoma → CDC4/CIN KRAS/BRAF → Large Adenoma → P13KCA/PTEN P53 → Carcinoma

(2) CpG island methylator Phenotype [CIMP]

The second pathway involves inactivation of tumor suppressor genes through hypermethylation of gene Promoters.

This Process is otherwise Physiologic, but in these cases, it gets accelerated.

The excessive Promoter methylation occurring in CpG islands is called CpG island methylator Phenotype.

Usually, it happens in association with a mutation in BRAF gene and it is associated with more aggressive & lethal CRC.

Tumors of this pathway arise as Sessile Serrated Adenoma, so this is also called Serrated Carcinoma Pathway. They occur more in Proximal colon.

(3) Microsatellite instability

This is a secondary consequence of either CIN or CIMP.

During DNA replication, DNA Polymerase are prone to errors while copying the correct number of nucleotides. DNA Mismatch Repair system identifies these errors & removes faulty sequences.

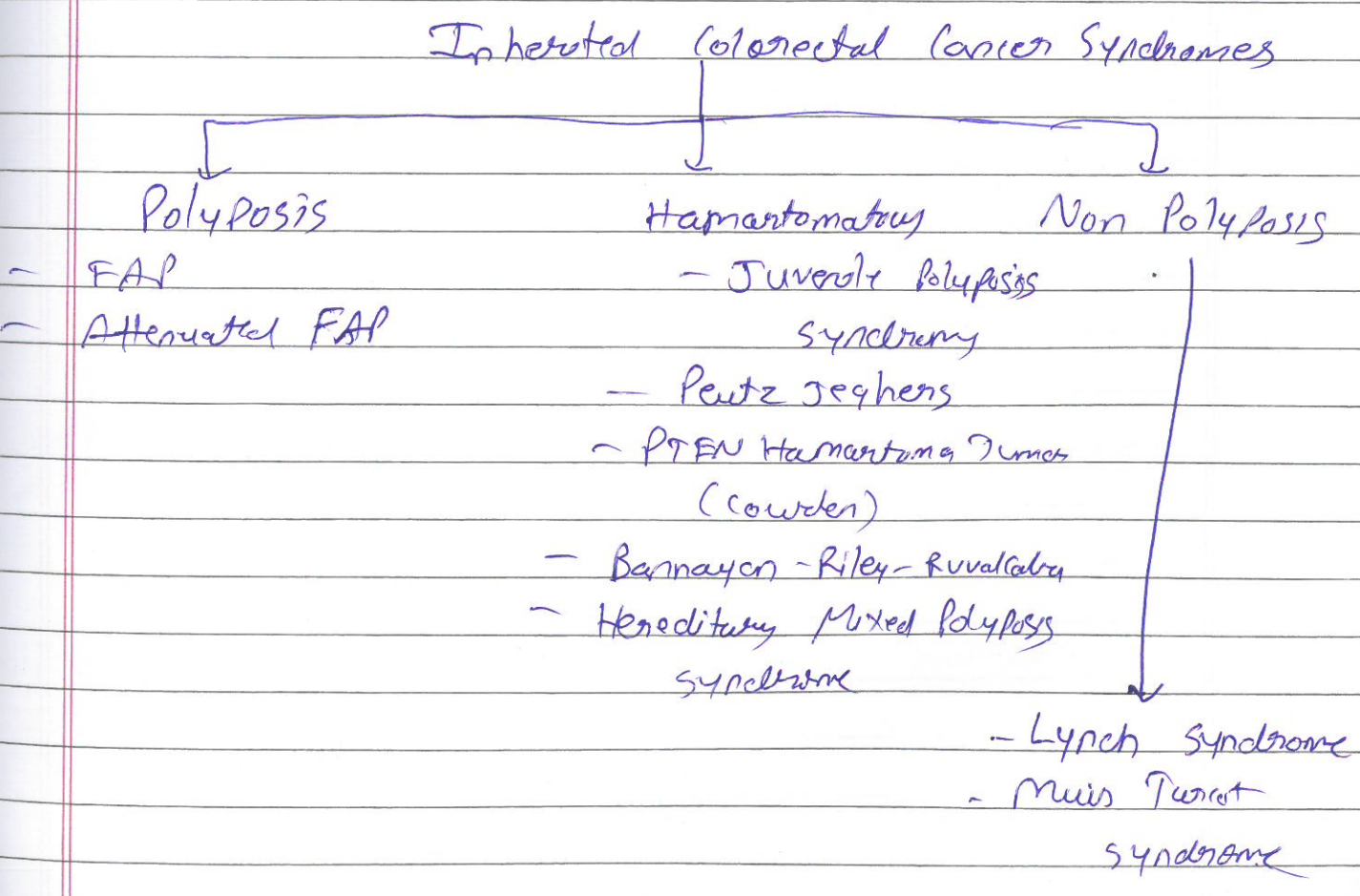
In the absence of DNA MMR Pathway, there is a high Probability of faulty DNA being incorporated in the cell.

CRC & MSI can occur in three circumstances

1) 12% of all CRC begin as CIMP tumors but when methylation occurs at both alleles of one of the DNA MMR genes, MSI ensues & overwhelms CIMP background.

2) 3% of all CRC occur in the setting of Lynch syndrome of which, most have MSI.

3) A very small proportion of CRCs begin in the CIN pathway and develop bi-allelic mutations of the DNA MMR genes, after which, MSI ensues. This is a "Lynch-like" syndrome.



Neuroendocrine Tumors of GI tract

Neuroendocrine neoplasms are defined as epithelial neoplasms with predominant neuroendocrine differentiation.

Gastroenteropancreatic (GEP) NETs have two major categories

① Well differentiated → solid, trabecular, gyriform, or glandular pattern.
- → Uniform nuclei
- → Salt & Pepper chromatin
- → Finely granular cytoplasm

② Poorly differentiated NE carcinomas → All are high grade carcinomas that resemble small cell Ca or large cell Ca of lung.

* A small subset of high grade Neuroendocrine NEOPLASM are well differentiated. The clinical behaviour of these neoplasms is between that of grade 1 or 2 NETs and Poorly differentiated NECs. They are called "NET G3"

WHO Classification of GEP neoplasms

	Differentiation	Grade	Mitotic rate (Per 2mm²)	Ki-67 Index (%)
NET G1	Well	low	< 2	< 3
NET G2	Well	Intermediate	2-20	3-20
NET G3	Well	High	> 20	> 20
NEC (Small cell)	Poor	High	> 20	> 20
NEC (Large cell)	Poor	High	> 20	> 20
MiNEN	Well / Poor	Variable	Variable	Variable

MiNEN → Mixed Neuroendocrine - Non neuroendocrine neoplasm.

In most MiNENs, both neuroendocrine & non neuroendocrine components are poorly differentiated, neuroendocrine component has proliferative indexes in the same range as other NEC.

* Poorly differentiated NEC cannot be graded, but are considered "high grade" by default.

Pathological finding → Well differentiated NETs have "organoid" arrangement of cells
→ Abundant neurosecretory granules, stain strongly to chromogranin & synaptophysin.
→ may secrete specific bio-amines like insulin, glucagon, VIP, somatostatin etc.

→ Amyloid deposition indicates insulin secreting PNET
→ Glandular architecture with abundant psammoma bodies seen in duodenal or ampullary somatostatin secreting NET

Staging → European NET society (ENETS) proposed a staging scheme ~~[illegible]~~, which could be applied to all disease stages.
This histological grading scheme uses only proliferative rate to stratify the grades & requires both mitotic count & Ki67 index to be measured.
If there is discordance, then the higher of the two indices is used.

AJCC has separate staging systems for all organs.

TNM for Pancreatic NET

T_1 - Tumor limited to pancreas, < 2cm

T_2 - " 2-4cm

T_3 → " >4cm, or invading duodenum or CBD

T_4 → Tumor invading adjacent organs or wall of large vessels (celiac / SMA)

N_0 → No LN

N_1 → LN (+)

M_{1a} → Mets only to liver

1_b → Atleast one extra hepatic site

1_c → Both hepatic & extra hepatic.

⇒ High grade, Poorly differentiated NEC

- There are small cell & large cell variants of NEC

- Cut off is Ki 67 > 20%
  Mitotic rate > 20/2 mm²

88% these pt have distant mets or LN mets & Median survival is 11 month.
5 yr OS → 16.1%

Treated by Platinum based chemo.

In 40% cases, poorly differentiated NEC contain non-neuroendocrine component.

* If a neoplasm has a neuroendocrine component & a gland forming component, both exceeding 30%, the 2019 WHO classification calls the MiNEN. Previously they were called Mixed Adenoneuroendocrine Carcinoma (MANEC).
At present, these tumors are treated like Pure NEC.

⇒ High Grade, Well differentiated

These NET G3 are less likely to respond to Platinum based chemo, compared to NEC.
Generally, these do not progress to NEC.

Diagnosis of Carcinoid Syndrome & localization

Carcinoid syndrome manifests due to release of serotonin & other vasoactive peptides into systemic circulation
Primarily associated with midgut tumors (distal small intestine, proximal colon).
Hindgut & foregut (including lung) rarely produce it.

Biochemical testing for carcinoid Syndrome

Presence of carcinoid syndrome is considered when pt have otherwise unexplained severe diarrhea and/or flushing.

Apart from well differentiated NETs of GI tract, well diff. NET of Pancreas may cause severe diarrhea like gastrinoma or VIPoma.

1) Urinary 5-HIAA → Useful initial diagnostic test.
5 HIAA is the end product of serotonin metabolism.
Sensitivity & Specificity of 90%.

Tryptophan / serotonin rich food must be avoided 3 day prior to the test, to prevent false +ve.

Most useful in pt of midgut carcinoid.
Foregut & Hindgut lack the enzyme dopa decarboxylase, hence cannot produce serotonin. These tumors produce 5-HT, but there is no testing for it.

In carcinoid syndrome, Urine 5 HIAA ranges from 99-2070 mg/day

2) Urinary excretion of Serotonin - It is useful in a pt of foregut NET with carcinoid syndrome as they don't produce 5 HIAA.

3) Chromogranin → Chromogranins (CgA, CgB, Cg C) are proteins that are stored & released with peptides & amines in a variety of neuroendocrine tissues.
It increases with increase in tumor burden.
CgA is more sensitive than CgB & CgC.

In general, CgA is nonspecific marker of NET.
There is no fixed cut off for diagnosis. False Positive can occur in pt taking PPI. Also in conditions like hyperthyroidism, hyperParathyroidism, MTC, Pheochromocytoma, Chronic atrophic gastritis, Chronic hepatitis, Ca colon, IBD, IBS, Pancreatic adenoca, pancreatitis.

Therefore, it is not recommended as a screening test, but in patients of established diagnosis, to look for tumor Progression, response to Rx or recurrence.

4) Blood Serotonin concentration → Not a standard dynostic test.

Tumor localization & Staging

① CT Scan → CT scans are recommended for all types of NET except tumor with low probability of spread such as type 1 or type 2 gastric NET or T1 rectal NET.

Most NET liver mets are hypervascular, but 6-20% are hypovascular. Liver mets enhance during arterial phase & washout in portal phase

The ability of CT to localize the site of primary tumor in pt i. carcinoid is variable

→ NET originating in Jejunum & ileum are difficult to identify coz of small size. Arterial phase might help. Small intestinal NET often produce mesenteric masses with fibrosis. Classic finding on CT is a mass-like process with soft tissue "spokes" radiating into mesenteric fat.

→ Appendiceal NET may not be seen on CT due to size. It shows features of appendicitis

→ Colonic NET tends to be large (>2 cm) & more frequently involve ceum/ascending colon. CT cannot differentiate it from adenoma.

(2) MRI → Most sensitive method to detect liver mets. Even MRI can underestimate total tumor burden, esp when lesions are small. Best modality is hepatic arterial phase i T2 imaging.

(3) Somatostatin Receptor Imaging → Most well differentiated NETs express high level of somatostatin receptors & can be imaged with radiolabelled SSA.

Octreoscan → Utilized ^{111}In-Pentetreotide. Its accuracy improved with addition of SPECT.

^{68}Ga DOTATATE → PET tracer use this, in combination with CT scan to improve detection & staging of NET.

* Poorly differentiated NET do not express Somatostatin receptors & are NOT routinely evaluated with this.

(4) Endoscopy → Upper & lower endoscopy for visualization of primary site.

TREATMENT → Localized Disease

* Treatment of choice for a localized, well differentiated NET is surgery

Appendix → Tumor < 2cm have a low probability of metastases at presentation.
Upto 30% of larger tumors are already metastasized at presentation, mostly to regional nodes.

If detected incidentally after appendectomy, Rt hemicolectomy should be done if size > 2cm, or those with mesoappendix invasion in tumors 1-2cm.
Hemicolectomy is also done for - Positive margins
- Higher proliferative rate
- LVI
- Mixed histology.

Small intestine → most commonly found in the ileum within last 60cm.

Treatment is surgical excision. Resection of primary may be advised even in the presence of distant metastasis.

Even among those with distant mets, 5yr OS is 40-85%, 10yr OS is 40-60%.

Prognosis also depends on margin status.

Ampulla of Vater → TNM staging

T_1 - Invades mucosa/submucosa only ≤1cm (duodenal)
- ≤1cm, confined to sphincter of Oddi (ampullary)

T_2 - Invades muscularis or >1cm (duodenal)
- Invades through sphincter into duodenal submucosa or muscularis propria or >1cm (ampullary)

T_3 - Invades pancreas or peripancreatic tissue

T_4 - Invades serosa or other organs

There is a high likelihood of LN mets, even if tumor <2cm. Whipple is advised.

Rectum → Most rectal NET are small, localized. They are mucosal or submucosal in location. Tumor size & depth of invasion are determinants of mets. (60% pt have mets with size >2cm)

In tumors <2cm, the rate of mets was 2% if confined to submucosa & 48% if muscularis & beyond. Additional prognostic factors are mitotic index & LVI.

Treatment options for localized rectal NET include conventional endoscopic resection, TEM, TAE or a radical resection.

Tumor <1cm, confined to mucosa & submucosa can be treated by endoscopic resection, esp if they lack other risk factor. (Mitotic rate >2/2mm²)

>T2 & >2cm tumors should be treated with radical resection (LAR or APR).

For tumor 1-2cm in diameter, T2, radical surgery is offered in case with ↑Ki67, ↑mitotic rate LVI or size >1.5cm.

Colon → They are staged similar to Rectum. They are more aggressive than rectum.

Well differentiated colonic NETs have the worst prognosis of any gastrointestinal NET. They are usually right sided & present later.

Their treatment is similar to colonic adenoca

Stomach → Gastric NETs are subdivided into three categories

1) Type 1 → 70-80%
   → Associated c chronic atrophic gastritis
   → Gastrin rises in response to gastric achlorhydria.
   → Raised gastrin stimulates neuroendocrine cell hyperplasia & multifocal Polypoid NETs
   → Behaviour is indolent

2) Type 2 → Due to underlying Zollinger Ellison syndrome, raised gastrin level stimulates multifocal gastric NET.
   Seen in 5% patients.

3) Type 3 → 20% of. In absence of ZES or atrophic gastritis.
   Most aggressive. Mets in upto 65% of. Treatment is gastrectomy / lymphadenectomy.

For Type 1 & 2 NETs smaller than 1-2 cm, endoscopic resection is adequate therapy

Antrectomy is a controversial option for Type 1 gastric NETs. It reduces hypergastrinemia & leads to tumor regression

In a series by Borch K et al, 10 patients had antrectomy for Type 1 Gastric NET. 9/10 remained tumor free for an average of 65 month.

Post treatment follow up

Post treatment surveillance is not recommended < 2cm appendix and superficial low grade rectal tumors < 1cm in size.

For all else,

3-12 months → CT(A+P) or MRI
CT thorax for lung or thymus NET
Assay of Biochemical marker as indicated.

> 1 yr Postresection → Same as above, every 12-24 month.

> 10 yr → Continue surveillance as indicated

Metastatic Well differentiated Pancreatic NET

~~Head Treatment~~

Clinical Presentation :- * Some pt remain asymptomatic for years.

* Symptom may arise due to tumor bulk or Peptide hormone oversecretion.
* Carcinoid syndrome may arise due to secretion of Serotonin & other vasoactive peptides.
  Carcinoid Syndrome seen in midgut carcinoids, not in foregut or hindgut. But, in pt with extra intestinal carcinoid (Ovarian or bronchial), Syndrome can develop in the absence of liver mets.

Prognosis - A major factor impacting survival is the primary tumor site.

	Site	Survival (months)
Grade 1, 2	Pancreatic	50
	Small intestine	103
	Colon	14

Another major prognostic factor is histologic grade, which is assigned on mitotic rate or ki 67 index.

Other prognostic factors → Disease burden, distant extra hepatic mets, race, age.

Imaging → Triphasic helical CT(AP) is recommended to image metastatic NET.

They enhance most intensely with IV contrast during early arterial phase & washout in delayed portal phase.

According to ENETS guidelines, MRI is superior to CT for liver mets

Somatostatin receptor based imaging → 90% NET except insulinoma have somatostatin receptors. They can be imaged with Ga^{68} DOTATATE. It is a preferred option for smaller tumor volume or occult primary tumor.

DOTATATE is a long acting octreotide analogue. So, therapy ī octreotide should be stopped 24 hr prior to the scan.

Long acting preparations should be stopped 5-6 weeks before study & pt shifted to short acting.

Biochemical Monitoring

1) Urinary 5HIAA → Elevated levels are highly specific for serotonin secreting NET (midgut)

2) Measuring the peptide in case of functioning pancreatic tumors (insulin, glucagon, VIP, somatostatin)

3) CgA - Used in pt ī foregut & Rectal NET

Plasma CgA have been shown to correlate with treatment response & have prognostic value.
Elevated CgA have shorter OS times.

But :- 1) There is wide variability in CgA ranges in the setting of metastatic disease.

2) Unreliable marker of metastatic disease In pt treated with somatostatin analogs, res it can be falsely low.

3) Not recommended as a diagnostic marker for NET as it can be falsely elevated in other conditions like PPI use, liver failure, kidney failure.

Local treatment

For initial management of hepatic mets from GEP NETs, in whom complete resection is possible, surgery is appropriate in the absence of extrahepatic mets, diffuse bilobar involvement or compromised liver function.

If unresectable, then surgical debulking is not preferred.

- Resection of primary → If symptomatic, primary disease should be resected. If primary & liver mets both are amenable to curative resection, surgery should be performed.

Benefit of resecting asymptomatic small bowel primary in pt i unresectable mets has not been established.

Hepatic predominant disease

(1) Surgery → Surgery is an option if mets are resectable. Poorly differentiated NEC is a contraindication

Studies for hepatic resection in NET

1) Sarmiento JM et al → OS was 61% at 5 yrs
35% at 10 yrs
Median survival → 81 months.
Almost all pt developed recurrence.

2) Bagante F et al → largest case series
5 yr DFS is 46%
OS is not reported.

So, intrahepatic disease Progression & recurrence rates are high, but resection of neuroendocrine liver mets can provide symptom control & associated i long term survival.

NCCN advises consideration of cytoreductive surgery or ablative therapy if near complete treatment of tumor burden can be achieved.

(2) Non Surgical

1) Ablation → Most common technique is RFA.
→ They are only useful for ≤ 3cm lesions

→ Its role may be adjunct to surgery, like in case of intrahepatic disease recurrence

2) Hepatic artery embolization → HAE, TACE, TARE
Can be an alternative to medical therapy also as a palliative technique for symptomatic patients with hepatic predominant unresectable NET.

✓ RETNET → Randomized Embolization Trial for Neuroendocrine Tumor metastases to liver is a trial to determine optimal embolotherapy technique for NET liver mets. Pt will be randomized to bland embolization or TRANS arterial chemoembolization.

(3) Liver transplant → Not a standard option

Management of Primary tumor

Small bowel → Resection of small bowel primary should be done, asymptomatic or otherwise, if both primary & mets are resectable.

If asymptomatic primary but mets are not resectable, nothing should be done.

If symptomatic Primary, resection of primary should be done, even if mets are unresectable.

Small bowel NET can cause desmoplasia & fibrosis, which may lead to obstruction, or ischemia. Resection should be done to prevent it.

Guidelines & data for resection of asymptomatic Primary with unresectable mets is conflicting.

Pancreatic → In resectable mets, an aggressive surgical approach should be tried, to remove both Primary & metastatic site.

In an unresectable disease, best medical therapy including long acting somatostatin analogs is first line approach.
HAE, TACE, TARE can be used.

Systemic therapy

The disease can be Potentially resectable
Unresectable symptomatic
Unresectable asymptomatic
Progressive disease

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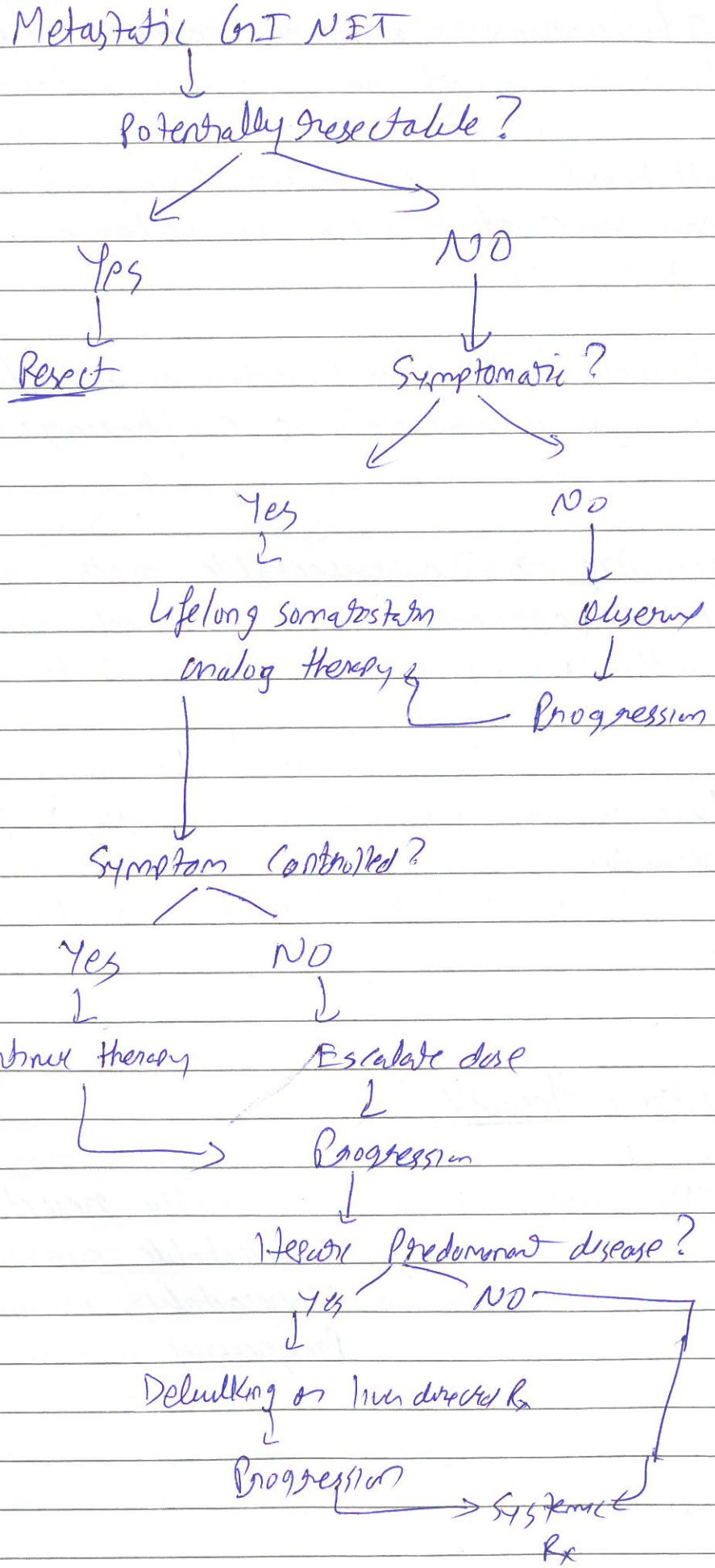


Systemic therapy → If tumor expresses somatostatin receptors, start everolimus or radiolabelled somatostatin analog. [^{177}Lu-Dotatate]

If not, everolimus.

Trials of Ca Stomach

Neo adjuvant → MAGIC
→ FLOT / PETCARA / RAMSES
→ TOPGEAR
CRITICS II } - on going
ESOPEC
→ POET

(1) MAGIC trial → 503 pt ☐ Potentially resectable gastric (74%), distal esophageal (11%) or OG Jn (15%) adeno Ca were randomly assigned to surgery alone Vs surgery + perioP ECF.

Eligibility → PS 0-1
Stage T2 or higher
No distant mets.

	Surgery	ECF + Surgery
Curative resection	70%	79%
T1/T2 disease	37%	52%
N0/N1	71%	84%
5yr OS	23%	36%
Local failure	21%	14%
Distant mets	37%	24%

Hazard ratio for death → 0.75
" " PFS → 0.66

(2) FLOT4-AIO trial → Compared FLOT Vs ECF.

Phase II trial. 300 Patients were enrolled.
FLOT was associated with higher pCR (16 VS 8%)

Complications → At least one serious adverse event in 25-40% pt in both groups.
FLOT has less grade 3/4 nausea, fatigue & vomiting, but more grade 3/4 neutropenia.

Phase III trial enrolled 716 pt ε gastric or GE jn tumors.
ECF/ECX → 91% completed Preop CT
37% " Post op CT

FLOT → 90% completed Preop CT
50% " Post op CT.

At followup of 43 months,

	FLOT	ECF
OS	50 months	35
3yr OS	57%	48%
Peri OP complica	50%	51%
Complications more	Diarrhea Neutropenia Infection Sensory neuropathy	Nausea Vomiting Thrombo-embolic events.
PFS	30 months	18 months

Dosages 5 FU [2600 mg/m² over 24 hrs) + Leucovorin (200 mg/m²) + Oxaliplatin (85 mg/m²) + Docetaxel (50 mg/m²)

(3) RAMSES study → FLOT + Ramucirumab

(4) PFT RARCA trial → FLOT Vs FLOT + Trastuzumab + Pertuzumab

↑ pCR rate, but higher toxicity.
R0 resection, morbidity & mortality are comparable. So, did not proceed with phase III of the trial.

For pt c good PS, FLOT is recommended above ECF.

For pt c poor PS, FOLFOX or CapOx is used.

(5) German Pre Operative therapy in EG adenoca trial (POET) → Limited to EG Jn tumors
→ Evaluated preop CT-RT
→ The only phase III trial that compared Neoadjuvant CRT to Chemo alone.

→ pt with T_3 / T_4 N_x M_0 were randomly allocated to

NACT [Cisplatin + 5FU + leucovorin] x 15 week

NACT + CRT [Same regimen x 12 wk + 3 wk of CRT]

CRT → RT concurrent with cisplatin & etoposide

Study closed due to poor accrual.

Results → (CRT vs Chemo)
Ro resection rates similar [72 Vs 70]
pCR higher in CRT (16 Vs 2)
Rate of neg LN higher in CRT [64 Vs 39%]
Improved 3yr survival in CRT (47 Vs 28%)

(6) TOPGEAR → 3 × ECF Vs 2 × ECF + 5FU based CRT

Both groups received adj. ECF

(7) CRITICS II → Pre OP (CapOx + Docetaxol)
Vs
Same regimen f/b CRT f/b surgery
Vs
CRT f/b surgery.

(8) ESOPEC → Neoadjuvant CRT f/b surgery
Vs
FLOT

Adjuvant Trials

CLASSIC trial → Cap OX
ACTS-GC → S1
CRITICS → NACT f/b surgery { Chemo / CRT

INT 0116 → MacDonald regimen

ARTIST → Cap + Cisplatin Vs CRT
ARTIST 2 → S1 Vs S1 + Ox Vs SOX + CRT

CALGB 80101 → INT 0116 Protocol Vs
Post op ECF ~~adds~~ before and after
5 FU + CRT

PRODIGY → Neoadjuvant Docetaxel + Oxaliplatin + S1 f/b adjuvant S1
Vs Surgery + Adjuvant S1

① ACTS-GC trial → 1059 Patients with stage II or III gastric cancer who had undergone potentially curative D2 gastrectomy

Adjuvant S1 | Surgery alone

5 yr OS	72%	61%

② JACCRO GC07 trial → Docetaxel + S1 Vs S1 alone

3 yr RFS →	68%	57%
3 yr OS →	78%	71%

Grade 3 adverse events were higher with Docetaxel + S1.

(3) CLASSIC trial → 1035 pt c Stage II - IIIB

↓

D2 gastrectomy

CapOx | Observation.

Median follow up - 34 months.

DFS →	74%	59%
3yr OS →	83%	78% [Borderline
5yr OS →	78%	69% Significant]

* only 60% pt completed all adjuvant cycles.

CapOx → [Cap 1000 mg/m² BD on D1-14 + Oxaliplatin 130 mg/m² on D1] × 8 cycles.

Guidelines for Chemo Vs CRT

ESMO → pt c ≥ IB gastric cancer who have undergone upfront surgery, adjuvant chemo or CRT can be given.

NCCN → T3-4 N+ or less than D2 dissection → Chemo + CRT
If R+ resection → CRT alone
If D2 dissection → Chemo alone.
[If node +ve, CRT can be considered]

④ INT 0116 → After Potentially curative resection of E&GJ tumors, (T1-4 N0-1)

556 pt

	Adjuvant CRT	Observation
3yr DFS	48%	31%
3yr OS	50%	41%
Median survival	36 months	27 months
5yr OS	43%	28%

Grade 3&4 toxicity rate was 41% & 32% resp in CRT group.

Majority tumors were T3/T4
85% had N+ disease

D2 was done only in 10% pt.
54% pt did not even have D1 clearance.

⑤ ARTIST trial → Chemo Vs CRT.

458 pt with D2 gastrectomy

60 Capt+Cis	20 Capt+Cis f/b Capt-RT f/b 20 Capt+Cis
3yr DFS →	* Not significant

But, in node positive disease, significantly better DFS in CRT arm (76 vs 72%)

Secondary end point was ~~OS~~ OS, which was not significantly different.

⑥ ARTIST 2 → Stage II/III, N+ disease, D2 gastrectomy

- Adjuvant S1 x 1 yr
- S1 + 0% (50%)
- 20 Gy/10# + CRT + 40 Gy/20#

Interim analysis → No significant benefit for addition of RT to 50% in terms of DFS

⑦ CRITICS trial → 788 pt ≥ Stage I_B - IV

↓

3 ECX NACT

↓

Surgery

- 3 ECX
- 45 Gy/25# ± Cisplatin + Cap.

No significant difference in OS, PFS or local recurrence.

Criticism → Only about half the pts could complete full treatment

* Since all pt received NACT, it did not address the relative merits of Chemo Vs CRT.

* Large proportion of early disease, which would not benefit from RT anyways.

The ONLY trial to show benefit of adding RT to Chemo → Yu et al

68 pts undergoing D1/D2 resection

Chemo (5FU + Leucovorin) | CRT (as per INT 0116)

3y DFS	29%	56%
OS	44%	68%

→ Dutch D1D2 trial shows that benefit of CRT is more with D1 or R+ resection.

② CALGB 80101 → 546 pt, stage I_B-IV

↓

Surgery

5FU+LV + 5FU based CRT | ECF + 5FU based CRT

22% EGJ tumors, rest gastric.

OS was not significantly better with ECF
ECF had lower rates of diarrhea, mucositis

Ongoing trials → TOXAG study → CRT + Chemo with CapOX + Trastuzumab

→ INNOVATION trial ~~NACT (FOLFOX)~~

Vs

NACT [FLOT / CapOX / FOLFOX]

Vs

NACT + ~~FOLFOX~~ Trastuzumab

Vs

NACT + Trastu + Pertu

all patients are Her2+ve Ca stomach.

PRODIGY → ~~Neoadjuvant~~ Neoadjuvant DOS Vs adjuvant SI

PFS significantly superior in DOS arm.

Thyroid Class

1st investigation → USG & TSH

Most specific finding on USG for Malignancy
↓
Taller than wide

7 gene panel test in AUS is "Rule-in test"

Hobnail variant → >30% Hobnail cell (+)

Preffered timing of completion thyroidectomy
is within 10 days or after 6 weeks

Bet^n this period, there is ongoing fibrosis
& inflammation, so high chance of nerve injury.

H ILO dual → For RAI

Maximum dose which can be given to a patient
in lifetime → 600 mCi

Empirical Vs Therapeutic dose?

OS advantage in intermediate risk group & for RAI?

↓

OS advantage not there, but needed for TG monitoring.

- Low dose scan not always required. Can be skipped & high dose given directly, then post therapy scan needed.

Trials of TKI

Recent Updates in Ca Rectum

Molecular classification CRC

CMS 1 → MSI, CIMP high
~~MSI intermediate~~
(14%)
MSI immune
BRAF mutations
Immune infiltration & activation
Worse survival & Relapse

CMS 2 → SCNA high
(37%)
Canonical
WNT & MYC activation

CMS 3 → Mixed MSI status
(13%)
Metabolic
SCNA low
CIMP low
KRAS Mutation.
Metabolic deregulation

CMS 4 (23%) → SCNA high
Mesenchymal
stromal infiltration, TGFB activation, angiogenesis

Worse RFS & OS

Implication for daily practice
Pathologic & Genetic analysis done.

Treatment approach

Old → Cisplatin based long course RT
↓
Surgery
↓
Chemo

New → SCRT → Chemo → Surgery → Chemo

	Old	New
Distant mets	26.6 %	19.8 %
Locoregional failure	6 %	8.7 %
Disease related failure	30.4 %	23.7 %

Total neoadjuvant therapy

PROSPECT study

FOLFOX 6 → Surgery → FOLFOX ×6

FOLFOX 6 → CRT → Surgery → FOLFOX 6

Chemoradiation → Surgery → FOLFOX 8

Ongoing trial.

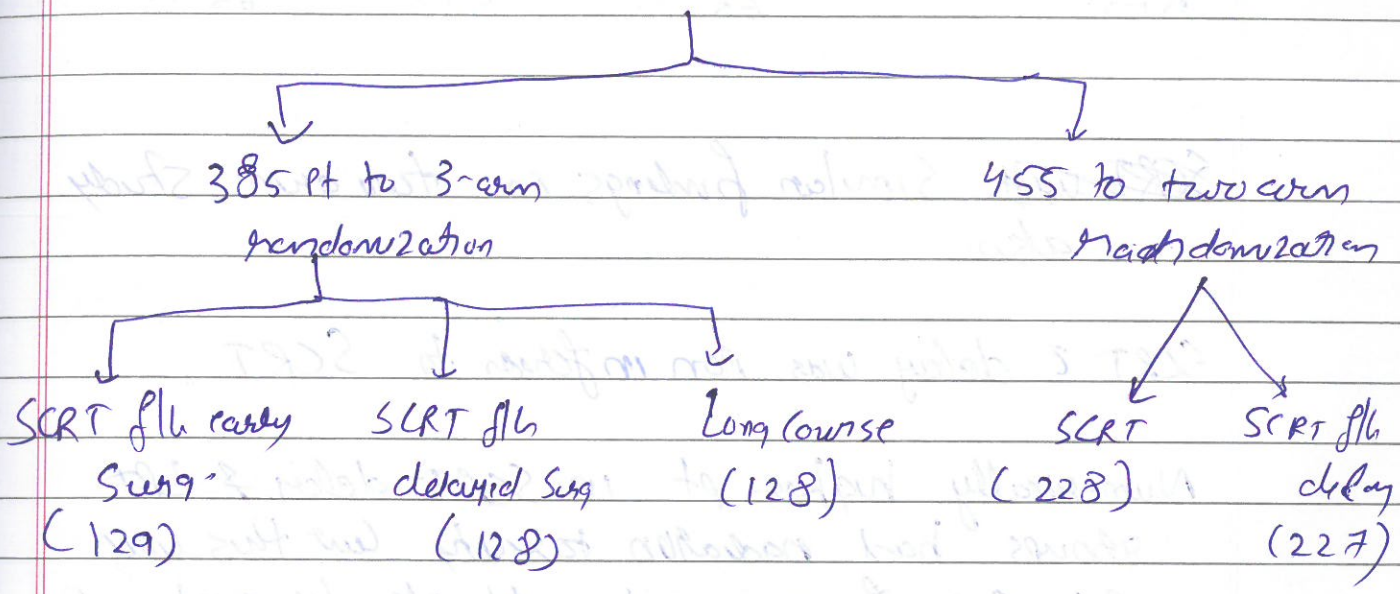
Immunotherapy → Depends on MSI-H biology.

3-5% of advanced CRC have MSI-H.

Young Adult onset CRC

Stockholm II trial

There were two arms of randomization { 3 arm study
2 arm study.



No chemo was used in any arm.

* In the long course arm, there were more patients with tumor higher up the rectum, so more case of Ant. resection.

* Median interval to surgery in 3 arm study
SCRT → 8 day
SCRT f/b delay → 47 day
Long course → 76 day

* No significant difference bt^ the groups w.r.t Local recurrence, mets, OS or intercurrent death.

Median time to LR

	SCRT	SCRT-delay	LR
	28.3 month	22.1	33.3
5yr OS	73%	76%	78%
RFS	65%	64%	65%

~~SCRT with~~ Similar findings in two arm study also.

SCRT & delay was non inferior to SCRT

Numerically higher pt in SCRT-delay & LR groups had radiation toxicity but this was not significant, It could also be explained by the fact that early surgery might "mask" the effects of radiation toxicity.

Non Muscle Invasive Ca Bladder
[Campbell notes]

NMIBC = Ta, T1 & CIS

Approx. 70-80% bladder tumors are non muscle invasive. at presentation with 60-70% as Ta, 20-30% as T1 and 10% as CIS.

Most common symptom → Painless hematuria (visible or non visible)

Visible hematuria → 10.9% Risk of cancer
Microscopic " → 2.5%

Other symptom → Irritative voiding symptoms

Risk of Progression
- Ta G1 → 5-10%
- Ta G3 → 15-40%
- T1 G3 → 30-50%
- Ca in situ → >50%

AUA Risk stratification Scheme

Low Risk → low grade, Solitary Ta ≤3cm
Papillary Urothelial Neoplasm of low malignant Potential.

Intermediate risk → Solitary low grade Ta >3cm
Multifocal low grade Ta
High grade Ta <3cm
low grade T1

High Risk → Any recurrent disease
High grade Ta
Any CIS
Any BCG failure in high grade pt
Any variant histology
Any LVI
Any High grade Prostatic involvement

PUNLMP → Papillary Urothelial Neoplasm of Low Malignant Potential.
These are benign papillary tumours with orderly arrangement of cells & minimal nuclear atypia.

Low grade Ta lesions recur at rate of 50-70%. and Progress in < 5%. cases.

High grade T1 lesions recur @ 80% & Progress in 50% pt in 3yrs.
This behaviour is grade-dependent, than Stage dependent.

Management

CT urography done to assess concomitant lesions in extravesical urothelium.
The overall risk of such tumors is ~ 5%.

High risk factors for concomitant disease → Tumor at trigone
→ Concomitant CIS
→ High risk disease (AUA)

TURBT is diagnostic as well as therapeutic.

After all visible tumor has been resected, additional chips should be taken from muscle base to look for muscle involvement.

Resection of diverticular tumors has a high risk of perforation. So, low grade diverticular tumors should undergo conservative resection & fulguration at base. If final histopath is high grade, re-resection be done.

Repeat TUR has to be performed if there is no muscle in the initial specimen, or there is incomplete resection of T_1 high grade tumors. Also in high risk, high grade Ta disease.

High grade T_1 → Repeat in 6 weeks, since there is 25-30% risk of upstaging to muscle invasive disease in repeat TURBT

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Other options → Random bladder biopsies by cold cup biopsy
They are positive in only 10% of the cases, and are NOT indicated in low risk cases.
No consensus on their use in high risk cases.

→ Laser Resection → Allows ablation of small papillary tumors upto 2.5 cm.
→ Nd YAG laser is used for it.
→ Most significant complication of Nd YAG is perforation of adjacent bowel.

Fluorescence Cystoscopy, Narrow Band Imaging, optical Coherent Tomography, Confocal laser endomicroscopy

Penetrance?

Diff b/t familial & hereditary cancer?

Genetic Predisposition Syndromes in Breast

There are three classes of genes, according to the risk they confer

Rare, high penetrance	Rare, intermediate penetrance	common, low penetrance.
BRCA1 (17q 21)	CHEK 2	FGFR2
BRCA2 (13q 12.3)	BRIP 1	TOX3
p53 (17p 13.1)	ATM	LSP 1
PTEN (10q 23.3)	PALB 2	TGFB 1
CDH1 (16q 22.1)		MAP3K1
STK11 (19p 13.3)		CASP8

① Hereditary Breast & Ovarian Cancer Syndrome (HBOC)

- Caused by BRCA mutations.
- BRCA mutations result in truncated protein products. BRCA protein products are tumor suppressor genes which maintain genomic stability via facilitating double stranded DNA repair through homologous recombination.

  Mutation results in defective DNA repair, which leads to rapid accumulation of mutations.

- Prevalence of BRCA Mutations: BRCA1 → 1/300, 2 → 1/800

- The integral role of BRCA 1/2 in DNA repair holds potential as a therapeutic target for BRCA related cancers.

- PARP inhibitors → When PARP inhibition is applied to tumor cells deficient in double strand DNA repair [as in BRCA mutation], these cells cannot replicate, undergo cell cycle arrest & cell death.

Trials of PARP inhibitors

1) OlympiAD trial → BRCA+ve, HER2-ve metastatic breast Ca, who have previously received chemo in neoadjuvant, adjuvant or palliative setting

→ 42% reduced risk of disease progression or death
2.3 month improved PFS.

→ Olaparib is also used for BRCA+ve advanced Ovarian cancer after treatment with three or more lines of chemo, and as maintenance chemo for ovarian Ca following response to Platinum based chemo.

2) BROCADE 3 trial → Phase III trial for addition of veliparib to Pacli + Carbo in advanced BRCA+ve Ca Breast.

Numerically superior improvement in veliparib arm, not significant in Phase II trial
BROCADE 3 is ongoing trial.

3) EMBRACA Dual → Talazo Parib Vs Physician's choice of chemo in BRCA +ve Ca Breast

4) BRAVO → Trial for NIRAPARIB.

Risks of various cancers in BRCA1

Risk by age 70

BRCA1 → Initial Ca Breast → 57-65%.
↙ Second Ca Breast → 3% Per years
Cumulative 72% Ovary → 40% [16-65%]
Prostate → None to 2-3 fold increase
Male Ca Breast → 1%.
Pancreatic → 1-4%.

BRCA2 → Initial Ca Breast → 45-49%.
↙ Second " → 3% Per years
Cumulative 69% Ovarian → 18% (10-27%)
Prostate → 7.5-39%.
Male → 6%.
Pancreatic → 2-7%.

Tumor Profile

BRCA1 → Triple negative phenotype [7-28% triple -ve are BRCA1]
→ Occurs in 3rd/4th decade
→ 13% of BRCA tumors are Medullary.
General Population → 2%.
→ Higher grade, faster doubling rate, reduced survival
→ Avg age to develop ovarian cancer → 38.6 yrs
→ Worse OS. compared to those without a mutation

Imp-> In case of Ca Ovary, BRCA 1/2 carriers have BETTER survival & more responsive to chemo

BRCA2 > BRCA1

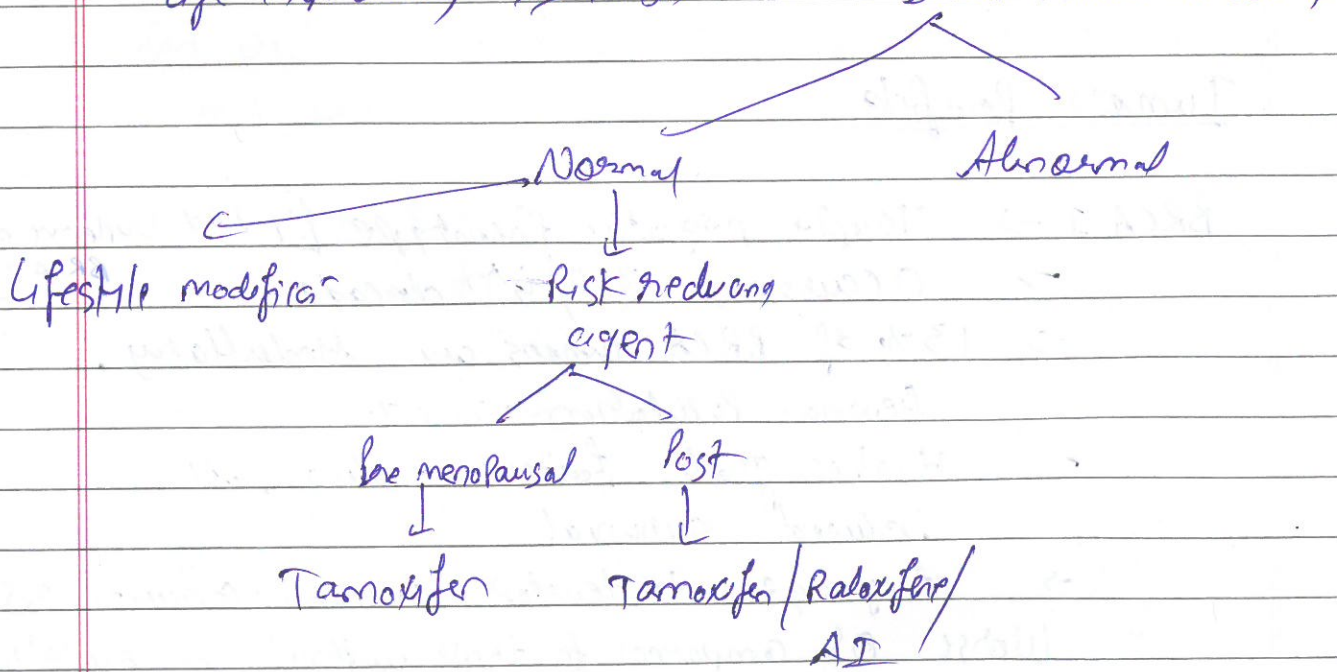
BRCA2 → Tend to be ER+ve
→ Later onset disease
→ Higher grade than Sporadic
→ Avg age of onset is 43.6 yrs.
→ Tend to develop ovarian cancers at a later age, compared to BRCA1
→ Worse cancer specific survival, but OS not significantly diff.

Screening → Annual digital mammo, starting 10 yrs prior to the age of onset in youngest family member, but not less than 30.

→ Annual breast MRI to begin, ~~not less than~~ 10 yrs Prior to age of onset in youngest family member, but not less than 25.

Risk reduction Strategies

1) If women desire risk reducing therapy & Life expectancy ≥ 10 yrs → Breast cancer Screening



Tamoxifen → 20 mg/day × 5 yrs is shown to reduce risk by 49% in patients ↑ increased risk.
In BRCA pt, this risk is less well studied, but retrospective data suggest there may be a benefit.

Raloxifene → Data is limited to post menopausal women with 5 yr risk of ≥ 1.7% as per Gail Model, or history of DCIS.

→ 60 mg/day is as efficacious as Tamoxifen; In long term, the efficacy is lower, but toxicity profile is favourable.

→ No data on BRCA carriers.

AI → 25 mg Exemestane/day is found to reduce relative incidence of invasive breast cancer by 65%. at a median follow up of 3 years.

1 mg Anastrozole/day reduces relative risk by <5%. at 5 yrs.

Retrospective data suggest that AI can reduce contralateral breast cancers in BRCA 1/2 patients with ER +ve breast cancer who contribute AI as adjuvant Rx.

Prophylactic surgery in the form of B/L mastectomy or bilateral salpingo-oophrectomy is considered for those with highest level of risk.

Causes 90-94% reduction in Ca Breast incidence

Two prospective studies in BRCA Patients
Meijers-Heijboer et al → 100% Risk reduction
Rebbeck et al → 90-95%.

Testing Criteria

Indicated in i) Affected or unaffected individual with a 1st or 2nd degree blood relative meeting the criteria

i) Individuals with any blood relative with a known Pathogenic / likely pathogenic variant in a cancer susceptibility gene

2) Personal h/o cancer

① Breast cancer with at least one of the following
- → Diagnosed age ≤ 45 yr
- → Diagnosed age 45-60 yr with
  - * Unknown or limited family h/o
  - * Second breast cancer at any age
  - * ≥ 1 blood relative with breast / ovary / prostate Ca at any age.

- → Diagnosed age ≤ 60 yr ~ triple -ve cancer
- → Diagnosed any age ~
  - Ashkenazi Jew ; or
  - * ≥ 1 close blood relative ~ breast cancer ≤ 50 yr or ovarian / pancreatic / high or v. high risk group. Prostate cancer at any age.

- → Diagnosed at any age ~ male breast cancer.

② Epithelial ovarian cancer at any age

③ Exocrine Pancreatic cancer at any age

④ Prostate cancer at any age with
→ Mets, intraductal / cribriform, high or very high risk histology

→ NCCN high risk group / Ashkenazi Jew, or family history of breast / ovary / Prostate Ca at any age.

⑤ Individual with mutation on tumor genomic testing, that has clinical implications if also identified in the germline.

⑥ Individual who meets criteria of 4-Tumors or Cowden / PTEN.

⑦ TO aid in systemic therapy decision making

3) Family history of cancer
→ An affected or unaffected individual with a first or second degree blood relative meeting any of above criteria (except ⑦)

→ If the affected relative has pancreas / prostate, then only 1st degree relatives to offered testing

→ Affected or unaffected individual who doesn't meet any criteria, but has ≥ 5% probability of BRCA Variant on Tyrer-Cuzick, BRCAPro Score.

4) Individuals who meet these criteria but tested negative with previous limited testing.

Testing MAY BE considered in:-

1) Multiple Primary breast cancers (ages 50-55 yr)
2) Ashkenazi Jew individual
3) Individual who doesn't meet any criteria but has probability of 2.5-5% on models.

Management

* Breast awareness starting age 18 yr.

* Clinical breast exam, every 6-12 months starting 25 yr.

* Breast Screening
  - → Age 25-29 → Annual MRI, or Mammo. with tomosynthesis if MRI is not available.
  - → Age 30-75 → Annual mammo + MRI
  - ≥75 → Based on individual.

* Counselling for risk reduction mastectomy.
  Risk reduction BSO bet^ 35-40 yr, upon completion of child bearing [at 40-45 yr in pt of BRCA 2]

- Those who do not undergo salpingo-oophorectomy, should undergo TVUS with serum CA125 for ovarian cancer screening, starting age 30-35.

- Consider risk reduction agents

Early Breast Cancer

Trials showing equivalence of BCT & Mastectomy

1) Umberto Veronesi study → Higher local recurrence, but similar OS. Included tumor size ≤ 2cm
Milan I study.

2) Danish DBCG-82TM

3) EORTC 10801 - Included tumors size ≤ 5cm

4) NSABP B-06 → Study to evaluate efficacy of BCS in Stage I/II tumors. Compared pt operated with lumpectomy alone, or lumpectomy + RT Vs total Mastectomy.

Trials to avoid PORT after BCS

1) CALGB 9343
2) PRIME II

→ Women > 70yrs, ER+ve, T < 3cm, node neg. taking adjuvant Tamoxifen.

Trials for Partial breast irradiation

1) START-B trial → 50 Gy/25# Vs 40 Gy/15#
No significant diff in LR
Lesser RT related side effects in 40 Gy

2) IMRORT LOW trial → Patients with T ≤ 3cm resected to margins ≥ 2mm given partial breast irradiation [NOT accelerated though].

3) Italian trial → WBI Vs APBI. No diff. in survival or IBTR.

Ongoing trial → RAPID trial

Trials of NACT

1) EBCTCG [Early Breast Cancer Trialists' Collab. Group]

→ Primary outcomes were tumor response, extent of local therapy, local & distant mets, breast cancer death & mortality overall.

Results → 69% in NACT arm completed the chemo
→ BCS rate higher in NACT arm
→ More local recurrence in NACT arm.
→ No diff. in rate of distant recurrence, or mortality.

Increased LR may be attributed to increase in BCS.

2) German Breast Group → pCR is associated with improved DFS in Luminal B / Her2 -ve, Her 2 +ve and triple negative. But not in Luminal A or ~~Her~~ Luminal B / Her2 +ve.

Phylloid tumors

* Surgery is primary modality.

Prognostic & predictive factors – Surgical Margins
- Age
- Tumor size
- Surgical extent
- Mitotic activity
- Stromal overgrowth

Role of adjuvant RT is unclear.

WHO Classification

	Stromal cellularity & atypia	Stromal overgrowth	Mitotic index	Margins
Benign	Minimal	Minimal	0–4	Pushing
Borderline	Moderate	Moderate	5–9	Zone of microscopic invasion
Malignant	High	High	>10	Infiltrative

Accuracy of core biopsy → Sensitivity – 82%.
Specificity – 93%.

Vascularity on USG can help to differentiate bet" fibroadenoma & phyllodes. lesion at least 2cm on USG has 2.2 times higher rust of being a phyllodes

Extent of Surgery - BCS can be done, if oncologic resection is possible.

Margins → Mean local recurrence ~~increased~~ of 31.5% if margins positive.

Pseudopodia → Pseudo capsule like projections around the tumor tissue. If line of resection passes thru it, it can cause recurrence. Hence, there is need to excise 1-2cm margin of normal tissue.

JCO 2020 published a paper showing that in cases with positive margin, LRR is 2.7%, but in this cohort, Maximum patients (60/75) has benign phyllodes.

So, according to this paper, there is no need for re-excision of a margin for benign phyllods. BUT median tumor size here was only 3cm.

TMH Audit → Nair, Chitkara et al.

433 pt
- 40.9% Benign
- 19.4% borderlines
- 30.5% Malignant

Median tumor size → 6cm
48.3% underwent BCS. No impact on LR by type of surgery.

Factors that resulted in detriment of DFS were
1) Sarcomatous histology
2) History of previous excision.

Excision → Remove overlying skin & underlying muscle coz of same mesenchymal origin.

In Tata study, Patients having recurrence / incomplete excision following resection outside had a much poorer DFS. Therefore, "en bloc excision" is recommended at first go.

NO Role of lymph node assessment.
Lymph node involvement even in sarcoma < 5%.

Reduce risk of recurrence

* Negative surgical margin.

* Tumor size, margin status, necrosis & mitosis are associated with recurrence

* Histological subtype influences risk of recurrence.

* LR almost always develop near primary tumor bed. In pt c multiple events, there is a higher risk of transformation to malignant from benign.

* Even in benign phyllods, risk of recurrence is 4.7 - 30%.

Adjuvant Rx - Chemo is reserved for metastatic phyllodes

Mainstay of adjuvant Rx is RT.

Role of adjuvant RT is in Malignant phyllodes
Recurrent phyllodes
large borderline phyllodes

Ca Esophagus [Up to Date]

Preoperative Chemoradiotherapy

Trials comparing surgery with or without NACT/RT

1) Bosset et al → NACT RT does not improve OS but improves DFS

2) Urba et al → No survival difference

3) Scandonavian trials 4 groups of patients were taken — surgery only
— NACT f/b surgery
NART f/b surgery
NACT-RT f/b surgery.

Groups with Pre op RT had survival benefit
No survival benefit in Chemo.

4) Burmeister et al → NACT-RT does not significantly improve OS or DFS. But, patients with squamous histology had better outcomes. However, trial was underpowered to demonstrate its significance

5) Walsh et al → For adeno Ca only.
Pre op NACT RT (CF) Vs surgery alone.

Result → Survival advantage seen in multimodal Rx

6) CALGB 9781 → Phase III trial of trimodality therapy in Ca esophagus.

Pre op Cisplatin + 5FU & concurrent RT was used.
Significant improvement in 5 yr survival seen.

7) NEOCRTEC 5010 → NAC RT f/b Surgery Vs Surgery alone for locally advanced SCC esoph.

Vinorelbine + Cisplatin, concurrently & RT given

CRT group had higher Ro resection rate
higher OS (100 month Vs 66 month)
prolonged DFS

8) CROSS trial.

RT alone Vs ChemoRT

1) RTOG 8501 → Landmark trial that compared RT alone (64 Gy in 32 #) Vs CRT (Cisplatin + 5FU + 50 Gy/25#)

Surgery was NOT a part of treatment schema.
CRT group received 2 additional cycles of chemo after RT.

CRT group had significantly lower locoregional failure rates.

2) INT 0123 → 236 pt ± non metastatic SCC & adenoca received concurrent Cisplatin & 5 FU (Just like RTOG 8501) but were assigned to two RT doses

50.4 Gy 64.8 Gy.

Higher ~~dose~~ dose doesn't improve survival & DFS.

Trials Comparing Pre op CRT Vs Surgery alone.

1) CROSS Trial → 363 pt ± esophageal & EGJ Tumors (86 SCC, 273 adenoca, 4 others)
Majority distal esophageal, 11% EGJ.

Randomized to Pre op CRT ± Pacli Carbo

29% pt treated ± CRT had PCR
Median OS significantly higher ± CRT.

In latest analysis, NACRT has a clean effect on reducing isolated locoregional & synchronous distant relapse, it has no effect on isolated distant relapse rates.

2) CALGB 9781

3) ~~Add~~ NEOCRTEC 5010

Meta-analysis by Australasian Gastro intestinal Trials group

→ ~~Clear~~ Strong evidence for a survival benefit of neoadjuvant CRT ~~or~~ (CT) over surgery alone.
Clear advantage of CRT over only chemo has NOT been established.

Induction Chemotherapy

German POET Trial → Discussed in Trials of Ca Stomach.

Surgery in CRT responders → Approx 50% ~~of~~ SCC & 25% adenoca pt has pCR after NACRT.

Analysis by National Cancer Database and another analysis by Taiwan Cancer Registry demostrates survival benefit of trimodality therapy over definitive RT / CRT.

SCC → Definitive CRT provides long term survival in upto 27% pt of SCC. However, without surgery, there is a higher rate of locally persistant / recurrent disease.

CRT alone Vs Trimodality

1) Stahl et al → Pt of locally advanced SCC were randomly allocated to

- Induction chemo f/b CRT f/b surgery (40 Gy)
- Induction f/b CRT (60 Gy)

OS was equivalent
Local PFS better in surgery group
Treatment related mortality higher in surgery.

2) FFCD 9102 → 444 pt i T3 N0-1 (a esophagus (84% SCC, 11% Adeno)

↓

CRT

↓

Any Response?

- 30 CRT
- Surgery.

Similar OS & 2yr survival
Significantly lower rates of local recurrence in Surgery group

Among the non responders, survival was significantly higher for pt who underwent Surgery

Cochrane analysis of these trials suggest:-

→ No impact of surgery on survival [High quality evidence]

→ Moderate quality evidence that esophagectomy improves LR rates.

↳ Low quality evidence that surgery increases mortality.

If definitive CRT is chosen, the regimen can be either cisplatin/5FU or paclitaxel/5FU.

Adeno Ca → No randomized trials comparing trimodality vs CRT alone in adeno Ca.
Data from retrospective analysis suggest inferior outcomes of non surgical management

largest such retrospective study is from MD Anderson Cancer Centre.

For non responders to CRT, early surgery should be considered if operable.

Optimal timing of surgery after CRT
-> 5-7 weeks.

Post op complications can increase if surgery done before 4 weeks. Risk of mets increases if done after 7 weeks.

Trials for NACT only Vs Surgery

Negative trials -> US INT 0113

-> Ancona et al -> Only those who had pCR had a significantly improved survival

-> Schumacher et al

-> Roth et al

Positive trials 1) MRC trial - 20 CTF

2) MAGIC trial [Adeno Ca only]

3) Allum et al - OE02 trial

4) Boonstra et al [SCC only]

5) FFCD/FNCLCC trial by Ychou et al [Adeno Ca only]

Chemotherapy Vs CRT

1) Bussmeister et al → No improvement in survival from CRT compared to chemo alone, but increased Ro resection rates and improved margin status seen.

2) POET Trial

3) Swedish trial → Improved pCR rates, margin status & lower rate of LN positivity in CRT but no difference in OS or PFS.

Neoadjuvant Vs Adjuvant chemo

JCOG 9907 trial → Pre op Vs Post op CTF 5 yr OS higher in Pre op group

For early stage diseases

cT1N0 → Upfront surgery / Endoscopic management

cT2N0 → NCCN < SCC → Upfront surg if <2cm & well diff
Adeno → NACRT

ASCO 2020 guideline → Initial surgery if <2cm, well diff.

French FFCD 9901 trial failed to show any benefit for NACRT in stage I/II pt.

Role of Adjuvant therapy

CheckMate 577 trial → Adjuvant Nivolumab for patients receiving NACRT and having residual disease.

Benefit is seen irrespective of PDL1 status or histology.
The trial has 70% Adeno Ca pt.

Ongoing trials → KEYNOTE 585 → Use of checkpoint inhibitors in pt undergoing NACT only

KEYNOTE 975 → Use of ~ in pt undergoing definitive CRT.

Cytotoxic Chemo → Potential benefit of adjuvant chemo was suggested in two retrospective analyses derived from National Cancer Database.

Optimal regimen is not defined, two different agent than neoadjuvant should be used.

Surgery trials of Ca Stomach

1) $D_1 D_2$ trial → D_2 is associated with lower locoregional recurrence & gastric cancer related deaths than D_1

2) JCOG 9501 → D_2 + Paraaortic lymph node dissection DOES Not improve survival rate

Extent of LNectomy

cT_1aN_0 & $cT_{1b}N_0$ (< 1.5 cm, well diff.) → D_2

$cT_{1a}N_0$ (other than above) → D_{2+}

cT_{2-4} or $N+$ → D_2

* Level 10 dissection (splenic hilum) is NOT a part of Standard Lymphadenectomy.

D_{2+} lymphadenectomy?

Level 10 with or without splenectomy for cancer of Upper Stomach invading greater curvature

Level 14v (SMV node) for distal stomach with mets to level 6 nodes.

level 13 nodes for cancer invading duodenum. The nodes are metastatic in cancer limited to stomach. But if it reaches duodenum, they become regional

level 16 after NACT for extensive LN involvement.

3) JCOG 0110 → Prophylactic splenectomy does not add survival benefit in proximal advanced gastric cancer.

So, splenectomy not required for cancer of upper 1/3 NOT invading greater curvature. Because in such pt, if level 10 node is involved, the disease ~~if~~ would have spread to other parts of body also. So, no benefit

Role of splenectomy for tumors invading greater curvature is equivocal, coz chances of mets to splenic hilum is high.

4) RCT by Yu W et al → Same number of nodes can be harvested at level 10, even without splenectomy.

5) JCOG 1001 → Role of omental bursectomy.
5 yr OS bet^n two groups is similar.
Rate of pancreatic fistula is higher in bursectomy group.

So, omental bursectomy not reqd.

Removal of omentum → T_1/T_2 → Omentum > 3cm from gastro-epiploic artery may be preserved.

T_3 or deeper → Removal of greater omentum

6) TOP-GC trial → Randomized Phase II non inferiority trial comparing omentum preserving & omentum removing gastrectomies. Similar short term outcomes.

7) JCOG 1711 (ROAD-GC) trial → Phase III trial of TOP GC. Ongoing.

8) JCOG 9502 → Comparing left thoraco-abdominal & abdominal transhiatal approach for total gastrectomy in OG 5° tumors.

Transhiatal is superior.

Evidence for lap. Surgery.

Stage	Surgery	Trials	
Stage I	Distal Gastrectomy	JCOG 0912 KLASS 01	[Compared 5yr Survival & 3yr survival resp. Lap ≅ Open
locally advanced	Distal	KLASS 02 CLASS 01	
~~Early~~ Stage I	Total	CLASS 02 KLASS 03	[Only compared morbidity & mortality Oncological outcome Pending]

9) REGATTA Trial → Gastrectomy + Chemo Vs Chemo alone for advanced Ca stomach with a single non curable factor [mets to liver/peritoneum/para-aortic node]

D2 resection only done.
Metastatic site not resected. Only primary site resected.
Did not show any significant benefit

10) AIO-FLOT3 → Effect of NACT & Surgery on survival of pts with limited metastatic gastric or GEJ^{n} tumors. Phase II Trial.

Metastatic site also resected.

Survival benefit seen with surgery.

11) FLOT 5 → Phase III Trial of FLOT 3.

Extended gastrectomy with NACT in pt c extensive LN met?

Weakly recommended for cases that fulfill the following criteria & have no other non curative factors.

- A small number of nodal swellings limited to no. 16 A2 B1 region and/or swollen LNs that are borderline resectable around branches of celiac artery.

Adjuvant & Neoadjuvant treatments

North America → Adjuvant CRT
East Asia → Adjuvant chemo
Europe → Perioperative chemo

- Preferred regimen for period chemo → FLOT 4 trial.

Neoadjuvant FLOT Vs SOX → Phase II trial.
SOX is non inferior.

Is perioperative chemo superior to adjuvant chemo?

Chinese trial by Xue et al → SOX or CapOX as NACT Vs same agents as adjuvant found no significant survival difference between them.

PRODIGY trial → Neoadjuvant DOS [Docetaxel, Oxaliplatin, S1] f/b surgery
Vs Surgery f/b S1

RESOLVE trial → perioperative SOX is superior to post operative XELOX [Capt Oxaliplatin] in locally advanced Ca Stomach

1. Patients with MSI high, gastric cancer can benefit with surgery alone, even without adjuvant chemo.
In fact, pt ~~c~~ MSI-H did not benefit from chemo.

Data from CLASICC, MAGIC trials.

Role of adjuvant CRT after D_2 dissection → ARTIST

Intra Peritoneal Chemotherapy

In GASTRIC HIP level → Gastrectomy + HIPEC - Ongoing.

Indications D Prophylactic → For pt undergoing gastrectomy to prevent peritoneal recurrence.

2) Curative → HIPEC + CRS in pt ~~c~~ Peritoneal mets. Cure rate of 15%.

3) Palliative → TO prevent re accumulation of ascites, control mets.

Master Class Obstruction Jaundice

→ WHO Step ladder Pain Pathway

→ Hlo disturbed sleep? Significance - whether it is due to itching or due to hepatic encepb.

How to differentiate OJ from medical Jaundice from history?
- Colon of stool

Hlo fevers?

Include Supraclavicular nodes in general exam of GI / Thorax case.

*. "Performance Status is ECOG 1" should be said. Not "ECOG is 1".

Periampullary carcinoma → 2cm region around ampulla

What to look for in USG A+P?
→ Presence of stones in CBD / CBD
→ Mets → Peritoneal nodules.
→ IHBR
→ Ascites

Why Pancreatic head dimensions difficult to assess on USG?
Presence of large bowel gas.

Cholestatic phase of hepatitis can mimic features of obstructive jaundice. To differentiate the two, IHBR dilation needs to be seen.

Early A:G ratio reversal → Chronic liver disease
→ Nutritional deficiency.

Pancreatic protocol → 1.25 mm cuts
Dye injection → 3-5 ml/sec

Plain CT
↓
Pancreatic Parenchymal phase (30-40 sec)
↓
Portal venous (60-80 sec)

Intestine gas ideally should be zero

Vessels relation to be seen.

→ Liver nodule, ascites, Peritoneal disease or Retroperitoneal nodules.

→ "No aberrant anatomy of celiac artery or SMA & its branches".

✓ left renal vein is adjacent to SMA on CT

Para-aortic nodes on CT?

Biopsy in an operable tumor?
Not always required.

Ca Ovary

Etiology

1) 1st degree relatives → 3-7 times increased risk with earlier age of onset

2) BRCA1 → >50% lifetime risk
   BRCA2 → 12-20% lifetime risk

Other genes → BRIP1, RAD51C, RAD51D

3) Incessant ovulation hypothesis → Higher number of ovulations → higher rate of spontaneous mutations & repair. Factors included in this are
   - Early menarche
   - late menopause
   - Nulliparity

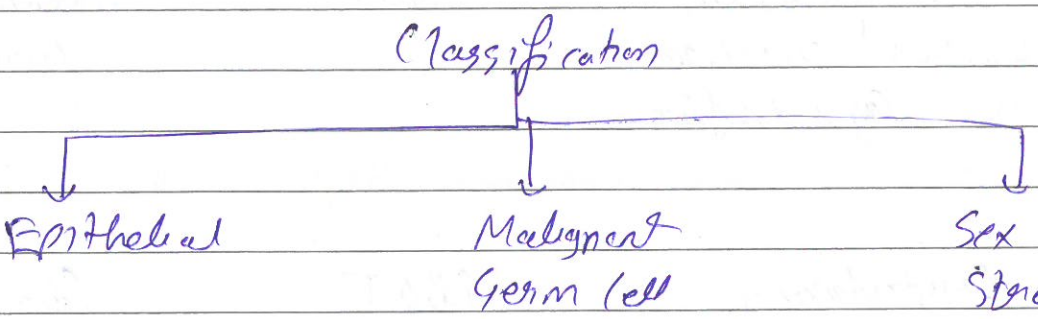
4) Gonadotropin hypothesis → LH & FSH may be directly involved in pathogenesis. Therefore, infertility is a risk factor.

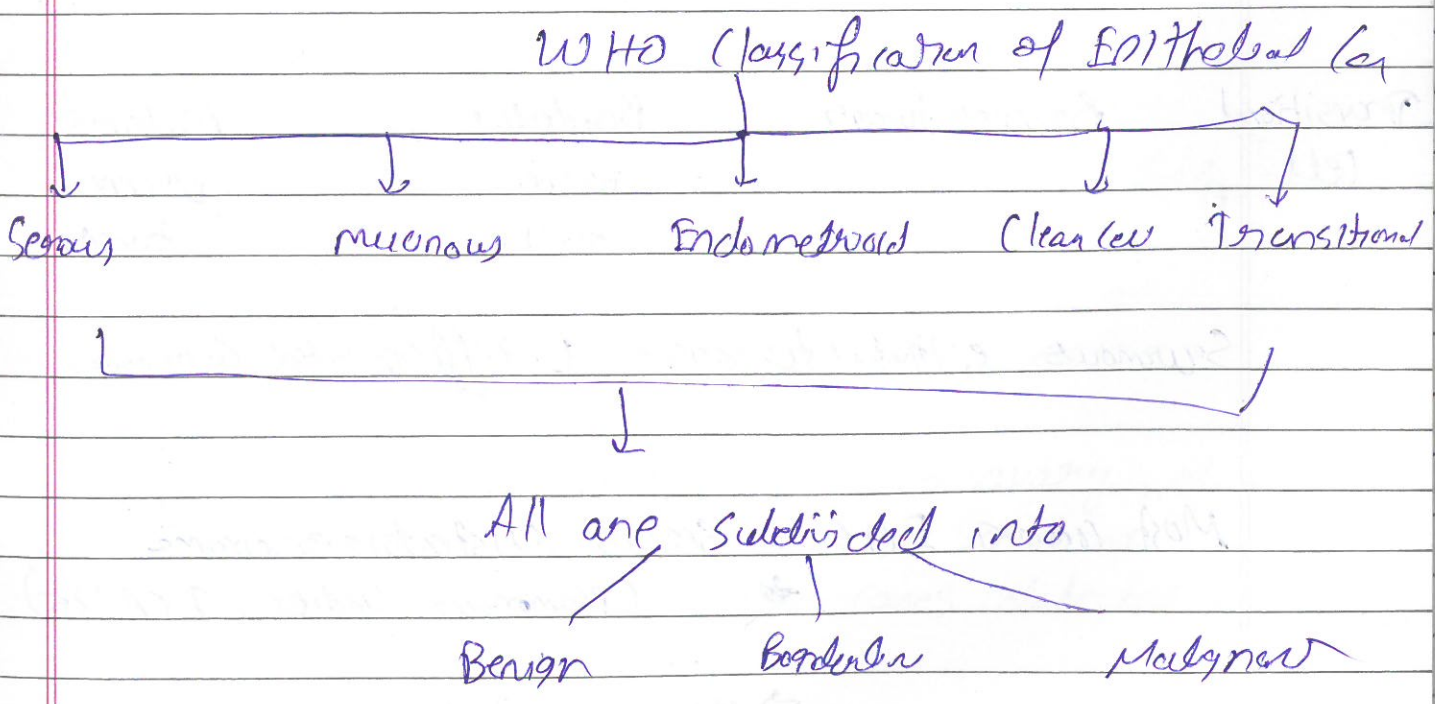
Pregnancy - reduces number of ovulations & suppresses secretion of gonadotropins, therefore it is protective.

5) OCP reduced ovulations and are thus, protective
   HRT has higher estrogen dose, & may be involved in estrogen induced carcinogenesis

6) Benign conditions → Endometriosis
PCOS [seen in CASH study]
Pelvic inflammatory disease

7) Risk reducing salpingo-oophorectomy (RRSO) is recommended for BRCA 1/2 mutations. BUT it doesn't provide full protection, as there is 1–2 % chance of developing primary peritoneal carcinoma.





	Benign	Borderline	Malignant
Serous	Cystadenomas Adenofibromas Surface Papilloma	Serous Borderline Ovarian tumors (SBOT)	Serous low grade Ca Serous high grade Ca
Mucinous	Cystadenoma Adenofibroma	MBOT	Mucinous carcinoma
Endometrioid	Endometriosis cyst Endometrioid cystadenoma (or) Cystadenofibroma	EBOT	Endometrioid carcinoma
Clear cell	Cystadenoma	CBOT	Clear cell tumor
Transitional cell	Brenner tumor	Borderline Brenner tumor	Malignant Brenner tumor

Squamous epithelial tumors – Undifferentiated carcinoma

Most common EOC → Serous cystadenocarcinoma
(Psammoma bodies, ↑CA 125)

→ Mucinous cystadenocarcinomas
(↑CEA (A125 - normal)

→ Endometrioid Ca

→ Undifferentiated Ca

→ Clear cell Ca.

Clear cell & Undifferentiated are most aggressive.

Screening

1) CA 125 → Expressed in 75% of cases, Principally in Serous subtype
   → lack of sensitivity for early detection

Accepted uses – TV determine whether a pelvic mass is malignant

– TO determine whether a cancer of unknown origin has come from ovary

– Monitoring response

– Surveillance of pt in remission

– Screening in high risk pts
[like those ± BRCA 1/2].

2) PLCO Trial – Screening with TV-USG + CA125
↓
90 pt diagnosed ± Ca ovary, of whom 60 were detected through screening.
However, 72% cases detected were Stage III/IV

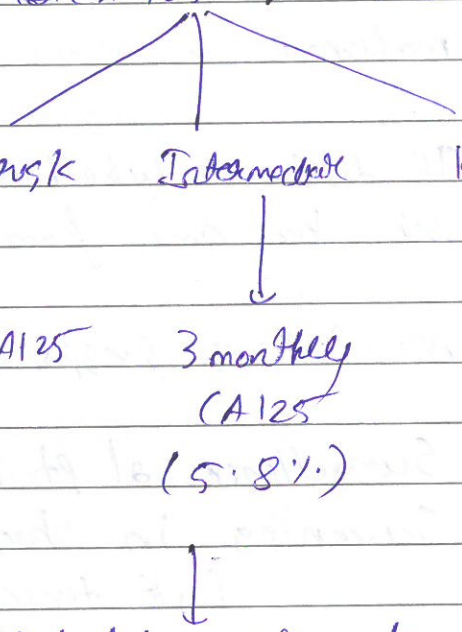
Conclusion – Screening does not affect mortality rate.

3) ROCA score → Risk of Ovarian Cancer Algorithm.

- Developed to improve sensitivity of CA 125 in EOC

By monitoring ROCA score, disease may be intervented before it starts to spread.

ROCA study → 4057 women ↓ no family history underwent CA 125 & ROCA scoring.



Total of 10 went underwent Surgery.

Positive Predictive value of detection → 40%
Specificity → 99.9%

Other studies for screening

1) UK Collaborative trial of Ovarian Cancer Screening [UKCTOCS] → No significant effect of CA125 in screening, in reducing mortality.

2) UC Pilot study

For women = high risk who defer rrSO, ROCA is an acceptable alternative for screening, although its impact on mortality is unknown.

rrSO Protocol — Recommended for patients at risk of Hereditary Breast & Ovarian Cancer syndrome.

- 3.5-4.6% cases, occult ovarian, fallopian tube or primary peritoneal cancers detected after rrSO.

Components of Protocol

1) Minimally invasive laparoscopic surgery

2) Survey abdomen, bowel surfaces, omentum, appendix & pelvic organs

3) Biopsy any abn peritoneal findings

4) Pelvic washing for cytology.

5) Total BSO - Removing 2cm of proximal ovarian vasculature / IP ligament, all tubes

upto cornua, all peritoneum surrounding ovaries & tubes, ESP peritoneum involving areas of adhesion bet" tube and/or ovary & pelvic sidewall

6) minimal handling of organs

7) Ovaries & tube to be placed in an endobag

8) Fallopian tubes should be examined by sectioning & Extensive examination [SEE-Fim] of fimbriated end.

Role of hysterectomy with BSO is not well defined, although these patients are at a increased risk of endometrial cancer.

Differential diagnosis of Adnexal Mass

1) Hydrosalpinx & Paratubal cysts
2) Ectopic Pregnancy
3) Tubo-ovarian abscess
4) Intra uterine Pregnancy in bicornuate uterus
5) Distended Sigmoid colon
6) Distended bladder or hydronephrotic kidney

Imaging → Primary workup is a TV-USG and/or CT/MRI A+P.

→ PET/CT is recommended if lesion indeterminate on USG. or CT, if it alters management

USG Algorithm for Predicting likelihood of ovarian malignancy → International Ovarian Tumor Analysis [IOTA]

* Acc. to ACOG Protocol, Pelvic examination & appropriate Imaging to be done first.

↓

Premenopausal → [CA125 >200
Ascites
Abdominal or distant mets
1 or more 1st degree relatives
↑ Ca Breast or Ca ovary] → Refer to Gyn. Onco.

Post menopausal → Any CA 125 elevation (rest all same)

HE4 → Product of WFDC2 gene, overexpressed in Ovarian carcinoma pt.

→ Elevated HE4 associated with advanced stage & Serous histology.

ROMA test → Test to determine risk of Malignancy in a Pelvic mass:

- → uses CA125 & HE4.
- → Can be used in Preoperative "triage" of Patients with Pelvic mass.

OVA1 & OVA2 → OVA 1 combines five biomarkers

- 1) CA125
- 2) β_2 microglobulin
- 3) Apo A1
- 4) Transferrin
- 5) Prealbumin

(1, 2: Raised; 3, 4, 5: Decreased.)

Gives a score on a scale of 1–10. Abnormal score for Premenopausal women > 5 & that for Post menopausal is > 4.4.

OVA2 → CA125
FSH
Apo A2
Transferrin
HE4

Single cut off → 5

Other tumor markers → Inhibin
→ AFP
→ β HCG
→ LDH
→ CEA
→ CA 19-9

Nutritional assessment by Prognostic Nutritional Index or Subjective Global Assessment

FIGO Staging

Management

Cytoreductive surgery

* Study by Bristow et al demonstrated that the most important determinant of survival was maximal cytoreduction, with each 10% increase in tumor resection associated with 5.5% increase in survival.

* LION study → no role of lymphadenectomy in clinically node negative patients.

* Patients in remission who ultimately experience a recurrence may also be candidates for additional cytoreduction, if they have ≥12 months of remission, localized disease, medically optimized

* Initial surgery should include Hysterectomy & BSO & debulking of all visible disease.

* Laparoscopy assessment prior to laparotomy should be done to assess feasibility.

* Fertility sparing surgery may be considered for patients who wish to preserve fertility & have apparent early stage disease and/or low risk tumors

If both ovaries need to be removed, then uterus should be spared for IVF techniques.

* Optimal cytoreduction → Residual disease < 1 cm in maximum diameter or thickness

- Aspiration of ascites and/or lavage & cytology should be done. For obvious disease beyond ovaries, it will not change management or staging.

- All peritoneal surfaces visualized

- Hysterectomy & BSO should be done

- For diseases limited to ovary/pelvis (Stage I/II), omentectomy should be done for staging.

For Stage III/IV, omentectomy is curative.

Role of lymphadenectomy → meta analysis shows that systemic lymphadenectomy improves OS in early stage Ca Ovary, but doesn't improve PFS.

Ca Penis [IASO master class]

Risk factors

1) Phimosis → OR 11-16
2) Chronic penile inflammation
3) Smoking → 5x risk
4) PUVA therapy
5) HPV → HPV 16, 18
   → DSS is 96% in HPV +ve
   82% in HPV -ve.

→ p16 is overexpressed. If p16 is negative then p53 is overexpressed

Premalignant lesions

Lesions sporadically associated ~ SCC
1) Bowenoid papulosis
2) Lichen sclerosis

Premalignant lesions (upto 1/3 transform to SCC)
- Penile intraepithelial lesions
- Giant condyloma acut (Buschke Lowenstein)
- Bowen's disease
- Paget's disease

WHO Classification

Non HPV associated	HPV associated
- SCC, common type (MC)	- Basaloid (M.C)
- Pseudohyperplastic Ca	- Papillary Basaloid
- Pseudoglandular	- warty
- Verrucous	- warty Basaloid
- Carcinoma cuniculatum	- Clear cell
- Papillary Ca	- Lymphoepithelioma - like Ca.
- Adenosquamous	
- Sarcomatoid (highest mortality)	

Penile biopsy

- Ring block
- Edge-wedge biopsy given

Information needed → Diagnosis
→ Depth of invasion
→ Presence of vascular invasion
→ Grade.

- Depth till lamina propria layer.

* M.C. site → Glans (30%), coronal sulcus or foreskin.

Lab changes → Hypoalbuminemia
→ Hypercalcemia - As a paraneoplastic syndrome due to release of PTHrP

Imaging

1) USG → 1st by Horenblas et al.
   → Sensitivity for detecting corpus cavernosum invasion is 100%
   → More accurate estimation compared to physical examination alone

2) MRI → Most sensitive modality.
   → Superior soft tissue contrast
   Better spatial resolution
   • lack of ionizing radiation.

   → Better assessment of fascial planes
   → Best evaluated on T2 weighted images
   ~~eg~~ used of superior contrast resolution
   Left hypointense fascial layers (Buck fascia tunica albuginea) & adjacent hyperintense corporal bodies.

   → SCC appears hypointense.

   → Induration of artificial erection to be done.

For tumor size, examination > MRI > USG
Infiltration of cavernosum → Exam = MRI > USG.

Management of Primary

- Tis, Ta, low & intermediate T_1
- High grade T_1, T_2, T_3.

Penile Preserving Strategies

1) Lasers — LR ~ 35%.
2) Mohs Micrographic Surgery
3) Circumcision — LR 15.4%.
4) WLE + STSG
5) Glans resurfacing — excising glans epithelium & subepithelium & ↳ STSG
   - Indicated in CIS as well as pre-malignant lesions of glans.
   - LR ~ 4%.
6) Glansectomy — T_1 & T_2 tumor confined to glans.

Ca testis

Risk factors :- Five well established risk factors

1) White race →

2) Family history of Ca testis → Relative risk ↑ affected brother is 8–12 x , RR ↑ affected father is 2-4x. Approx 1-4% new GCT have family h/o.

3) Personal history of Ca testis → 12x.

4) Cryptorchidism → Risk is 4-6 times, if affected gonad is cryptorchid, but falls to 2-3 times if orchidopexy is performed in childhood.

5) Germ cell Neoplasia in situ (GCNIS) → Most GCT arise from GCNIS, except spermatocytic tumor, Prepubertal germ cell tumors.

→ It is present in adjacent testicular parenchyma in 80-90% of cases.

→ 5-9% pt of GCT in one testis have GCNIS in opposite testis.

→ It is thought to arise from malignant transformation of primordial germ cells or gonocytes during fetal development, that failed to differentiate into pre spermatogonia.

→ Seen as testicular microlithiasis on USG.

Pathogenesis – Hypothesis of a testicular dysgenesis syndrome which resulted from environmental and/or lifestyle factors & genetic susceptibility.

→ Increased prenatal estrogen exposure has been hypothesized as a risk factor but is controversial.

→ Most consistent genetic finding is gain of material from chromosome 12p, except in spermatocytic tumors. It is in the form of i12p [isochromosome 12p]. It is also found in ITGCN.

→ KIT ligand is important for gonocyte development and polymorphism in c-kit gene can be connected to malignancy.

→ Other overexpressed genes → cyclin D2, KRAS

→ Seminomas are usually hypertriploid, NSGCT are hypotriploid.

→ There is evidence that epigenetic regulation of gene expression plays a role in pathogenesis of GCT. Global hypomethylation is more common in seminoma than NSGCT.
Yolk sac tumor, choriocarcinoma & teratoma are hypermethylated.

→ For hereditary risk, gr/gr risk on chromosome Y, is implicated, esp in pt of infertility. It is assd. ε 2-3 fold increased risk.

-> Strongest associated single nucleotide polymorphism were at 12q22 in KITLG gene.

-> Among familial cases, age at diagnosis is 2-3 yrs younger and higher incidence of B/L tumors.

Extragonadal GCT

* Approx 5% post pubertal GCT are extragonadal in origin and most develop in midline anatomic locations

Two theories → 1) They originate from germ cells that misigrated along the genital ridge and were able to survive.

2) Reverse migration from the testis to extragonadal locations.

* Primary mediastinal NSGCT are less sensitive to chemo, compared to testicular, and have poorer prognosis. They are more likely to have yolk sac component and have higher AFP values.

* Mediastinal NSGCT also. ↑ Klinefelter Syndrome.

* Retroperitoneal GCT have same biology & prognosis as testicular GCT.

Histologic Classification

1) Seminoma → Most common type of GCT
   → Diagnosed by 4th / 5th decade of life.
   → Stain for βHCG in 15%. cases, but of no prognostic significance.
   → IHC - PLAP +ve
   CD117 +ve
   CD30 -ve

2) Spermatocytic tumor → They do not stain for OCT 3/4, PLAP or PAS.
   → Peak incidence in 6th decade of life
   → Usually benign, cured by radical orchidectomy alone.

3) Embryonal carcinoma → consists of undifferentiated malignant cells resembling primitive epithelial cells from early stage embryos with crowded pleomorphic nuclei.
   → Most undifferentiated type
   → High rate of mets
   → Presence & proportion of EC has been associated with occult mets in stage I NSGCT.

4) Choriocarcinoma – Elevated βHCG levels
   – Hematogenous spread
   – Prone to hemorrhage, sometimes spontaneous, or after initiation of chemo.

- Stimulation of receptors for TSH & LH by HCG can occur.

5) Yolk Sac tumor → Endodermal Sinus tumor
→ Schiller Duval bodies, which resemble endodermal sinuses
→ Raised AFP.

6) Teratoma → Well differentiated tumors are labelled mature teratomas.
→ Frequently found in metastatic sites of NSGCT
→ Resistant to chemo
→ May contain many genetic abnormalities, including isochrome 12p.
→ Sometimes teratomas can transform into a somatic malignancy like RMS, adenoca or PNET. These tumors are called "Teratomas with somatic type malignancy".

Signs & Symptoms

* Painless enlargement of testis
* Pain is associated in NSGCT
* Vague scrotal heaviness or discomfort
* Regional or distant mets at diagnosis is present in approx 2/3 NSGCT & 15% Pure Seminoma.
* Abdominal mass due to bulky retroperitoneal mets

* Pulmonary mets may cause cough, dyspnea, hemoptysis.

* 2% pt have gynecomastia due to ↑HCG, ↓androgens or ↑estrogen (in leydig cell tumors).

Investigation

1) Scrotal USG → Typical GCT is hypoechoic and two or more discrete lesions could be identified.

→ Increased flow on doppler

→ Testicular microlithiasis as a sign of GCNIS

→ Sometimes, a "burnt out primary" is encountered and a stellate scar is seen on USG

2) Tumor Markers - AFP is elevated in 50-70% of low stage NSGCT and 60-80% of advanced NSGCT
Secreted by EC & yolk sac tumors.
Pt ↑ Pure seminoma who secrete AFP are classified as NSGCT
HCG levels are elevated in 20-40% of low stage & 40-60% of advanced NSGCT. $t_{1/2}$ - 24-36 h.
15% seminoma secrete HCG
Secreted by Chorio Ca & EC

LDH is a non specific marker, mainly used for prognostic assessment at diagnosis. Magnitude of LDH elevation correlates with bulk of disease.

In a Pt c testicular mass c retroperitoneal & lung mets in whom chemo has to be started urgently, may be started on chemo based on AFP & HCG values

These pt should undergo orchidectomy after completion of chemo.

Post orchidectomy, tumor markers should be done within 4 weeks.

★ Radical inguinal orchidectomy is the standard for diagnosis as well as Primary surgical management ★

Testis Sparing Surgery

- No role in Proven malignancy c normal contralateral testis
- may be considered for organ confined tumors < 2-3 cm in Pt c synchronous bilateral tumors, or in Pt c solitary testis.
- Intra Op frozen must be sent
- Biopsy from adjacent Parenchyma should be performed to r/o GCNIS.
- For Pt c GCNIS, adjuvant RT 20 Gy should be given.

* Patients with extragonadal GCT should undergo orchiectomy if pattern of mets is consistent with a right or left sided testicular primary.

Staging Imaging Studies

* Most common route of tumor dissemination is via lymphatics, first to retroperitoneal lymph nodes, then to distant sites

* Retroperitoneum is the initial site of spread in 70-80% pt.

* For Right testis tumors, the primary drainage site is the inter-aortocaval lymph nodes inferior to renal vessels, followed by paracaval & para-aortic.

* For left testis, the landing site is para aortic lymph nodes

* Pattern of lymph drainage is from right to left. So, contralateral spread is more common in right sided tumors. When it occurs in left sided tumors, it is asso. c bulky disease

* Retroperitoneal lymphatics drain into cisterna chyli behind right crus of diaphragm. Thus, retrocrural lymph node metastasis may be visible.

- Enlarged retroperitoneal nodes are found in 10-20% seminoma & 60-70% NSGCT.

But, 25-35% rate of Pathologically involved nodes in CSI NSGCT with "normal" CT scan.

Size cut off for Significant LN purity

+ For Primary landing zone, the size cut off is 5-9mm. So, LN this size should be viewed as suspicion.

+ Currently no role of FDG PET in routine evaluation of NSGCT & seminoma.

Clinical Stage II disease is subclassified based on size of nodes on imaging

$II_A \rightarrow$ <2cm

$II_B \rightarrow$ 2-5cm

$II_C \rightarrow$ >5cm

CT imaging studies be done within 4 wk of initiating Rx.

Chest imaging → Screening CXR in the absence of retroperitoneal disease is sufficient

- CT should be performed in patients with elevated markers post orchidectomy or evidence of metastatic disease on examination or imaging.

- If βHCG > 10,000, brain imaging could be done as it indicates metastatic choriocarcinoma.

Prognostic Classification of Advanced GCT [IGCCCG classification]

	Seminoma	NSGCT
Good	- Any primary site, and no non pulmonary mets and Normal AFP any HCG, LDH - 90% Seminomas - 5 yr PFS 82%. 5 yr OS 86%.	- Testicular/Retroperitoneal primary - No non pulmonary mets and Good markers LDH < 1.5 x AFP < 1000 ng/ml HCG < 5000 IU/ml.
Intermediate	Any primary Non pulmonary mets. Normal AFP, any HCG, AFP 10%. Seminoma 5 yr PFS → 67%. 5 yr OS → 72%.	Testicular/Retro peritoneal No non pulm. mets. Markers: AFP - 1000 - 10,000 LDH - 1.5 - 10 x HCG → 5000 - 50,000 5 yr PFS - 75%. OS - 80%.
Poor	—	Mediastinal primary or Non pulm. visceral mets or AFP > 10,000 LDH > 10 x HCG → > 50,000 5 yr PFS - 41%. OS - 48%.

Stockholm III trial

Total Pt → 840

Three arm randomization → SCRT → 129
→ SCRT ī delay → 128
→ LRT → 128

Two arm randomization → Short course → 228
→ ~~Short~~ course → ~~227~~ 227
ī delay

Primary endpoint was time to LR.
Median time to LR → SCRT → 33.4
SCRT ī delay → 19.3 months
LRT → 33.3

Cumulative LR incidents → SCRT → 8/357
SCRT ī delay → 10/355
LRT → 7/128

SCRT deemed non inferior to SCRT ī delay & LRT

Radiation toxicity higher in SCRT ī delay > LRT
Post op complications lower in SCRT ī delay.

PCR → 0.3% SCRT
10.4% SCRT ī delay
2.2% in LRT.

Secondary end point was OS, frequency of post op Mortality (within 30 days of surgery.

No significant difference among three groups w.r.t OS.

So, SCR with delay is a feasible option.

Suspected extra gonadal GCT

- Approx 5%. GCT are extra gonadal in origin.

Out of patients with metastatic GCT without a testicular mass, → ⅔ have ITGCN in testis
⅓ have burned out primary.

- If serum markers ↑, testis USG normal, biopsy is not needed. But if markers are also (N), then biopsy from mass is to be done.

- Pt suspected of extragonadal GCT should undergo orchidectomy at some part of treatment, if thy pattern is consistent c right or left sided tumor or there is sonographic evidence of burned out primary.

Impact of ca testis treatment on fertility

- 52% men have oligospermia at diagnosis & 10% are azoospermic

- Virtually all pt become azoospermic after chemo Recovery after radiation therapy may take longer.

- RPLND may lead to ejaculatory dysfunction.

Here, Sperm cryopreservation advised prior to starting treatment

Treatment

Staging

cTx - Tumor cannot be assessed
cT0 - No clo primary tumor
cTis - Ca CNIS
cT4 - Scrotal involvement.

pTx, T0, Tis - Same as above
pT1 - Limited to testis, without LVI
pT1a - < 3cm
T1b - > 3cm

pT2 - Limited to testis with LVI
or
Invading beyond soft tissue, epididymis, Penetrating visceral mesothelial layer covering the external surface of tunica albuginea.

pT3 - Directly involves spermatic cord
pT4 - Invades Scrotum

cN1 - Single node, <2cm, or multiple nodes all <2cm
cN2 - Single node 2-5cm or " 2-5cm
cN3 - any node >5cm

pN1 - ≤ 4 nodes positive, all ≤ 2cm in size
pN2 - >5 nodes positive all 2-5cm in size, or
ENE(+)
pN3 - any node >5cm in size.

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Serum markers

S_x – Markers not available

S_1 → LDH < 1.5x , HCG < 5000, AFP < 1000

S_2 → LDH 1.5 - 10x or HCG 5000 - 50000
or AFP 1000 - 10,000

S_3 – LDH > 10x , HCG > 50,000, AFP > 10,000

Stage I → pT1 - T4 N0 Sx

I_A – pT1 N0 S0

I_B – pT2-4 N0 S0

Stage I_S – pTx / any pT N0 S1-3

II_A → Any T N1 S0

~~II_B~~ Any T N1 S1

II_B → Any T N2 S0/S1

II_C → N3 S0/S1

III_A → Any T Any N M1a S0/S1

III_B → M0-1a S2

III_C → M0/M1a S
M1b Any S

NCCN guidelines

Suspicious testicular mass
↓
- Clinical exam
- Tumor markers
- Testicular USG
↓
- Radical inguinal orchiectomy
- Consider contralateral testicular Bx for bilateral suspicious masses

↙ Pure Seminoma
↘ NSGCT

Pure Seminoma

Work up → (T (A+P)
→ CXR → CT thorax if CXR is abn or positive abdominal CT
→ Repeat tumor markers
→ Brain MRI indicated if βHCG > 5000 or extensive lung mets or non pulm. visceral mets.
→ Recommend sperm banking
↓
Staging
↙ ↓ ↓ ↘
IA, IB IS IIA, IIB IIC, III

Stage IA, IB

- Surveillance for pT-T3
- Carboplatin 1-2 cycle
- RT (20-25.5Gy)

Stage Is → Repeat tumor markers measurement and imaging to scan for evaluable disease

Follow up after surgery alone
H&P every 3-6 month in 1st yr
every 6 month in 2nd yr
6-12 monthly in 3rd yr
Annually in 4th & 5th

CT → At 3, 6 & 12 months in 1st yr
every 6 months in 2nd yr.
Annually there after.

Plus after adjuvant chemo/RT
H&P every 6-12 month x 2yrs.
Annually x 3yrs

CT - Annually.

Stage IIA → RT to include para-aortic & ipsilateral iliac nodes dose of 30 Gy

→ BEP x 3 cycles
EP x 4 cycles

IIB → BEP x 3 cycles
EP x 4 cycles

→ RT if ≤ 3cm disease, to a dose of 36 Gy.

IIC, III ← Good risk → BEP x 3 cycle / EP x 4 cycle

Intermediate risk → BEP x 4 cycle
VIP x 4 cycles

Post chemo Management

CT(A+P+T), Tumor markers

1) NO residual mass, or mass ≤ 3cm & normal markers - Surveillance
If recurrence found during surveillance, then second line chemo.

2) Residual mass > 3cm and normal tumor markers

→ Surveillance

→ PET CT, 6 weeks or more Post chemo

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PET CT → Negative → Surveillance

→ Indeterminate → Repeat Scan in 6-8 week

→ positive

Resection of mass
or Biopsy

Viable seminoma

Complete resection

Incomplete

2. EP/TIP/VIP/
VeIP × 2 cycle

Second line
Chemo

Negative

Surveillance

3) Progressive disease on tumor markers
→ Second Line ~~therapy~~ therapy

Second line therapy

Relapse ≤ 2 yrs
- Chemo - Conventional dose VeIP or TIP
- High dose
- Consider surgical salvage if solitary site
- Clinical trial

Relapse after 2 yrs
- Surgical salvage if resectable (Preferred)
- Clinical trial
- Chemo.

Management of NSGCT

Post orchiectomy work up same as seminoma

- Stage I
- IIA, IIB
- IIc, III; Brain mets.

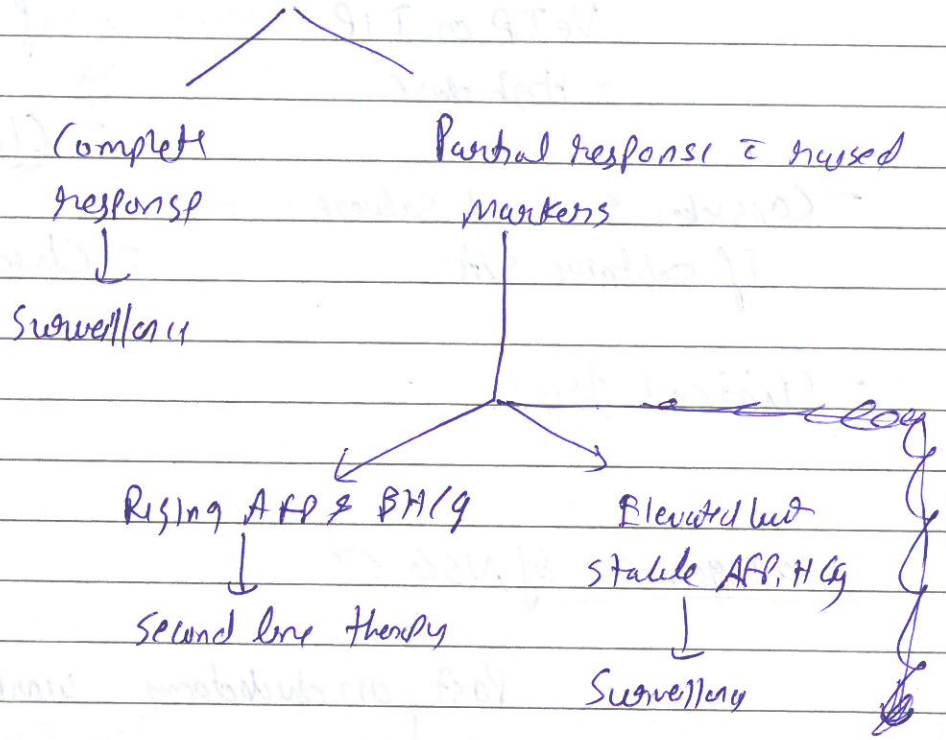
Stage I → Risk factors for recurrence
- LVI
- Spermatic cord invasion
- Predominance of embryonal component

No risk factors → Surveillance / Nerve sparing RPLND / BEP x 1 cycle

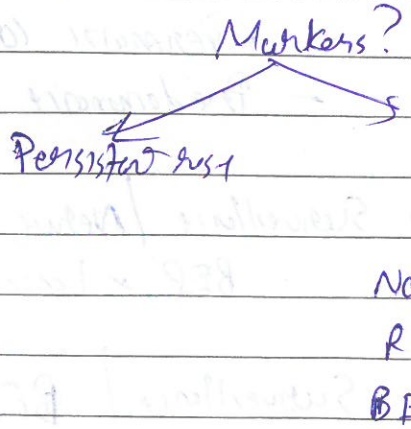
Risk factor(+) → Surveillance / BEP x 1 cycle / Nerve sparing RPLND

Any recurrence during follow up → Second line treatment

Stage Is → BEP × 3 cycle
EP × 4 cycle



Stage IIA - RPLND is preferred for Stage II tumors with transformed teratoma, and should be considered for Stage II tumors with teratoma predominance in pt & normal markers.



Persistant/rise → BEP x 3 cycles

[For Good risk IS
IIA, IIB, IIC
IIIA]

EP x 4 cycles

↓

Response

Complete → Surveillance, or, Nerve sparing BIL RPLND

Partial (Residual mass on ↑ markers)

Only residual mass markers (+) → Surgical resection

- Teratoma → Observe
- Embryonal/yolksac/Chorica/seminoma → EP/TIP/VeIP x 2 cycles

Mass ± ↑ markers

- Rising AFP/βHCG → Second line Rx
- Elevated but Stable → Observe
- Mildly elevated & normalising → Resection

Stage IIB → Markers?

- Negative → Lymph node mets within lymphatic drainage?
  - Yes → BEP/EP or Nerve Sparing RPLND
  - No → BEP/EP
- Persistent raised → see previous

Post chemotherapy management in Stage IIA/IIB

- Abdomen + Pelvis CT
- Markers
  - Negative markers, NO residual mass or mass <1cm → Surveillance (Preferred)
  - mass ≥1cm on CT → B/L nerve sparing RPLND
    - Teratoma → Observe
    - Anything else → 2◯ EP/TIP/VeIP

Management after RPLND in Stage $I_A - III_B$

pN_0 → Surveillance

pN_1 → Surveillance (Preferred)
→ BEP × 2 cycle
EP × 2 cycle

pN_2 → BEP / EP × 2 cycle (Preferred)
→ Surveillance

pN_3 → BEP × 3 cycle
EP × 4 cycle.

Primary t/t of intermediate risk III_B, Poor risk III_C

- Primary chemo BEP × 4 cycle
VIP × 4 cycle

↓

Further treatment as discussed in "persistent rise"

Management after 2nd line chemo

* No mass, markers negative → Surveillance
→ nerve sparing B/L RPLND

* Partial response, mass but markers -ve → Resection

Teratoma ← → Anything else

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- Markers ↑, Mass ⊕
  - Elevated & rising markers → Third line therapy
  - Elevated but stable → Observe
  - Mildly elevated & normalizes → Resection

Points from Campbell

- Seminoma has more favourable natural history.
- At diagnosis, pt of Stage I, II, III are 85%, 10% & 5% in Seminoma & 33, 33, 33 in NSGCT
- Seminoma is exquisitely sensitive to radiation therapy & platinum chemo.
- Radiation therapy is a standard for CS I, IIA, IIB seminoma, but no role in NSGCT

~~Risk of Seminoma at~~

Stage I NSGCT
- → Surveillance
- → RPLND
- → Chemo

Surveillance – Rationale for surveillance is that 70-80% pt are cured by surgery alone, & relapsing pt can be cured by chemo.

* Disadvantage is long term follow up & more intensive therapy required at relapse.

* More than 90% relapses occur within 2 years

* For bulky (>3cm) relapse, induction chemo is given. <3cm relapse managed by RPLND.

RPLND → Rationale for RPLND :–

* Most common site of occult disease
* 15-25% incidence of teratoma, which is resistant to chemo
* low risk of recurrence after full RPLND
* Avoidance of chemo in >75% cases
* low morbidity ~ nerve sparing approach.

Disadvantage is risk of laparotomy & experienced surgeons may not always be available

* Long term cancer specific survival approaches 100%, less than 2% risk of late recurrence.

Primary Chemo → Goal of primary chemo is to minimize the risk of relapse and allow men to avoid RPLND

Disadvantage – Does not prevent ↓/treat teratoma
– long term CT imaging reqd.

Chemo → BEP 1/2 cycles.

It is associated with lowest risk of relapse, but relapse is chemo resistant.

★ So, surveillance is for low risk pt, RPLND/chemo for high risk.

RPLND Vs Primary Chemo for Stage IIA/IIB

RPLND – Advantage – 13-35% pt have pathologically negative nodes & avoid chemo

– 30% Retroperitoneal teratoma, resistant to chemo

– long term cancer specific survival is 98-100%.

Disadvantage → Additional therapy required in ~50% pt
→ Full induction chemo needed for residual disease
→ High quality RPLND not possible everywhere.

Primary Chemo :– Advantage – Complete response is achieved & surgery avoided in 60-80%.
– Can be delivered anywhere
– Cancer Specific Survival is 96-100%.

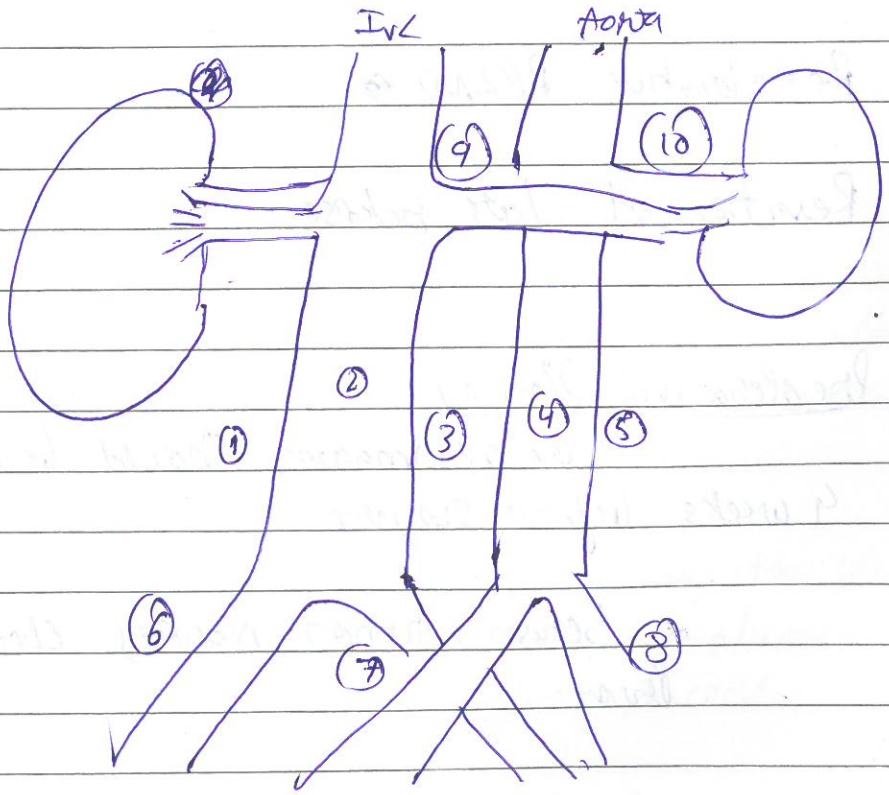
Disadvantage - long term toxicity of chemo
- Risk of relapse ī chemo refractory GCT.

Growing Teratoma Syndrome (GTS)

Patients with declining or normalized serum tumor markers, might present with enlarging (usually cystic) masses. These pt are considered to have growing teratoma syndrome.

In this case, chemo is interrupted & pt taken for surgical resection.

RPLND



Stations
1 → Paracaval
2 → Precaval
3 → Interaortocaval
4 → Preaortic
5 → Paraaortic
6 → Rt iliac
7 → Inter-iliac
8 → left iliac
9 → Rt hilar
10 → left hilar.

Different subtypes of RPLND

1) Primary RPLND → Performed after orchiectomy for CS I or low volume CS II NSGCT + normal serum tumor markers.

2) PC-RPLND (Post Chemo) → Done after induction chemo

3) Salvage PC RPLND → Performed after completion of induction & salvage chemo.

4) Desperation RPLND → Done despite elevated tumor markers

5) Re-operative RPLND

6) Resection of late relapse

Pre operative Planning

- Re of imaging should be done within 4 weeks before surgery

- Serum tumor markers checked 7-10 days prior.

Steps

(1) Exposure of retroperitoneum -

* Root of mesentery is opened at inferior to of cecum, to the medial aspect of IMV.

* In case of larger masses, incision can be turned around the cecum & into white line of Toldt upto Foramen of Winslow. IMV can be ligated in case of larger left para-aortic mass.

* Plane betn mesentery & retroperitoneal fat is developed by dissecting along anterior surface of gonadal vein.

(2) Split & Roll technique → large lymphatics over left renal vein should be ligated & divided.

* When the chosen template involves splitting over both great vessels, split is performed on aorta first to avoid pre caval right sided accessory lower pole renal arteries.

* If nerve sparing technique is performed, the split should be stopped at the IMA & post ganglionic sympathetic fibres identified before proceeding.

(3) left para-aortic packet is rolled inferiorly off the left renal vein. left gonadal & lumbar vein are doubly ligated & divided.

This packet is rolled up to left crus of diaphragm.

(4) Interaortocaval packet

* If Rt sided nerve sparing technique is to be performed, then IVC split → roll is to be performed next.

* IVC split is performed from the left renal hilum to the crossover of the right common iliac artery where it is continued inferolaterally till right ureter.

* Lymphatic tissue is rolled medially off the IVC. Once the medial aspect of IVC is controlled, the tissue is rolled laterally off IVC.

* Tissue is rolled medially off aorta. The right sympathetic trunk is encountered at right lateral borders of interaortocaval packet.

(5) Right Paracaval packet is the smallest.
It is rolled laterally & superiorly off the (common iliac artery and) crossover of right ureter is reached.

(6) Nerve preservation → * Left post ganglionic sympathetic nerves are first identified as they course along the lateral borders of aorta & left common iliac artery.

* Fat above it can be swiped to show them running obliquely towards aorta

* The right sided post ganglionic nerve fibres are best identified as Pre caval & inter aorto caval tissue is noted medially off the IVC.

Post chemo RPLND histologic outcomes

Fibrosis → 40%. — CSS & RFS 95%.
Teratoma → 45%. CSS 82.3%. RFS 60%.
Viable GCT → 15%. long term survival 50-70%.

Factors associated ∈ Poor prognosis
1) >10% viable tumor
2) Intermediate / poor risk category
3) Incomplete resection

Desperation RPLND

* Generally patients with elevated tumor markers are not candidates for RPLND, and are given standard or high dose chemo

* But if they fail to respond, then surgery needs to be performed. That is called desperation RPLND.

* 5yr OS ∈ Desp-RPLND is 53.9%.

Selection criteria

- Declining or Plateauing tumor markers after chemo

- Slowly rising after initial complete response to last chemo

- Resectable disease

- As a last resort in a patient with rising markers & all chemo options exhausted.

Complications

① Infertility & ejaculatory dysfunction

* Before development of unilateral templates and nerve sparing RPLND, most patients undergoing RPLND were anejaculatory.

* Ejaculatory function was preserved by
  1) Changing the boundaries of dissection

  2) Prospectively identifying post ganglionic sympathetic fibres and superior hypogastric plexus

* Post operative paternity can be expected in 75% of men undergoing primary (a) sparing RPLND

(2) Pulmonary - Exacerbated due to Rx of Bleomycin

(3) Ileus → 0-1% in Primary RPLND

(4) Lymphocele - Avoided by meticulous ligation of large lymphatics.

(5) Chylous ascites

Ongoing trials in breast

1) SOUND - To avoid SLNB in N0 pt

2) TADEN - Targeted axillary dissection

Targeted axillary dissection - Clip placed at initial node biopsy from to NACT.
During surgery, SLNB + clipped node both removed.

If Sentinel node & clipped node same, then FNR is 6%

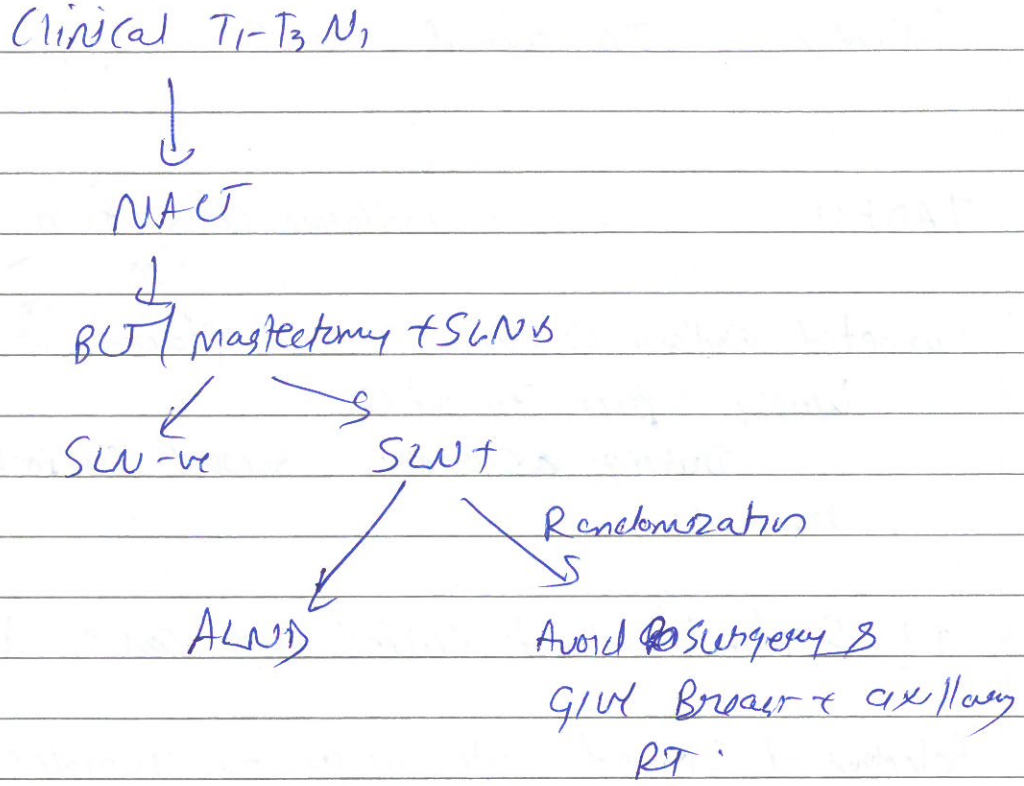
Selection of clipped node only → Targeted lymph node biopsy

TLNB + SLNB = Targeted axillary nodal dissection.

In post NACT pt. FN rate with SLNB only is 10%.
SLNB + TLND is 1.5%.

Techniques for targeting - I[131] seed
- Mag seed
- Micro implant/ tracker
- Carbon tattooing.

Future - NSABP B051
Alliance A011202
AXSENA
] - To avoid ALND if TAD (+)


Clinical T1-T3 N1
NACT
BCT
Mastectomy + SLNB
SLN -ve
SLN +
Randomization
ALND
Avoid Surgery &
CIVI Breast + axilla
RT.

Trials of Ca Breast

DCIS

(1) Role of RT

1) NSABP - B17
2) EORTC 10853
3) UK/ANZ
4) Swedish trial

} Significantly improved DFS but no improvement in OS.

5) Meta analysis by Early Breast Cancer Trialist Group
→ RT halved the rate of ipsilateral breast events.

6) RTOG 9804 → Benefit of RT in low risk DCIS - Yes!

7) ~~EORTC~~ ECOG E5194 → low grade lesions, ≤2.5cm has low rate of recurrence without RT.

(2) Endocrine therapy

DNSABP B24 - Excision + RT + Tamoxifen / Placebo

32% ↓ invasive recurrence
16% ↓ DCIS recurrence
32% ↓ CBC

2) NSABP B35 → Tamoxifen Vs Anastrozole
↓ risk of breast event

(3) NSABP B-43 - Her2 +ve DCIS, randomized to lumpectomy +RT alone, Vs Lumpectomy + RT + 2y Herceptin

Ongoing trial.

Carcinoma Breast

Trials for BCS

1) NSABP-B04
   - Node negative → RM
   - Node negative → Mastectomy + RT
   - Node negative → Mastectomy
   - Node Positive → RM
   - Node Positive → mastectomy + RT

No survival advantage of RM over mastectomy + RT
40% node Positive in RM patients.
In mastectomy only group, only 19% pt developed nodal disease.

2) NSABP B06 - Lumpectomy + ALND ± whole breast RT vs MRM in T1-2 disease.

No difference in DFS/OS bet" lumpectomy & MRM but, there were differences in LRR among the three arms
Lumpectomy alone → 39.2% LR
Lumpectomy + RT → 14.3%
Mastectomy → 16.2%

3) Milan I → Lumpectomy + RT vs RM.
No diff. in OS, but local recurrence significantly higher for BCT (8.8%) vs RM (2.3%)

4) CALGB 9343 & PRIME II → RT can be omitted in age ≥ 70 yr, ER+ve, T1 N0 on Tamoxifen.

5) EORTC 1081 → BCT + RT Vs MRM
Similar OS, but higher LRR in BCT.
larger tumors were taken in this Trial, compared to NSABP B06 & Milan 1.

6) EBCTCG Trial → Rate of BCS increases Post NACT

Trials for NACT

1) NSABP B18 → 1523 pt randomized to surg f/b 4 OAC Vs 4 OAC f/b surgery.
36% had cCR & 43% had partial response
13% had pCR
37% axillary downstaging.
Significant More pt in NACT had lumpectomy (67% Vs 60%)

No significant diff in DFS & OS, but trends towards improved DFS/OS.
Better DFS/OS in pt c pCR.

2) NSABP B27 → 4 AC → Surgery → 4 Docetaxel
Vs
4 OAC → 4 Taxol → Surgery.

Second group had higher pCR rate (26.1%) but no benefit in DFS/OS.

⇒ IMPACT trial → Neoadjuvant hormonal therapy
Pt treated to neoadjuvant tamox or anastrozole on both
Post menopausal, ER+ve, operable or locally advanced.

44% pt received BCS after anastrozole, 31% after tamoxifen

3) NSABP B40 → Taxol → 4DAC
vs
Taxol + Cap → 4DAC vs
Taxol + Gem → 4DAC
↓
Secondary randomization was to receive bevacizumab or not.
All pt were Her2-ve.

NA Bevacizumab shown to ↑ pCR, ↑OS but not DFS
No effect of capecitabine or Gem.

4) NSABP B41 → Neoadjuvant trastuzumab or lapatinib or both.
Similar pCR rates for trastu & lapatinib (52% vs 53%) but a non significant increase in pCR for combination (60%).

5) CTNeoBC pooled analysis → Highest survival advantage given by pCR in case of Triple-ve & Her2 +ve disease

6) NSABP B51 / RTOG 1304 → Ongoing Trial
→ Utility of PORT + axillary RT in N+ pt who undergo NAC and become node negative. TWO arms
Mastectomy arm < No RT / Chest wall + nodal RT
BCS arm < Chest wall RT / nodal + chest wall RT

8) Neo Sphere → Neoadjuvant trastuzumab + Pertuzumab
Phase II trial.

SLNB trials

1) ALMANAC trial → First large prospective RCT comparing SLNB with ALND
→ Better quality of life & fewer morbidity with SLNB.

2) Sentinel Node Vs Axillary Clearance (SNAC) trial
1088 women c cN0 randomized to
SLN alone / SLN + f/b ALND

Primary end point → Increase in arm volume.
Sec " → Axillary morbidity
Result → lower rates of morbidity
Sensitivity - 94.5%
FNR - 5.5%
NPV - 98%

3) NSABP B32 → 5611 pt { SLN + ALND / SLN → ALND only if +ve.

Primary end points - OS, DFS, regional control.

Result - 97% identification rate
9.7% FNR
Similar OS, DFS & LRR

4) IBCSG 23-01 – ~~[illegible]~~ $T_1 - T_2 < N_0$

Sentinel node with micrometz

ALND | SLNB alone

- No diff in DFS & OS
- More morbidity with ALND

5) ACOSOG Z0011 → 891 pt, $T_1 - T_2$ N_0

↓

Lumpectomy + SLNB

~~[illegible]~~

1-2 node +ve

	ALND	No ALND
10 yr OS	83.6%	86.3%
LRR	3.6%	1.8%

6) Z0010 →

7) AMAROS Trial → Positive SLNB

ALND | Axillary RT

5 yr axillary recurrence	0.43%	1.19%
Lymphedema	28%	14%

8) ~~ACOSOG~~

SLNB after NACT

1) ACOSOG Z1071 → 649 pt ↑ cN1 & 38 pt ↑ cN2

↓

NACT

↓

SLNB + ALND

PCR → 41%, 20.6% had residual nodal disease confined to SLN only & 31.1% had nodes in both SLNB & ALND.

FNR → 12.6%

~~FNR~~ FNR reduced by dual dye & ≥ 3 nodes removed.

2) SENTINA → Four arm, prospective trial of 1737 pt

Women who were cNo underwent SLNB before NAC (arm A)

If SLNB was positive, a second SLNB done post NAC (B)

cN+ received NAC directly, & if they became ycNo, it was arm C.

If they remained ycN+, they were arm D.

Detection rate 80% in arm C
FNR → 14.2%.

Detection rate 60% in arm B, FNR - 51.6%.
FNR decreased with use of dual dye technique.

3) SN-FNAC → FNR - 8.4%, which decreased to 4.9% if ≥2 nodes were removed.

Post Mastectomy Radiation

1) MA.20 trial → T1 - T2 undergoing whole breast irradiation with ALND or ALND + nodal RT.
All patients had 1-3 +ve nodes
Nodal RT improved locoregional & distant DFS but not OS.

2) EORTC 22922 → Pt underwent mastectomy. Some had pN0 Randomized to ALND / ALND + nodal RT
DFS improved.
OS improved but not significant

3) START-B trial → 50 Gy |25 # Vs 40 Gy/15 # (Hypo #)
No significant diff.

RT related side effects less common in hypofrac. group

GEC-ESTRO trial → Evaluated Multicatheter APBI in Stage I, HR+ve patients Post lumpectomy. No significant diff. bet^n APBI & WBI.

4) IMPORT LOW → Partial breast Irradiation (not accelerated)

T ≤ 3cm, resected to 2mm margins. Recurrence rates at 5yr were exceptionally low.

5) RAPID trial → Ongoing.
→ Increased Grade 1 & Grade 2 toxicities in APBI arm.

6) EORTC 22881-10882 → Boost to tumor site after RT.

Adjuvant Hormonal Therapy

1) EBCTCG review → Review of over 60 studies for adjuvant tamoxifen. Tamoxifen reduced LRR & prolonged survival.

2) NSABP B21 → Three arms [≤ 1cm size, node negative]

Lumpectomy +ALND+RT	Lumpectomy+ALND +Tamox	Lumpectomy+ALND+Tamox →RT

RT alone resulted in 49% lower hazard rate of IBTR than tamoxifen alone.
RT + Tamox resulted in 63% lower hazard rate than RT alone & 81% than tamox alone.

So, RT is always needed & RT+Tamox is best.

3) NSABP B14 → Tamoxifen Vs Placebo

10yr recurrence →	4.3 y.	14.7 y.

3) ATLAS Trial → for time duration of tamoxifen (10 yr Vs 5 yr)
OS & DFS improved ↑ longer duration

4) BIG 1-98 – Upfront AI Vs Tamox f/b AI

5) Tamoxifen & Exemestane in Early Breast Cancer

Both demonstrated equal rates of tumor regression. So AI can be used in post menopausal women at some point.

6) ATAC Trial → Anastrozole Vs Tamoxifen
Significantly ↑ DFS
↓ mets
↓ CBC.
Fewer gynecological problems & vascular events but ↑ arthralgia & fractures.

7) MA 17 → Additional 5 yr of AI Vs Placebo after initial 5 yr of AI + tamoxifen.
Significant improvement in DFS (not OS) in long b/c arm.

8) NSABP B42 → Same as above.

9) TEXT (Tamoxifen & Exemestane Trial) – Role of ovarian suppression in early, HR+ve tumor.

10) SOFT (Suppression of Ovarian Function Trial)

Role of Bisphosphonates

EBCTG study → Adjuvant use of bisphosphonates ↓ recurrence in post menopausal.

Adjuvant Chemo Trials

1) CALGB 9344 → Role of Paclitaxel after AC.

2) CALGB 9741 → Dose dense Pacli (every 2 weeks) led to lower risk of recurrence & improved survival

3) Anthracycline in Early Breast cancer (ABC trial) → Role of anthracyclines

4) NSABP B-31 → Trastuzumab given 1yr beginning concurrently ± taxol

5) HERA → Trastuzumab given sequentially after chemo

6) BCIRG 006 → Trastuzumab concurrently ± docetaxel as in TCH regimen. [Docetaxel, Carboplatin, Herceptin]

7) APHINITY → Addition of pertuzumab to Trastuzumab

8) ExtaNet → Neratinib after completion of 1yr Trastu. Shown to reduce recurrence in triple +ve cancers.

KATHERINE trial → Her 2+ve early breast cancer ē residual disease after NACT, given T DM 1 or Trastu in adjuvant.
Invasive DFS significantly higher ē TDM 1.
Risk invasive recurrence or death is 50% lower ē TDM 1.

9) Adjuvant Capecitabine for breast cancer after pre operative chemo (maruda et al)

→ OS longer
→ DFS longer (highest in Triple -ve)

Local therapy in Stage IV cancer

1) TMH trial → No evidence to suggest that loco regional therapy improves survival in pt ē metastatic breast cancer.

2) Turkish trial (MF07e01) → Improved survival seen with ER/PR +ve, Her 2 -ve, age < 55 yrs, and bone-only mets.

3) SUBMIT
POSYTIVE
JCOG 1017
} - Results pending.

→ CREATE-X trial → Role of adjuvant Capecitabine in Her2 negative Ca Breast after PCR with NACT

Capecitabine arm had significant 5 yr OS benefit (89 Vs 83 %) & DFS benefit

Triple negative subgroup showed significant OS & DFS benefit, but no benefit in HR+ve subgroup

Other Preventive trials

(1) Million Women Study → Role of HRT in Ca Breast

↑ risk of cancer seen with estrogen only (RR = 1.30) & E+P (RR = 2) & tibolone. Max risk increases with combination HRT.

10 yr of HRT results in 5 additional breast cancers per 1000 users of estrogen only HRT & 19/1000 users of E+P.

(2) Prospective trials of Ca Breast Screening

a) Health Insurance Plan (HIP) trial – 1st trial

2) MMST I trial

3) Swedish 2 county trial (Greatest ↓ in mortality)

4) Stockholm trial

5) UK AGE trial. – Significant ↓ in breast cancer mortality was noted after more than 10 yr follow up.

Annual mammo offered starting age 40 yr in the intervention arm, vs routine medical care in control arm

(3) Risk reducing agents

1) NSABP-P1 → Tamoxifen in Ca Breast

2) NSABP-P2 → STARR - Tamoxifen Vs Raloxifene

(4) Intra op Partial breast irradiation

1) ELLIOT

2) TARGIT-A Trials

Advanced Ca Breast / Metastatic Ca Breast trials

1) PALOMA 2 → Palbociclib + Letrozole in advanced Ca Breast c no prior treatment had better median PFS than letrozole alone.

2) MONALEESA 2 → First line ribociclib + letro in HR+ve, Her 2-ve advanced/recurrent Ca Breast had better median PFS than letro alone

3) OLYMPIAD Trial → Role of Olaparib in BRCA+ve, Her 2-ve Metastatic Ca Breast. Median PFS longer c Ola.

ISGPS Guidelines for Ca Pancreas

(1) Post op Pancreatic fistula

Pancreatic fistula is an abnormal communication betⁿ the pancreatic ductal system and another epithelial surface containing pancreas-derived, enzyme-rich fluid.

Dsis → Any measurable volume of drain on or after POD3 with amylase level >3 time the upper limit of normal, associated with clinical features of leak.

If only drain amylase is raised, with no clinical features, it is not considered POPF.

	A (no)	B	C
1) Increased amylase >3x	yes	yes	yes
2) Persisting peripancreatic drainage > 3 week.	no	yes	yes
3) Clinically relevant change in management	no	yes	yes
4) POPF specific percutaneous or endoscopic intervention	no	yes	yes
5) Angiographic procedures for bleeding	no	yes	yes
6) Sign of infection related to POPF	no	yes	yes
7) POPF related organ failure	no	no	yes
8) POPF related death.	no	no	yes
9) Re operation	no	no	yes

"Grade A" is not considered POPF any more. It is called Biochemical fistula. / Biochemical leak.

② Classification System of Pancreatic anastomosis

Factors associated with leaks

- Pancreatic Remnant related - MPD diameter < 3mm associated ↑ significantly ↑ risk of leak

- Gland texture ⇒ soft gland has significantly ↑ risk of leak than a hard, fibrotic gland.

- Pancreatic mobilization should not be done more than necessary (Strasberg et al)

Pancreatic anastomosis related

No statistically significant difference b/t the leak rates of PJ & PG.

Use of Stent → One study showed no significant difference with a stent irrespective of texture of pancreas.

But, Pearn et al found significantly lower fistula rate with stent

Classification of Pancreatic remnant

Type I → Duct size < 3mm
Type II → 3-8mm
Type III → > 8mm

Add A → Soft Pancreas
B → Hard Pancreas

Mobilization of Pancreatic remnant
PM 1 → < 1cm
PM 2 → 1-2cm
PM 3 → > 2cm.

Classification of anastomosis

I → PJ

II → PG

III → Any other variation.

Add A → Duct to mucosa

B → Duct ligation / invagination

S0 → No stent

S1 → Stented (internal)

S2 → External stent

S3 → other type of stent

Also to be recorded - Adjuncts like Inj octreotide, fibrin glue

Omental wrapping

- Type of suture material used
- Technique of suturing

(3) When to do Whipple in the absence of histology?

- Incidence of benign disease after Whipple for presumed malignancy → 5-13%.

- Incidence of malignancy in pt operated for chronic pancreatitis → 5-9%.

- M.C. diagnosis of benign disease in resected specimens → Pancreatitis, and most common of that is auto immune pancreatitis. (30-40%)

* TO diagnose AIP, EUS Guided Trucut biopsy, Serum levels of IgG4 & HISORt [Histology, Imaging, Serology, Other organ involvement] are used.

* When in doubt, a short term trial of steroids may be given to differentiate AIP from a malignant mass.

* Chronic pancreatitis, has a risk of developing cancer in 4% at a 20 year period.

Consensus Statements

1) In presence of a solid mass in the head of pancreas, that is suspicious for malignancy, biopsy proof is not needed to proceed for surgery

2) Before starting NACT or NACT-RT, biopsy proof is needed. In a resectable patient, ERCP brushing is preferred. Otherwise EUS-FNA is procedure of choice.

3) In a pt of CP in whom malignancy is suspected, resection is indicated even in the absence of histological proof

4) When a diagnosis of AIP is highly suspected, measurement of Serum IgG4, EUS-Trucut is done.
Steroids can be given over 4-6 weeks.

(4) Lymphadenectomy in Ca Pancreas

Lymph node stations name same as Gastric cancer.

Standard LNectomy → 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a
14b, 17a, 17b

12b → Lymph nodes along bile duct
12c → " " cystic duct
13a → Posterior aspect of superior portion of Pancreas
13b → " " inferior " "
14 → Rt lateral SMA
17a → Ant. aspect of superior portion of head of Pancreas
17b → Ant aspect of inferior "

Minimum lymph nodes to be harvested → 12-15
Lymph node ratio > 0.2 is indicator of Poor prognosis

If Pre OP chemo / Chemo RT given, < 15 nodes are acceptable.

(5) Borderline resectable Pancreatic Cancer.

- In patients with isolated venous involvement, there is no evidence supporting neoadjuvant therapy
- Clear evidence supporting Straight forward resection in reconstructable mesenteric-portal axis involvement

* Arterial resections have greater perioperative morbidity & mortality than venous resections.
Survival is higher, compared to not undergoing surgery at all. But these should not be recommended in all patients routinely.

* No level 1 evidence of benefit of NACT, ~~even~~ in pt with arterial involvement, but evaluation is recommended in trial setting.

* Margins to be seen in histopath report (viva)
- Anterior
- Posterior
- Medial (SMV groove)
- Cut end of pancreas
- SMA margin (most important)
- Bile duct
- enteric.

* Patients with suspected but not proven distant mets & patients ineligible for surgery due to comorbidity should be re-evaluated for operative intervention after supportive tt and/or NACT.

(6) Extended pancreatectomy

multivisceral resections are warranted in locally advanced diseases if R0 margins can be achieved.

Trials of Rectum

(1) Imaging

1) MERCURY

2) MERCURY II (for low rectal cancers)

(2) Treatment of early rectal cancers

1) ACOSOG Z0 6041 [Capox + RT < TAE / TME]

2) GRECCAR 2

3) Lezoche et al.

4) CARTS [TEM after chemo RT]

5) STAR-TREC ← surgery / SCRT f/b TEM / CTRT f/b TEM — ongoing.

(3) Trials for SCRT

1) Swedish trial

2) Dutch trial

3) MRC trial

(4) SCRT Vs Long course CTRT

1) Polish trial

2) TROG trial

(5) Long course RT + CTRT

1) FFCD 9203
2) EORTC 22921

(6) Duration of Surgery after Pre op RT

1) Stockholm III trial

2) GRECCAR 6 (CT RT)
3) Lyon R 90-01

(7) Role of adjuvant RT after upfront Surgery

1) NSABP R-01
2) NSABP R-02 [Adjuvant Chemo Vs Adjuvant CRT]

(8) Pre op Vs Post op therapy

1) German rectal cancer trial.

2) NSABP R03

3) Korean trial [for Neoadjuvant]

Other trial for lap → NSABP R04

(9) Trials of lap Vs Open

~~Positive~~ ~~COST~~ ~~COLOR~~

Positive — COLOR II
COREAN

Negative — ACOSOG Z6051
ALaCaRT

(10) Trial of Robotic → ROLARR

(11) Trials for TaTME

1) GRECCAR 11
2) Bordeaux trial
3) COLOR III

(12) Lateral node dissection → JCOG 0212

(13) Adjuvant chemo has no benefit in pt ~~with~~ Preop CRT
↳ T-CONR-RT

(14) Trials for ELAPE

1) ELAPE trial ~~Stop of the CRT~~
2) Huang et al
3) Yu et al

(15) TNT trials

1) PRODIGE 23 – long course CRT based FOLFIRINOX + TNT

2) POLISH II trial (SCRT based TNT)

3) RAPIDO trial "

(16) Wait & Watch trials

1) Halia Gramy

2) OPRA trial.

Trials of Ca Colon

(1) Trial for NACT

i) FOXTROT → ~~6 weeks~~
6 week FOLFOX f/b surgery f/b 18 wk FOLFOX
Vs
Surgery f/b 24 wk FOLFOX

Increased pCR rate
Increase Ro resection rate
No diff in post op complications

(2) Trials for lap Vs Open Surgery

1) COST
2) COLOR
3) CLASSIC
} - All + ve.

(3) COLD trial → D2 Vs D3 lymphadenectomy

(4) Trial for adjuvant chemo

1) Oxaliplatin — NSABP C07
— MOSAIC
— Cape / Ox trial.

2) Irinotecan – CALGB
– ACCORD-2
– PETACC-03
} – All -ve

3) Bevacizumab – NSABP C08
– AVANT
– QUASAR 2
} – All -ve.

4) Duration of Chemo → IDEA collaboration
[To show non inferiority of 3 months vs 6 month chemo]

Result → 3 month (cap/ox was non inferior in low risk pt of Stage III.

For the rest, it is 6 month FOLFOX
High risk disease (T4 or N2) has
DFS benefit for 6 month.

5) Chemo in Stage II → SACURA trial
– No benefit of using 4yr 5FU
adjuvant in Stage II, not even in
high risk.

6) Ribic et al → Impact of microsatellite instability in Stage II.

Pt of Stage II, randomized to receive chemo or not, then stratified according to MSI status.

MSI-H pt who didnt receive chemo had superior survival to MSS — MSI-L pt who

MSI-H pt who received chemo had no survival advantage.

7) ECOG 5202 → Ongoing Trial for pt of MSI-H & absence of LOH in 18q, where they are kept in observation.

(5) Trial for CME → Hohen berger et al.

(6) HIPEC Trials

1) COLOPEC → T4 N0-2 M0 or perforated cancer

2) PRODIGE 7

PRODIGE 22 / ECKINOX Trial

Resectable, high risk T3 T4 N0-2 cancers

Colectomy
f/u adjuvant Folfox
×6 months

FOLFOX ×4 cycles
f/u surgery
f/u FOLFOX ×8 cycles

In RAS wild-type pt, cetuximab was added in Peroperatory arm.

Primary end point → Tumor Regression Score
Sec " " → Toxicity, Peroperatory morbidity, quality of Surgery.

Result → Tumor downgrading seen (TRG 1-2 → 44%)
but not high as expected.

→ No benefit of adding cetuximab

→ No benefit in OS, DFS, RFS.

Lung trials

Screening trials

1) PLCO trial → Patients aged 55-74, randomized to annual CXR vs no screening.
No diff in lung cancer mortality.

2) ~~NLST~~ NLST trial → 55-74 yrs, with at least 30 pack-years of smoking, who currently smoke, or quit within last 15 yrs, randomized to LDCT screening with 1mSv LDCT or CXR.
Any non calcified nodule ≥ 4mm was deemed positive.
3 rounds of screening, one at baseline & 2 annually.

20% relative reduction in mortality seen
Rate of death from any cause was 6.7% lower in LDCT arm
24% pt on LDCT were "positive"

3) NELSON trial → 50-74 yrs pt, underwent CT at baseline, year 1, 3, 5.5 Vs no screening.

Overall referral rate for suspicious nodule → 2.1%
lung cancer mortality ← screened - 2.5/1000
no screen - 3.3/1000

Significant ↓ in mortality.

(2) Operative trials

1) JCOG 0802 → lobectomy Vs Segmentectomy for Early Lung (ongoing)

So far, shows ↑ blood loss, air leak, ICD insertion in Segmentectomy

2) ACOSOG Z0030 → Systematic mediastinal lymph node dissection Vs LN sampling.

Sampling ≈ dissection in No pt, but most pt in this trial were T_1 / T_2 only.

3) VIOLET study → VATS Vs Open lobectomy

↓ Post op stay
↓ cost
↓ OPD visit
↓ admission
↓ Blood loss
↓ time
LN upstaging 6.2 % Vs 4.8 %

VATS

4) MVU VLC trial → Multiportal Vs Uniportal VATS

Adjuvant Rt

1) Lung ART trial → No role of adjuvant RT after Rx resection

↗ Lung Adjuvant Cisplatin Evaluation

2) LACE meta-analysis → No significant benefit in OS/DFS in Stage II, but ↑ has a benefit of 5.4% survival in 5 yrs for all lung cancers.

3) CALGB 9633 → Tumors ≥ 4cm have survival benefit ± adjuvant chemo

3) JBR 10 trial → Improved survival in No tumors ≥ 4cm in size.

Non Surgical

1) RTOG 0236 → SBRT in biopsy proven ca lung < 5cm in size in pt who are medically ineligible for surgery.

4 yr control rate → 93%

4 yr OS → 40%

Majority of pt died of non cancer causes.

2) Pooled analysis of two RCT comparing SBRT ± surgery shows no diff in recurrence pattern or 3 yr DFS.

3 yr OS is better with SBRT. But both trials had 22 & 36 pt only.

3) RTOG 7301 → Established single modality RT dose of 60 Gy in 6 weeks.

3) RTOG 8311 → Dose escalation ± twice daily fractionation showed 64.8 Gy, twice daily gives best OS of 29% at 2 yr.

4) EORTC trial of standard RT Vs CHART
↓
Improved OS
↑ dysphagia.

5) RTOG 9410 → Concurrent Chemo RT > Sequential
3 arm trial — Cisplatin + Vindesine followed RT
CT/V ± concurrent RT
CT + etoposide ± concurrent RT

6) PACIFIC Study — Adjuvant Durvalumab after CTRT

Ca Colon lecture

Nodal stations

Pericolic (around the colon) – level 1 D1
Principle (along named vessels) – level 2 D2
Central (SMA, IMA nodes) – level 3 D3
Para central / para aortic nodes.

Risk of synchronous lesions → 30% [polyp / adenoma / cancer]
" " cancer → 3%.

If obstructed, do full colonoscopy within 6 months of surgery.

No role of PET CT in initial staging.

CEA has prognostic value.

CT chest is not routinely recommended. When should it be done?
→ Palpable lump
→ T3 / T4 or N+ lesion on CT abdom
→ Symptoms suggests
→ ↑CEA pre op

PET CT – if any suspicious findings on CT
– ↑CEA on follow up

low risk vs high risk Stage II:

- LN < 12
- Poorly differentiated tumor
- Vascular or LVI | PNI
- Obstruction or tumor perforation
- pT4 stage.

High risk Stage II → Consider adjuvant chemo.

CME → Complete mesocolic excision
CVL → Central vascular ligation

Rt & left hemicol are now called "mesocolectomy".

Plane of CME is betn TOldt's fascia & retroperitoneum

~~CVL~~

D3 dissection → Removal of nodes from surface of SMVS SMA.
After high ligation of vessels, go 1-2 cm beyond

D3 is more aggressive than CVL when it comes to lymph node removal. By CVL, we only go till the root of vessels. But in D3, we go beyond it.

Japanese respect less length of colon, but have more lymph node dissection.

D_2 Vs D_3 dissection

Avg number of LN retrieved is higher in D_3.

Who should go for D_3 dissection?

→ T_3 or T_4 lesions

COLD trial → D_2 Vs D_3

Equivalent 30 day mortality, leak rates, nodes retrieved
But node positivity is higher with D_3.
Oncological outcomes pending.

other ongoing trial → T-REx
RELARC
RICON.
Most trials going on for Rt colon cancers.

Locally advanced Colonic cancer

- Sigmoid is commonest site to have locally advanced cancer.

With local organ infiltration, multivisceral resection should be done, as it improves survival versus if not done.

Cap Vs Oper → COST, COLOR, CLASSICC

Adjuvant therapy

MOSAIC trial → Established role of FOLFOX as better than 5FU/LV in stage III.
No benefit seen in Stage II.

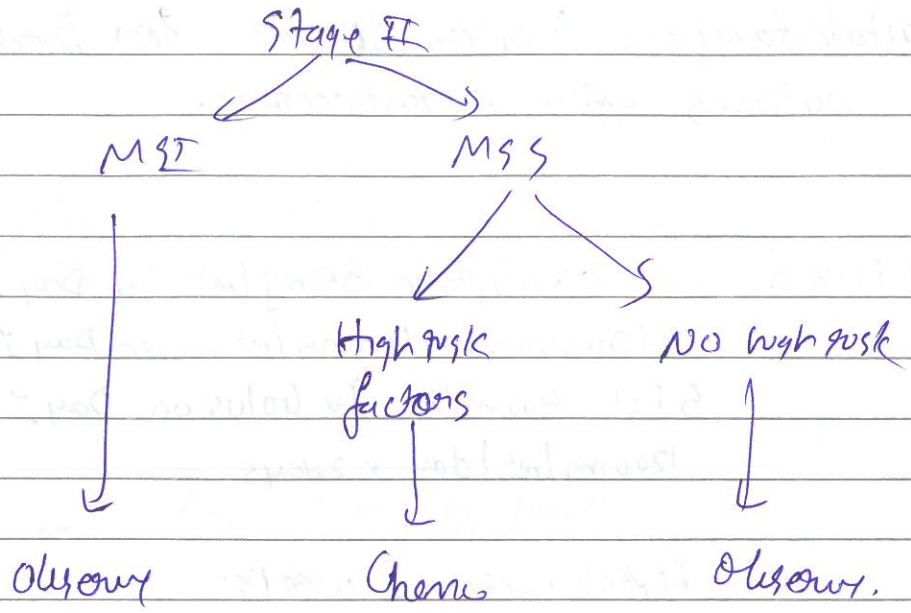
No direct comparison betn FOLFOX or CapOx.
12 cycles.

Stage III	CapOx	FOLFOX
Low risk (T_1/T_2 T_3 -N)	3 months	
High risk (T_4/N_2)		6 months

In stage II, there is benefit of chemo in only QUASAR trial.

High risk in stage II → pT4, <12 nodes, Poorly diff, LVI, PNI, perf/obstruction.

High risk pt can be considered for chemo.



NACT trial → FOXTROT trial

- Significant downstaging
- less apical node positivity
- acceptable morbidity & mortality.

17% pt progressed on chemo

Results → No significant benefit in Ro resection, DFS/RFS

Radiation in colon → INT 0130
Negative study.

SEER database analysis shows role of RT in T4 & Rt resection.

Metastatectomy → FONCA score for Predicting outcomes after metastatectomy.

mFOLFOX 6 → Oxaliplatin 85mg/m² on Day 1
Leucovorin 400mg/m² on Day 1
5FU 400mg/m² IV bolus on Day 1 f/b
1200mg/m²/day x 2 days

Repeat every 2 weeks.

Cape Ox → Oxaliplatin 130 mg/m²
Capecitabine 1000mg/m² Per Oral BD x 14 days.

Repeat every 3 weeks.

Rectum Case

My patient is a 50yrs old gentleman named ~~residing~~ residing at Gorakhpur, Uttarpradesh, presenting c/c/ chief complaint of

Difficulty while passing stool : 6month
Bleeding per rectum : 6month.

Pt was alright 6month back, following which, he started developing difficulty while passing stool. He had to strain for passing stools, and it was associated with passage of fresh blood per rectum. The bleeding per rectum was in the form of few drops of fresh blood. It was associated with a feeling of incomplete evacuation due to which patient to go to the toilet 4-5/day, and he complains of passage of mucus mixed with blood.

~~No h/o fever~~ No No ~~blood~~ vomiting, fevers, pain in abdomen or loss of appetite
No h/o urinary complains
No h/o breathlessness or any swelling in neck.

Patient ~~presented to us~~ took conservative treatment at a local hospital, and was then referred to our institute. Here, he underwent various investigations and was advised radiation therapy with an oral tablet. He completed the treatment and is now referred for further management to department of surgery.

He has undergone repeat imaging & testing.

Past H/o — No H/o similar complaints in the past
No h/o any surgery, no H/o
DM/HT/TB/BA/epilepsy/allergy.
No H/o any blood transfusion.

Personal H/o — Bowel habit alteration has been described before.
Bladder habits are unaltered
Sleep and appetite are ↓
Pt takes ~~mixed~~ Vegetarian diet
H/o addiction to ~~alcohol~~ tobacco 4-5/day : 20 years.

Family H/o — No h/o similar complaints in the family
No h/o any malignancy in the family.

Provisional diagnosis → Growth in the lower GI tract of malignant etiology, most likely rectum.

examination → Pt was examined in broad daylight with proper consent. He is moderately built & ~~nourished~~ moderately nourished;
Pt appears conscious, cooperative & well oriented to T/P/P.
P — 80/min in Rt radial
BP — 130/80 in Rt brachial
RR — 16/min
* ECOG performance status 1

No pallor | Icterus | cyanosis | clubbing | oedema
BMI → 22 kg/m².

Systemic

P/A – Inspection → Abdomen is scaphoid in shape, with umbilicus central. All regions move equally ⊂ respiration, no visible scar (sinus) dilated veins | fistula | visible peristalsis.

Hernial sites normal
Genitalia normal

Palpation – Inspectory findings were confirmed.
No local rise in temperature, no tenderness, no organomegaly, no palpable lump

Percussion – ~~Hyper~~ normal liver dullness
Tympanic note everywhere on abdomen

Auscultation – BS (+)
* Left SCL – (+)

P/R → Per rectal examination done after explaining the procedure & taking due consent in left lateral (Sims) position.

Inspection – Perianal skin is normal, no warts, no dilated vein/scar/sinus/fistula opening/ Hemorrhoids.
No fissure in ano

~~Palpation~~

Proctoscopy → Ulceroproliferative growth seen 1cm from anal verge, with its upper limit at 4cm from verge. It extends from 3'o clock to 7'o clock position. No other lesion seen, No internal hemorrhoids seen.

Palpation → Palpation performed after gently separating the buttocks with lignocaine jelly. ~~Post~~ A growth can be palpated at 1cm from anal verge over lateral wall of rectum. It is movable in craniocaudal & lateral axis. ~~Fecal~~ Fecal stuning present.

Sphincter tone normal, No tenderness

Other system – NAD

TO read → Anatomy
→ Trials
→ Doses of chemo regimen
→ MR TRG, Ryan TRG
→ MERCURY II, Grecian 11 / CARTS

classmate
Date
Page

Breast Case

My Patient is a 60 year old female named _____
resident of Ahmedabad, presenting c c/o
lump in left breast since 3 months

Pt was ok before 3 month. Then, she noticed a small lump in her left breast. The lump gradually increased in size to current status.

It was not associated with pain, nipple discharge, swelling in opposite breast, swelling over arm.
No h/o bony pain or headache

Past h/o – no h/o similar illness in the past
no h/o any surgery in the past
no h/o DM/HT/TB/BA/epilepsy/allergy.

Personal h/o – Pt takes a vegetarian diet, ~~[illegible]~~
Bowel/bladder – unaltered
sleep/appetite – unaltered
Addiction – No.
Menstrual history → $G_2 P_2 A_0 L_2$, adq. breastfeeding
menarche – 14 years
menopause – 45 years
Pt had regular menses, lasting 3-4 days in a 28 day cycle.
Age of 1st child → 22 yrs.

Family Hx — No f/h/o similar illness
no f/h/o any other malignancy.

G/E - Matron SCL nodes

ECOG status →

BMI →

L/E → Pt examined in different positions i/e sitting with arms by the side, arms raised overhead, arms over hip and sitting with leaning forward.

On inspection, breasts appear symmetrical on leaning forward, both breasts fall down equally.
Skin over both breasts appear normal. No sinuses etc.
Nipple and areola are normal bilaterally. No displacement seen, no puckering of nipple seen, No discharge visible.
No arm edema seen
No supraclavicular or axillary fullness

Palpation → Inspectory finding confirmed
→ No local tenderness, no local rise in temperature,
A lump of approx 2x1 cm can be palpated in upper inner quadrant of left breast.
No overlying SI is ~~No~~ fixed to the breast tissue

Shows restricted mobility. No skin tethering or fixity seen. ~~Skin over it~~

No fixity to underlying pectoralis muscle.

No nipple discharge.

Bilateral axillary nodes are not palpable

Bilateral supraclavicular nodes not palpable.

Systemic → NAD

Stomach Cass

50 Year old male patient, resident of Morbi, presented with c/o

vomiting since 3 months
loss of appetite since 2 months.

Pt was c/o 3 months back. Then, he developed vomiting, which used to occur 3-4 hours after food ingestion. It gradually progressed in severity, to current status, where pt has multiple episodes of vomiting within 1hr of ingestion of any solid or liquid. Vomitus is projectile, non bilious, containing food particles and is aggravated by oral intake.

Pt also complains of recent onset loss of weight and loss of appetite in the last two months.

No h/o blood stained vomitus
No h/o fever, generalized weakness, distension of abdomen.
No h/o black tarry stools
No h/o epigastric burning pain.

He presented to our institute where he underwent endoscopy & imaging.

Past Hlo — No Past Hlo Similar con
No Hlo DM/HT/TB/BA/allergy/epilepsy
No Hlo surgery/Blood trans —

Personal Hlo — Pt takes a mixed diet,
Appetite is decreased
Bowel/Bladder habit unaltered.
Addiction history of alcohol since last
25 years and smoking 3-4 sticks/day
since 25 years.

Family Hlo — No family Hlo similar complaints
No family Hlo malignancy.

G/E — Due consent — adequate height — ~~exposure~~
Cl/o wise TPR, ~~BP~~ moderately built and
Properly nourished,
P — 80
BP — 130/80
RR — 16
No Pallor/Cl/CE — Pallor seen in conjunctiva
Icterus in sclera conj

PS — 1
BMI — 20 kg/m²

P/A → Exposure from nipple to knee.

Inspection → Abdo — Scaphoid
Umbilicus — central.
All quadrants move equally
Visible lump in epigastrium VARICES

Hernial sites ✓
Genitalia ✓

Palpation → Inspection confirmed
No ↑ temp, no tender
palpable lump in epigastrium 4×5cm in size
overlying skin is free
On ~~sit test~~ head elevation, the size of lump is diminished.
~~✓~~ Lump moves well with respiration and visible peristalsis can be elicited by stethoscope on it.

left SCL - not enlarged

To read → ~~✓~~ LN stations
→ ~~✓~~ GOJ metabolic alterations
→ NACT (adjuvant) surgery trials
→ ~~✓~~ Methods of reconstruction
→ ~~✓~~ D1/D2 etc

EUS < sens
spec

CT < sens →
spec →

→ ~~✓~~ Classification systems:

→ ~~✓~~ CRS grades

Ca Colon Case

My patient is a 50 year old male named ____ s/o Ahmedabad, presenting c/c/o

~~Bleeding per rectum~~

Dark colored stools since 3 months,

Pain in abdomen : 3 months

~~Weakness : 1 month~~

It was c/o 3 months back, when he developed a dull aching pain in right side of abdomen. Pain was insidious in onset, gradually progressing in intensity. It was non radiating, and was relieved on passage of stools ~~on taking medicine~~. It was also temporarily relieved by taking medication. It was followed by passage of black, tarry stools on/off. Initially, the frequency of defecation was 1-2/day, but it gradually increased to 4-5/day.

No H/o abdo. distension, vomiting, nausea,
No H/o fever
No H/o fresh bleed per rectum.

Past H/o

Personal H/o -

Family H/o -

GIE →

To study — Risk factors & relative risk

- Amsterdam I/II, Bethesda
- DD of RIF lump
- Treats — Surgery
  - MAC
  - Adjuvant
  - CRS
- Screening

classmate
Date
Page

Oral Cavity cast

- Premalignant lesions
  - Nerve supply for pain in ears
  - NAC of Dr
  - Neck dissection Dr
  - Investigation Dr - Lab et al
  - Jones Brown defects.
  - Recon techniques.

Lip - surgeries

Parotid - facial (N) landmarks
  - Class. fraction of tumors.

Neck → levels & boundaries.