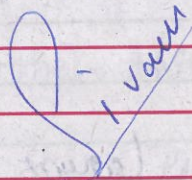
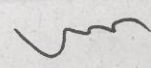


my name is Shivam Panda

INDEX

NAME : Shivam Panda S.T.D. : 2nd SEC : A ROLL NO. : 27

S. No.	Date	Title	Page No.	Teacher's Sign / Remarks
		NGS	2	
		New taxonomy of tumors	8	
		Liquid Biopsy	9	
				
		Biomarkers	13	
		Molecular diagnostics	16	
		Tumor Lysis Syndrome	39	
		Mandibular defects	45	
		Larynx Preservation Surgery	53	
		Ca Maxilla	63	
		Maxillectomy defects	80	
		CRC Screening	85	
		Surgical Mx Ca Colon	94	
		IASO Webinar Lung	102	
		Genetics of CRC	109	
		Inherited CRC Syndromes	113	
		HNPCC / Lynch Syndrome	130	
		Gastric Cancer in Japanese	136	
		Guidelines & LN Staining	141	
	2013-20	Paper analysis - General	143	
		HPB	60 146	



Paten analysis - Breast 148

Gene expression assays 149

Breast Cancer Screening 153

Non Surgical Rx for 160

HCC
Regional therapies for 168
HCC

IASO Welman Larynx 175

TORS 183

Next Generation Sequencing

1) Sanger Sequencing → Gold standard for sequencing.

NGS → 1st Generation - Sanger Sequencing
2 reads - forward & reverse

2nd Generation - Millions of reads

3rd Generation - Single molecule real time sequencing

NGS aka High throughput sequencing

Workflow

Sample extraction, DNA fragmentation

↓
In vitro adapter ligation

↓
Clonal amplification by PCR

↳ Bridge PCR

Pyrosequencing

Sequencing by
ligation

(Solid platform)

Sequencing by
Synthesis

(Illumina)

↓
Bioinformatics & NGS data

Variant calling

Data assembly
with base calling
at the level of
individual reads

Alignment of
assembled
sequence to
a reference
sequence

Page No. :
Date : | |

Read length $\rightarrow$ Avg number of contiguous nucleotide bases in a polynucleotide sequence that are produced by a particular sequencing instrument.

Call $\rightarrow$ Determination of a given base or base sequence by a sequencing instrument.

Coverage $\rightarrow$ Number of times a nucleotide base is read.

Call quality $\rightarrow$ Accuracy of the call determination.

Advantage of NGS over Sanger sequencing

- 1) More sensitive, can detect mutations even in a subset of human cells.
- 2) Qualitative, and can be used to simultaneously determine both nucleotide sequence & copy number variations.
- 3) Allows identification of multiple structural alterations. Such as insertion, deletion, rearrangements.

However there is a relatively high error rate in the short reads generated in sequencing process, and therefore deep coverage of each analysed genome is reqd.

Four groups of NGS Platforms

- 1) Cyclic Reversible Termination
- 2) Single nucleotide addition
- 3) Real time sequencing
- 4) Sequencing by ligation.

These are coupled with different imaging methods, including those based on measuring luminescent signals or four color imaging of a single molecular events.

1st genome to be sequenced entirely → AML using Solexa Platform.

Different Platforms

- 1) Roche 454 GS FLX → Template prep by Fragment mate-pair emulsion PCR
 → Sequencing by pyrosequencing
 → Fast run times
 → High reagent cost
- 2) Illumina → Template by Fragment mate-pair solid phase
 → Sequencing by reversible termination
 → most widely used.
- 3) SOLiD → Fragment mate-pair ^{emulsion} PCR
 → Sequencing by ligation
 → Inherent error correction
 → long run times.

4) Helicos Biosciences - Fragment mate-pair Single molecule
→ Reversible terminators
→ Expensive, high error rates

5) PacBio RS → Fragment Single molecule
→ Real time sequencing
→ Greatest potential for long reads
→ Highest error rates

6) Ion Torrent → Mate Pair emulsion-PCR
→ Non cleavable probe, sequencing by ligation
→ least expensive
→ shortest read lengths-

Uses of NGS

1) The first available cytogenetically normal AML subtype AML M1 revealed 8 genes & novel mutations. The second sequenced genome of AML revealed recurrent mutations in IDH1, encoding isocitrate dehydrogenase.

Follow up studies discovered that IDH1 & IDH2 are associated with prognosis in some subgroups.

Following this, complete sequences of cancer genomes, together with matched normal genomes of the same patient were reported.

2) Genome sequencing is used to identify genomic changes in a metastatic lesion by comparing it with primary, in breast & pancreatic cancers.

So, comparison was made between a basal like breast cancer, a brain mets, tumor xenograft derived from primary tumor and peripheral blood from the same pt.

Conclusion was that although metastatic lesions harbor an increased number of genetic alterations, majority of alterations of primary tumor are preserved.

3) First solid cancer to undergo whole genome sequencing is melanoma. Most somatic mutations were C:G > T:A, which is consistent $\pm$ UV light exposure mutation signatures previously reported in melanoma.

Another important aspect that the comprehensive nature of this melanoma study provided was that cancer mutations are spread out ~~evenly~~ unevenly throughout the genome, with lower prevalence in transcribed genes, suggesting that DNA repair takes place in these areas.

4) miRNAs discovered via NGS technology are known to influence growth & differentiation of cells, along with cancer related pathways such as apoptosis or stress response.

miRNA have been extensively studied in cancer, esp. glioma & breast cancer.

Page No. :
Date: | |

5) Long non coding RNA are greater than 200 bp. They are transcribed by RNA Polymerase II and can undergo splicing and polyadenylation. In a recent study, LNC RNA (steroid receptor RNA activator) existed in breast cancer cells.

6) Whole genome sequencing has allowed for the ability to characterize massive genomic alterations, termed chromothripsis (massive genomic rearrangement acquired in a one step catastrophic event during cancer development) and chromoplexy (complex ~~the~~ DNA rearrangements observed in genomes of cancer cells. First seen in (in prostate)).

Somatic Alterations detected by cancer genome analysis

1) Nucleotide substitutions → most frequently detected mutations in malignant tumors. On avg. human malignancies have one nucleotide change per million bases, but melanomas have 10x higher rate.

For years, the main focus was to detect the "missense" mutations which produce a change in amino acids. But with NGS, we can detect mutations ~~detect~~ ^{occurring} at a much lower rate.

The previously thought "silent" mutations are discovered to be of value in tumorigenesis.

2) Small insertions & deletion (indels) are also discovered by whole genome sequencing. They are less frequent but have an obvious impact in cancer progression.

3) Systemic identification of large chromosomal rearrangements by NGS $\rightarrow$ TMPRSS2-ERG in Prostate Cancer and EML4-ALK in NSCLC.

These studies have also discovered genes involving RAF kinase in prostate & gastric cancer & in melanoma.

4) Next generation sequencing have demonstrated the feasibility to analyze the pattern of copy number variations in cancer.

New Taxonomy of tumors

- Before the genomic revolution, cancers had been classified either based on location or on histology.
- However, it is histologically similar tumors having different clinical outcomes, and respond differently to identical therapies.
- Hence, frequency & distribution of mutations affecting cancer genes can be used to redefine the histology based taxonomy of a given tumor type.
- For eg. EGFR⁺ mutations in lung adenocarcinoma defines a subtype of NSCLC that has a distinctly enhanced prognosis, that responds to EGFR-targeted therapies.
Another subtype is EML4-ALK fusion positive NSCLC, that respond to ALK inhibitors.
- Colorectal cancers can be categorized according to mutational profile of genes in KRAS pathway.
Another subtype harbors BRAF mutations in approx 10% patients.

These mutations have been shown to impair responsiveness to anti-EGFR monoclonal antibodies.

* Molecular Classification of Ca Breast

Liquid Biopsy

- * 1st Publication on cell free DNA → 1948
- * ctDNA is Circulating tumor DNA. It is a part of cell free DNA [cfDNA].
- * This DNA is released from necrotic & apoptotic tumor cells.
- * Other components tested by liquid biopsy -
 - miRNA
 - Exosomes
 - Cell free nucleotides
 - Tumor educated Platelets.
- * Aims
 - 1) Screening & early detection of cancer
 - 2) Estimation of residual metastatic disease, metastatic progression (Prognostic info)
 - 3) Stratification & real time monitoring of therapies
 - 4) Identification of therapeutic targets & resistance mechanisms
 - 5) Understanding biology of metastatic development

Challenges of early cancer detection

- * In ageing non cancer controls, there are already tumor driven mutations present, so a multiplex DNA analysis is needed to differentiate betw true cancer mutations & false positives
- * Biomaterial repository $\rightarrow$ 45,000 individuals betw 45-74 yrs
 - $\rightarrow$ Biomaterials like blood cells, DNA, RNA, tooth plaques, skin punch etc
 - $\rightarrow$ collecting mutational data on prostate, breast & colon cancers
- * low CTC counts - low circulating tumor cells.
 - $\rightarrow$ ctDNA is less than 1% of sample.
- * CTC counts are associated with unfavourable prognosis in Ca Breast
- * Neoplasmin trial $\rightarrow$ NACT in Ca Breast given on the basis of CTC. Number of CTC provided independent prognostic marker apart from PCR

* Monitoring of CTC $\rightarrow$ Can early changes in CTC predict response to therapy?

In a meta-analysis, CTC counts were shown to be significant indicators of PFS.

International studies based on CTC enumeration

STIC CTC Metabreast study - Study in metastatic breast

Two arms

Clinician choice

CTC driven

decision

whether to
give chemo or
HT

on going study

- * Liquid biopsy analyses in metastatic patients are used to monitor response to therapy.
- * PD 21 expression on CTC in metastatic Ca Breast is found in $>60\%$ Pts.
- * Combination of immune markers plus info on mutational load is needed to define immune checkpoint therapies.
- * In Pts of metastatic castration resistant Ca Breast, if they do not have CTC, they have best response to therapy.

Page No. :
Date : / /

- * If they have (TC, but not the resistant variant), they have intermediate response.

- * Circulating tumor DNA contain identical genetic defects as the tumors themselves, and thus, blood can reveal tumor point mutations (EGFR, KRAS, BRAF), fusions (EML4-ALK) as well as tumor amplification (MET)

- * TRACERx trial $\rightarrow$ liquid biopsies were able to identify NSCLC patients likely to experience recurrence of their disease.

- * liquid biopsies are also used to monitor immunotherapy based on checkpoint blockade with anti PD1 & anti CTLA4 antibodies.

Mutational analysis for therapy

1st FDA approved 1st biopsy $\rightarrow$ EGFR testing.
Specificity - 99%.
Sensitivity - 66%.

- * Clonal evolution of KRAS mutated DNA that received antibodies. Under antibody therapy, KRAS mutation count goes down. When therapy stops, counts go back up.

Biomarkers

- Polymorphism is used to define genetic differences present in $\geq 1\%$ human population. But clinically, it is used to describe a non pathogenic genetic change.

Mutation is present in $< 1\%$ human population and is pathogenic.

Types of mutations

- Missense
- Non sense
- Silent

- Loss of function mutations are very common in tumor suppressor genes like CDKN2A or p53. They need "two hits".
- Oncogenes originate from deregulation / overactivity of genes that encode for proteins associated with survival, proliferation of cells. They need only one gain of function mutation.

- Two fold challenges — Different nucleotide alterations can affect the same gene (1)

Same driver oncogene may be mutated in different cancers. (2)

Example of (1) $\rightarrow$ Over 100 mutations in EGFR gene in NSCLC.

Example of (2) $\rightarrow$ Lung cancer, Neuroblastoma, Anaplastic large cell lymphoma } $\rightarrow$ ALK translocation

Uses of Biomarkers

- 1) In diagnosis →
- 1) BCR-ABL translocation to diagnose CML
 - 2) Detection of PML: RARA and variant translocations for detection of subtypes of acute leukaemia.
 - 3) TMPRSS: ETS translocation in Carcinoma
 - 4) RET-PTC translocation in Papillary thyroid cancer.

However, this approach has limitations as it requires dividing cells, and some translocations might not be detected on routine karyotyping, and need other techniques like FISH, PCR etc.

* Detection of structural & numerical chromosomal abnormalities is largely limited to hematologic malignancies.

- 2) In prognosis →
- 1) PML: RARA is associated with a favourable prognosis in APL.
 - 2) MLL rearrangements have intermediate prognosis in AML and poor prognosis in ALL.
 - 3) MYCN amplification occurs in approx 40%.

Undifferentiated neuroblastomas, and is associated with poor prognosis.

3) Predicting response to therapy

1) PML: RARA in AML is highly sensitive to All Trans Retinoic Acid therapy

2) Antibodies against PD 1, PD L1, CTLA 4

are transforming treatment of Ca lung & melanoma

3) Identifying slow & fast metabolizers of theophylline using polymorphisms in theophylline methyltransferase gene

4) Risk assessment & cancer prevention

1) Use of BRCA 1 & 2 mutation analysis for women with a strong family history of breast cancer. Early detection can help with risk reducing strategies.

Molecular diagnostics

Specimen Requirements

- * Samples include blood, bone marrow aspirates, fluids, fresh tissues in saline or tissue culture media, FFPE tissues
- * Blood & bone marrow should be drawn into anticoagulated tubes. Preferred anticoagulant is EDTA or ACD. Heparinized tubes are not preferred
- * Blood & bone marrow samples can be transported at ambient temperatures. Blood samples should never be frozen as it causes hemolysis which interferes with DNA amplification.
- * Fluids should be transported on ice. Tissues should be frozen and sent on dry ice.

Testing Process

Specimen receipt & accessioning



- * For DNA extraction, Preferred age for blood, bone marrow and fluid samples is < 5 days
For frozen or fixed tissue it is indefinite.
For fresh tissue it is overnight.
- * RNA is more labile than DNA, the preferred age for blood & bone marrow is less than 48 hrs.

* For each molecular oncology test, appropriate positive & negative controls are included in each run

* A blank control, containing the complete reaction mixture except nucleic acids, is also included to evaluate for amplicon contamination in assay reagents that may lead to inaccurate results.

Targeted Mutations analysis techniques

1) PCR

2) Real time PCR

3) RT PCR

4) AS PCR

5) Fragment analysis

6) Sanger sequencing

7) Pyrosequencing

8) Methylation analysis

9) Microsatellite instability analysis

10) FISH

Polymerase Chain Reaction (PCR)

- * PCR is ~~the~~ widely used in all molecular diagnostics laboratories.
- * Selected genomic sequences undergo repetitive temperature cycling (sequential heat & cooling) that allows for denaturation of ds DNA template, annealing of the primers to targeted complementary sequences on the template and extension of new strands of DNA by Taq Polymerase from nucleotides, using the primers as starting point.
- * Each cycle doubles the copy number of PCR templates for the next round of polymerase activity resulting in exponential amplification of selected target sequence.
- * PCR products (amplicons) are then detected by electrophoresis in real time systems simultaneously with the amplification systems, or by sequencing.
- * It is specifically designed to work on DNA templates because Taq polymerase does not recognise RNA as a starting point.
- * However, PCR can be adapted into RNA testing by including a reverse transcriptase step to convert RNA sequence into cognate cDNA sequence before PCR is performed.

- To detect low level mutant alleles, some PCR assay formats include use of chemically modified blocking oligonucleotides or lower denaturation temperature that impedes the amplification of wild type sequences.
- RT PCR can be used for relative quantification of minimal residue disease testing, such as BCR-ABL1 transcripts in CML.
- Stringent laboratory procedures needed to ensure that there is no contamination of amplicons in PCR.

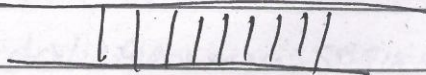
Components of PCR

- 1) DNA template → Sample DNA that contains the target sequence.
High temperature is used to separate the strands from each other.
- 2) DNA Polymerase → Enzyme that new strands of DNA complementary to the target sequence.
Most commonly used one is Taq Polymerase (from *Thermus aquaticus*).
Another one is Pfu DNA Polymerase (*Pyrococcus furiosus*). It has higher fidelity.

These enzymes can generate new strands of DNA using a DNA template & primers.
They are relatively heat resistant.

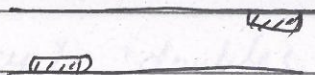
3) deoxy nucleotides (dNTPs) - They are the quintessential "raw material" or building blocks for new DNA strands.

1 - target sequence -

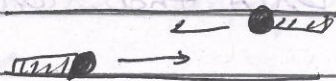


94-96°C

Strand separation



Primer Binding



New DNA Synthesis
in 1st cycle

Repeated 'n' times to get 2ⁿ copies

Basic steps of PCR -

1) Denaturation by heating to 96°C. This separates the strands and provides single stranded template.

2) Annealing (55-65°C) -> By cooling the reaction, the primers can bind to complementary sequences.

45
3) Extension (72°C) $\rightarrow$ Bind Taq Polymerase to extend the primers, synthesizing new strands of DNA

This cycle is repeated 25-35 times to get millions of copies of the DNA sequence.

The results of PCR are visualized using gel electrophoresis, where fragments of DNA are pulled through a gel matrix by an electric current, separating DNA fragments acc. to size.

DNA fragments of the same length form a "band" on the gel, which is stained by a dye to visualize.

Real time PCR

* PCR is performed with a PCR reporter that is usually a fluorescent dsDNA binding dye.

* So, with each amplification cycle, the fluorescence increases and it can be monitored in real time.

* Intensity of fluorescent signal for a given DNA fragment depends on its quantity.

* Crossing threshold [C_t] or Crossing Point [C_p]
→ The PCR cycle at which fluorescence rises above background.

* Qualitative assays using C_t as cutoff are used for determining presence or absence of a given target.

* Quantitative assays - The C_t of standards with known templates is used to generate a standard curve to which C_t values of unknown samples are compared.

The concentration of unknown samples is then extrapolated from values from the standard curve.

The quantity of amplicons is proportional to the target sequence.

* Qualitative assays used to detect point mutations.

* Quantitative real-time PCR has high analytical sensitivity for low mutant allele burden, so it's widely used for monitoring of minimal residual disease.

(F) RT PCR $\rightarrow$ Reverse Transcriptase PCR

- * Utilized for quantification of RNA transcripts
- * 1st step is to convert RNA into cDNA by a reverse transcriptase

RNA is isolated & reverse transcribed into cDNA using reverse transcriptase and either:

- 1) Random hexamer primers, which anneal randomly to RNA and reverse transcribe all RNA in the cell.
- 2) oligo dT primers, which anneal to the poly A tail of mRNA and RT only mRNA
- 3) Gene specific primers that RT only target of interest

PCR is then performed on cDNA with forward & reverse primers like in a standard PCR.

Uses: 1) Detecting gene fusions during translocation analysis; $\rightarrow$ Breakpoints of translocation occur within the introns of gene.

~~Here~~ These sequences can be variable, so designing a primer in DNA is difficult. However, mature mRNA has intronic sequence spliced out, leading to simpler primer design.

For eg. to detect reciprocal $t(15;17)$ translocation in RARA gene

Also used for quantitative detection of BCR:ABL fusion gene for prognostication & minimal residue disease testing in CML.

Allele Specific PCR

* Variant of conventional PCR

* Based on the principle that Taq Polymerase is incapable of catalyzing chain elongation in the presence of a mismatch betⁿ 3' end of primer and template DNA

* Selective amplification by AS-PCR is achieved by designing a forward primer that matches the mutant sequence at 3' end primer.

* Second mismatch within the primer can be introduced at -1 or -2 position to decrease the efficiency of mismatched amplification products.

* AS PCR is performed as two PCRs - one with wild type sequence & one with mutant allele. Both have different forward primers but same reverse primers.

* Detection of adequate PCR product in wild type is needed for quality control.

* Results of PCR are then visualized by either gel electrophoresis or Real time PCR.

Uses → Detection of Specific Point mutations

- multiple mutations can be detected

Simultaneously by including several mutation specific primers.

Example - BRAF V600E mutation

- KIT D816V mutation in systemic mastocytosis & AML.

Sanger Sequencing

- * AKA Chain termination method.
- * Three basic steps :-
 - 1) PCR with fluorescent chain terminating ddNTPs
 - 2) Size separation by Capillary gel electrophoresis
 - 3) Laser excitation & detection by sequencing machine.

1st step * DNA sequence of interest is used as a template for "chain termination PCR".

* Chain termination PCR works like standard PCR, with one major difference - addition of dideoxy NTP (ddNTP)

- * The user mixes low ratio of chain terminating ddNTPs with normal dNTPs in the PCR reaction. ddNTPs lack 3'OH group required for phosphodiester bond.
- * Therefore, when DNA polymerase incorporates ddNTP at random, extension ceases.
- * As a result, billions of copies of DNA sequence of interest are generated.

* In "manual" Sanger sequencing, four PCR reactions are set up, each with only single type of NTP (ddATP, ddTTP, ddCTP, ddGTP)

* In "automated" Sanger, all are mixed in single reaction.

2nd step - Chain terminated oligonucleotides are separated by size via gel electrophoresis

(Explain the principle of gel electrophoresis)

3rd step - Reading the gel to determine sequence of input DNA

* Because DNA Polymerase only synthesizes from $5' \rightarrow 3'$, each terminal ddNTP will correspond to a specific nucleotide in original sequence.

* Therefore, reading the gel bands from smallest to largest, we can determine the sequence from $5'$ to $3'$ in original DNA

Uses $\rightarrow$ Detection of KIT mutation in GIST & melanomas

$\rightarrow$ EGFR mutations in NSCL

$\rightarrow$ KRAS mutation in CRC & lung.

Fluorescent In situ Hybridization

- * Allows visualization of specific chromosome nucleic acid sequences within a cellular preparation.
- * Involves annealing of large single stranded fluorophore labelled oligonucleotide probe to cDNA target sequences within tissue or cell preparation.
- * Hybridization of the probe at the specific DNA region within nucleus is visible by direct detection using fluorescence microscopy.

Fluorescent dyes used $\rightarrow$ Digoxigenin

$\rightarrow$ Biotin

One of the first applications of FISH was chromosome painting, where competitive hybridization using entire chromosome specific libraries for chromosomes as probes and human genomic DNA as the competitor, was done.

It was used to identify Philadelphia Chromosome

Steps 1) Direct or indirect labelling of probe

2) Blocking DNA fragmentation +

3) Preparation of Slide

4) Denaturation of Probe and blocking DNA in a hybridization mixture

5) Addition of hybridization mixture

6) Denaturation of chromosome DNA

7) In situ hybridization

8) Probe detection

9) Visualization in microscope

* Can be used for quantitative assessment of gene amplification or deletion

* Qualitative evaluation of gene rearrangements.

* Two probes $\left\{ \begin{array}{l} \text{locus specific} - \text{complementary to gene} \\ \text{centromere specific} - \text{bind to} \\ \text{alpha satellite region near} \\ \text{centromere of a specific chromosome} \end{array} \right.$
 & help to identify number of copies of that chromosome.

Uses

1) Quantitative assessment - * A locus specific probe and a chromosome probe are labelled with two different fluorophores.

* Signal generated by each of these probes is counted and ratio of targeted gene to chromosome copy is calculated.

* The amount of signal produced by locus - specific probe is proportional to the number of copies of targeted gene in a cell.

Used for → Her2 gene testing by FISH

→ MYCN amplification in neuroblastoma

2)* For detection of deletion mutations and LOH studies, dual probe hybridization is performed using locus specific probes.

* LOH is a common occurrence in tumor suppressor genes and may contribute to tumorigenesis when the second allele is also inactivated by a second "hit".

* LOH studies are used to identify genomic imbalances, indicating possible sites of ~~TSN~~ TSN mutations.

* FISH is most commonly used for LOH studies.

3) Detection of gene rearrangements / Chromosomal translocation

→ * Done using locus-specific dual-fusion or break-apart probes

* Dual color - Dual fusion involves two probes located in two separate genes. Each gene probe is labelled in a different color. Detects translocation by juxtaposition of both probe signals.

* These assays are very specific for selected translocation. But they can only be used for detecting translocations that involve consistent partners.

* When fusion partners are different, it is not of use.

• For eg. $IGH-BCL2$ in follicular lymphoma.

* Break apart FISH → Dual colored probes flank the breakpoint region in a single gene that represents the constant partner in translocation.

* Rearranged alleles show two split signals, whereas normal alleles show fusion signals.

* Useful for genes which have multiple partners
 $11q$ EWSR2 gene in Ewing Sarcoma
 WT1 gene in desmoplastic small cell tumor
 ATF1 gene in clear cell sarcoma.

Advantages of FISH

- * Can be applied on a variety of specimen types, including FFFR tissues.
- * Relatively straight forward from a technical point of view.
- * Also provides copy number assessment of polysomy which is not possible in ~~PCR~~ PCR.

Drawback - Targeted approach that will detect only specific alterations.

- * Most probes are >100 kb in size, so small insertions or deletions won't be detected.
- * Can be contaminated with poor tissue preparation, fixation artifacts, nuclear truncations.
- * Some intra chromosomal rearrangements like RET-PTC can be challenging by FISH due to subtle rearrangement of probe signals on the same chromosome arm.

Whole Genome Analysis Methods

1) NGS - Described previously

2) Genomic microarrays - High density genomic microarrays are utilized for whole genome assessment of copy number changes, LOH & genotyping.

- * Comparative Genomic hybridization is carried out using DNA microarrays.

- * In CGH, DNA from a test (eg. a tumor) and DNA from a "reference", i.e. a normal individual are labelled differently.

- * They are then hybridized to a representation on the genome.

- * Hybridization of repetitive sequences is blocked by addition of Cot 1 DNA

- * Fluorescence ratio of test & reference hybridization signals is determined at different positions along the genome

- * This provides information on the relative copy number of sequences in the test genome compared with a normal diploid genome.

- * Microarray based formats for CGH (array CGH) are now widely used instead of chromosome-based CGH.

- * Arrays made from large genomic clones and cDNA have been used for this purpose.

Advantages - Higher resolution

- Dynamic range

- Direct mapping of aberrations to the genome sequence

- Higher throughput.

Array (GH) Platforms

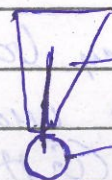
- * A number of different array platforms have been used for GH measurement in mammalian genomes.

- * Large insert genomic clones such as bacterial artificial chromosome, cDNA clones & oligonucleotides for array spots.

- * Analysis typically requires several hundred nanograms of genomic DNA from specimen when using some BAC arrays.

Three types of arrays

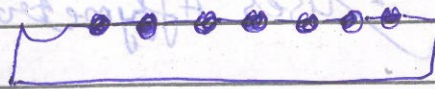
1) Spotted arrays on glass



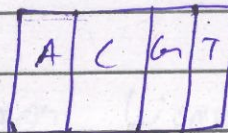
Spotting Pen

Drop of DNA in Solution

2) Self assembled arrays



3) In situ synthesized arrays



← Inkjet of nozzles

← Drops of individual nucleotides
Reactive surface.

Spotted arrays → Polytetrasine coated glass microscope slides provided good binding of DNA and a robotic spotter was designed to spot multiple glass slide arrays from DNA stored in microtiter dishes.

→ Using slotted pins, a single drop of a per in DNA solution could spot multiple slides.

→ One could fluorescently label the sample. Advantages are

- 1) Sensitive detection and large dynamic range
- 2) less expensive, less complicated
- 3) Allowed one to label two or more different samples in different colors and cohybridize the samples.

In situ Synthesized

✓ Uses Affymetrix technology.

• DNA sequences are directly synthesized on surface, hence only a small collection of 'reagents' [the 4 modified nucleotides, plus a small handful of reagents necessary for the de-blocking & coupling steps] are needed.

Self assembled arrays - This involves synthesizing DNA on small polystyrene beads & depositing those beads on the end of a fiberoptic array in which the ends of fibers were etched to provide a well that is slightly larger than one bead.

Different types of DNA could be synthesized on different beads and applying a mixture of beads to fiber optic cable would result in randomly assembled arrays.

Uses 1) Detection of copy number variations and LOH in CLL

2) Recurrent cytogenetic abnormalities in MDS

3) Genotyping - Widely used as single nucleotide polymorphism (SNP) genotyping platform

SNP microarrays are the only microarrays that are able to detect Uniparental disomy.

- ③ Expression Panels - Example of multigene panels like OncoPrint Dx, which is a quantitative RT-PCR based assay.

IHC for tumor biomarkers

- ① PD-L1 - Two PD-L1 IHC tests are available PD-L1 22C3 & PD-L1 28-8, for Pembrolizumab & nivolumab resp.
At least two viable tumor cells should be present
Scoring of PD-L1 IHC is based on Tumor Proportion Score
For melanoma, PD-L1 22C3 cut off is 1%.
For NSCLC, it is 50%.

- ② ALK-Pos → Used for lung adenocarcinomas
→ Tested by FISH assay.
→ Recently FDA approved VENTANA ALK CDx assay as a companion diagnostic to identify ALK positive NSCLC eligible for treatment with Crizotinib

(3) BRAF V600E → Antibody to BRAF V600E mutation can be employed as an alternative to molecular tests.

However, there are no internal controls in antibody test, so it can't replace molecular test.

ITC for tumor biomarkers

(1) PD-1 - It is a T cell co-inhibitory receptor. It is expressed on the surface of T cells and binds to B7-1 and B7-2.

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(2) VEGF - It is a growth factor that promotes angiogenesis. It is secreted by various cells, including tumor cells.

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Tumor Lysis Syndrome

TLS is a disorder of electrolyte, renal functions and in severe cases, cardiac & CNS abnormalities resulting from rapid breakdown or lysis of cancer cells.

Lab abn $\rightarrow$ $\uparrow$ uric acid $\geq 8 \text{ mg\%}$ or 25% increase
 $\uparrow \text{K}^+$ $\geq 6 \text{ mmol/l}$ or 25% increase
 $\uparrow \text{PO}_4^{3-}$ $\geq 4.6 \text{ mg\%}$ or 25% increase
 $\downarrow \text{Ca}^{2+}$ $< 7 \text{ mg\%}$

Clinical abn $\rightarrow$ $\uparrow$ Creatinine $1.5 \times$
 $\rightarrow$ Seizures
 Cardiac dysrhythmia
 Death.

The above are Cairo-Bishop criteria for TLS.

* Highest incidence seen with High grade NHL (42% lab & 6% Clinical).

Pathogenesis

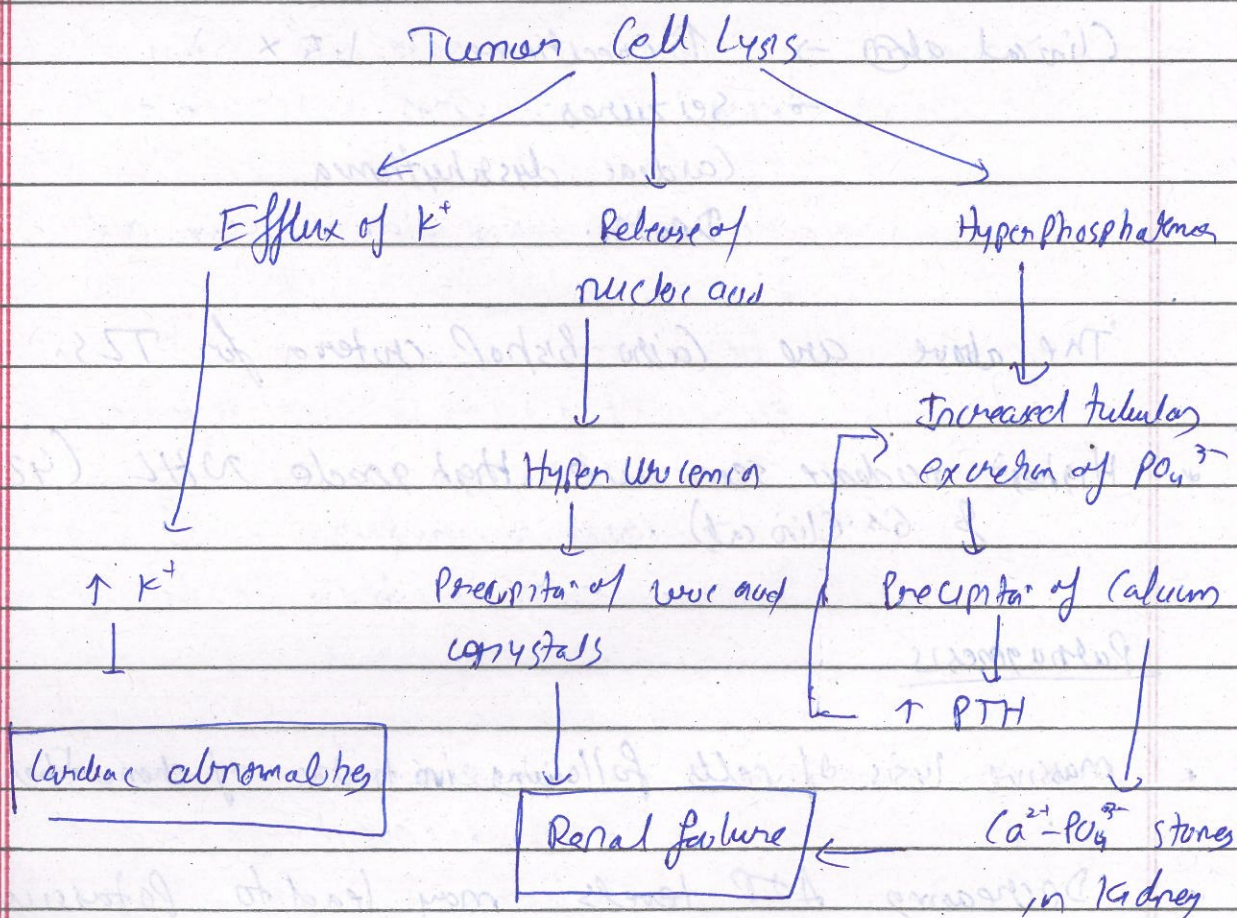
- * massive lysis of cells following initiation of chemotherapy
- * Decreasing ATP levels may lead to Potassium leakage, and rising K^+ might be the first sign of TLS.
- Phosphate released from cells is initially excreted via urine but once renal transport is saturated, its levels rise,

with eventual precipitation of Calcium.

* This leads to $\uparrow$ PTH, hyperphosphatemia & risk of Calcium phosphate crystals deposition in tubules leading to tubular obstruction.

* Hyperuricemia occurs due to increased metabolism of nucleic acid. Uric acid is the end product of Purine metabolism.

Precipitation occurs more readily when pH is acidic.



Monitoring $\rightarrow$ Any rapidly growing cancer

Laboratory values of K^+

Uric acid

PO_4^{3-}

(Creatinine)

along with routine blood tests should be monitored twice daily until risk of TLS has passed.

LDH levels may help determine the rate of breakdown

Management - * Preventive measures should be started 24 hr prior to initiation of chemo.

* Aggressive hydration of 3000 ml/m²/day.

Hyperkalemia $\rightarrow$ GI - I drip

$\rightarrow$ Cation exchange resins

$\rightarrow$ NaHCO₃

$\rightarrow$ loop diuretics

$\rightarrow$ If not responding to R $\rightarrow$ hemodialysis

Hyperphosphatemia $\rightarrow$ Hydration

$\rightarrow$ Oral phosphate binders

$\rightarrow$ Dialysis

$\rightarrow$ Oral calcium binders should be used $\bar{C}$ caution

Hyperuricaemia → Allopurinol should be started immediately.

→ levels of pre-existing uric acid will not decrease for 2-3 days. If rapid lowering is needed, Rasburicase should be given.

→ Enzymatic oxidn by Rasburicase forms allopurinol from uric acid which is 5X more soluble.

→ Single dose rasburicase 0.15 mg/kg is effective.

→ Use of Rasburicase should be limited to pt with established TLS or high risk of TLS.

Risk assessment

Negligible → low to medium tumor burden
low risk of cell lysis
(N) organ function

low → medium to high burden (bulky node, organomegaly, ALDH, leukocytosis)
low, moderate or unknown risk of cell lysis
(N) organ fⁿ

Moderate → medium to high burden
moderate or unknown risk of cell lysis
At (N) organ functions (nephropathy, audiosis, hypotension)

High risk → Medium or high tumor burden
→ High risk of relapse (elevated pre-treatment LDH - treatment was used)
→ (R) or also function of organ

Stadium → lateral oblique view
→ Frontal view - CT scan
Use of old is also scanned

Oral Cancer (IASO Video)

- Classification of marginal mandulectomy
- Role of CT/MRI
- Extent of neck dissections.
- ★ Tumor thickness & DOI are different

- Exophytic lesions can be effectively treated with RT alone, but not the case with endophytic lesions.

Skiaogram → Lateral oblique view
→ Frontal view - OPG.

Use of OPG is plan Segmental mandulectomy.

Mandibular defects & reconstruction

James Brown classification of mandibular defects

5M { Class I (angle) $\rightarrow$ lateral defect not including ipsilateral ramus or condyle
Class I_c (angle + condyle) $\rightarrow$ lateral defect including condyle.

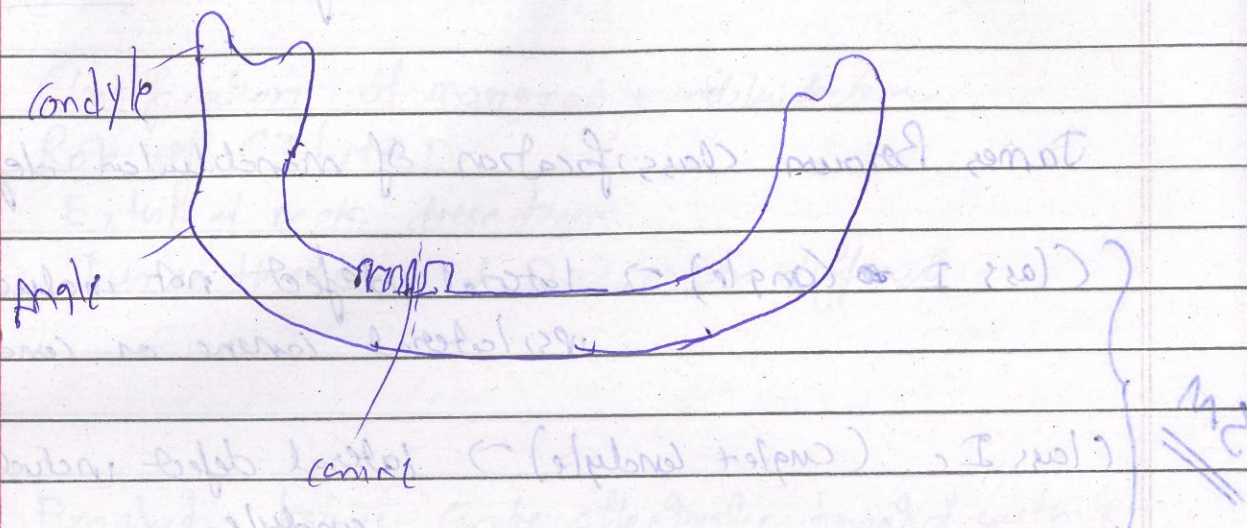
Class II (angle + ramus) $\rightarrow$ Hemimandibulectomy including ipsilateral but not contralateral ramus

II_c $\rightarrow$ HM including condyle [Classical Hemimandibulectomy]

Class III $\rightarrow$ Anterior mandibulectomy including both rami, but not angles

Class IV $\rightarrow$ Extensive anterior mandibulectomy including both rami and one or both angles.

IV_c $\rightarrow$ Both rami and one or both condyles (total Mandibulectomy)



- (2) HCL system by Jewer et al.
- H → Unilateral condyle but crossing midline
 - L → Unilateral no condyle but can cross midline
 - C → Both coronas
 - HC → lateral & condyle including both coronas
 - LC → lateral & both coronas
 - HCL → condyle lateral, central & contralateral lateral
 - LCL → Bilateral defects including coronas but not condyles
 - HCLT → Entire mandible

- (3) Urken et al → C = Condyle
- R = Ramus
 - B = Body
 - S = Symphysis
 - S^H → Stops at midline

Reconstructions

Four main flaps for reconstruction Free flaps (MC)

- Iliac crest (2nd MC)

Scapula (MC for Class II defect)

Radial

In the Jones Brown Classification, the size of defect & morbidity increases from Class I to IVc

Reconstructive options

- 1) Healing by Secondary intention / Primary closure
- 2) STSG
- 3) Skin graft substitutes
- 4) Reconstructive plate
- 5) Autogenous bone graft
- 6) Bone graft substitutes
- 7) Regional flaps
- 8) Free flaps
- 9) Transport disc distraction osteogenesis
- 10) Modular endoprosthesis, 3D Printed Prosthesis etc.

1, 2 & 3) - need no explanation.

4) Mandibular plating - options in plate selection include mandible reconstruction plates, miniplates, locking plates.

- Available in titanium & stainless steel

- Titanium is more biocompatible and mechanically similar to bone, thus, do not have to be removed after the graft has healed.

- They can be contoured easily to mandibular resection which maintains the occlusal plane and serves as template for bone graft.

5) Non vascularized free bone grafts

- The first attempt at free bone grafts for mandible reconstruction was completed by skyoff.

- They have much lower morbidity

- Greater remodelling, compared to vascularized bone grafts

- Donor areas include iliac spine, calvarial grafts, rib grafts,

- There is extensive resorption & 60% grafted volume is lost within 6 months

Recipient surgical bed must be vascularized & not irradiated.

- Poggel's 6cm rule $\rightarrow$ For defects $> 6\text{cm}$, vascularized free flap must be used.

6) Loco-regional flaps $\rightarrow$ PMMC - Pectoral branch of thoraco acromion artery

$\rightarrow$ LD flap $\rightarrow$ LD pedicle from axillary artery.

~~$\rightarrow$ Microvascular flap~~

7) Free flap $\rightarrow$

1) Fibula $\rightarrow$ Most commonly used microvascular free flap is an osseocutaneous free fibula flap.

* First introduced by Taylor in 1975

* Blood supply / pedicle is the peroneal artery, branch of popliteal or posterior tibial artery.

* longest in length, so used for Class I-IV defects

* Drawback - lack of height

- Absence of vestibular groove
- limitation of mouth opening
- Reconstruction of tissue surrounding the lip is difficult

- Smaller capacity to fill large defects
- ~~Not~~ Unreliable blood supply for skin paddle.

2) Scapula flap → Teo et al described vascularity of scapula & Schwartz used it for maxillofacial reconstructions.

- * Flap is well suited for larger reconstructions

- * Low donor site morbidity.

- * Dental implantation on scapula flap has also been more successful.

- * However, this membranous bone is considered inferior in quality compared to iliac crest or fibula.

3) DCIA flap - Deep circumflex iliac artery flap.

- * Used more for Class II/III defects.

- * Donor site morbidity is highest

- * Vessel is least reliable & pedicle is shortest.

Supplied by
Transverse branch of
Circumflex artery.

4) Radial bone flap - First used in oral reconstruction by Soutar.

Safe & reliable option for mandibular reconstruction

longer pedicle allows anastomosis in contralateral neck.

5) Metatarsal bone flap - Used for reconstruction of condyle

6) Rib graft flap -> Unpredictable growth seen
-> Recommended only for severe defects

Pre op Parameters to Predict Complications

- low BMD
- High WBC count
- low hematocrit

Radiated mandible? - Theoretical risk of flap failure by causing end-arteritis & thrombosis

- Choi showed no diff. betⁿ irradiated & non irradiated mandibles when underw free flaps flap.

8) Distraction osteogenesis & TDDO

- TDDO stands for Transport Disc Distraction Osteogenesis.

- A segment of bone is cut adjacent to the defect & is ~~used~~ moved gradually across the defect by a mechanical device.

- New bone forms betⁿ the two distracted bony segments.

- Piece of bone which is transported acts as a source of osteogenesis & is called transport disc.

9) 3D Planning & 3D Printing - First described by Markovitch et al in 1990

- CT guided stereolithographic models have enjoyed wide use in orthognathic treatment planning & surgery.

10) Tissue engineering using recombinant BMP2 Protein Rit grafts used as carrier for BMP2.

Contraindications - Involvement of Cricoid cartilage joints

- Involvement of the vocal folds

- Involvement of more than $\frac{1}{3}$ of vocal cord.

Larynx Preservation Surgeries

(1) Vertical Partial Laryngectomy

• Indicated for lesions that involve the supraglottic larynx, or anterior commissure

• Pt = reduced mobility of vocal cord, or those who failed to respond to previous radiation therapy for a locally advanced lesion that still remains confined to one side of larynx are also candidates for VP2.

Criteria for lesion $\rightarrow$ 1) lesion of mobile cord extending to Anterior commissure

2) lesion of mobile cord involving vocal process & anterior-superior portion of arytenoid

3) Subglottic extension $< 5\text{mm}$

4) Selected pt = fixed cord not crossing midline

5) Unilateral transglottic lesion not violating above criteria

6) True cord / AC lesion not involving more than anterior third of opposite cord.

* Preliminary tracheostomy done

- * Transverse incision at the middle of the vertical height of thyroid cartilage

- * Skin flaps elevated, sternocleidomastoid muscles retracted.

- * Incision made in the perichondrium of the thyroid cartilage in ~~thyroid notch~~ ~~midline~~, extending from thyroid notch to cricoid membrane.

- * Using a periosteal elevator, the ipsilateral ala of thyroid is lifted to the posterior margin

- * Using a power saw, a laryngeal fissure is created in anterior midline. Thyroid cartilage is divided

- * Disease is removed with adequate margins (describe all structures of hemilarynx)

- * Surgical defect is from ipsilateral AE fold to superior border of cricoid cartilage

- * No attempt is made to obtain mucosal closure.

- * Perichondrium is re-approximated, sternocleidomastoid sutured over it.

② ~~Subglottic~~

Post op → Feeding by nasogastric tube for 7 days

→ Clearing pulmonary secretions

→ Remove T-tube by 7 days after confirming

Satisfactory air passage.

Complications - Laryngeal, laryngeal stenosis

- Work-related, subcutaneous emphysema.

② ~~Subglottic~~ ~~subtotal laryngectomy~~
~~cricothyroid~~ ~~epiglottomy~~ (CTE)

Larynx Organ Preservation Strategies

Surgical

Non surgical

CT-RT.

Open

Endoscopic

- Vertical partial laryngectomy

- Transoral Laser

- Subglottic "

microsurgery (TLM)

- Subglottic "

- TORS

- Powered/microdebrider
excision

lobular excision

Classifier of VPZ - Type 1 - Standard Vertical

Type 2 - Frontal lateral

Type 3 - Antero frontal

Type 4 - Extended - any procedure

where one arytenoid is taken.

Surgeon who endeavours to undertake organ preservation surgery should

- 1) Have a thorough understanding of static & dynamic anatomy of larynx
- 2) Accurately assess cancer both clinically & radiologically
- 3) Have training

Principles of Organ Preservation Surgery

- 1) Local control & close follow up
- 2) Accurate assessment of tumor extent
- 3) Shift in concept of taking microanatomical unit as the functional unit.
- 4) Adhere to standard resection techniques.

Patient evaluation

- 1) Thorough history
- 2) Dynamic assessment of larynx - Fiberoptic Stroboscopy
- 3) Static assessment $\rightarrow$ Direct laryngoscope
- 4) CT/MRI
- 5) Head & neck examination.

- 6) Exclusion of synchronous lesion
- 7) General medical evaluation.

Subglottic laryngectomy

- * First described by Alonso & modified by Ogura

Subglottic cancer poses unique management issues due to :-

- 1) Association with Pre-epiglottic & Paraglottic Spaces
- 2) Rich lymphatic supply, leading to higher risk of mets & recurrence.
- 3) Distinct anatomical boundaries due to origin from laryngopharyngeal confluence.
- 4) Need for treatment of No neck & adjuvant CT-RT or SND.

Contraindication - Involvement of cricoid & thyroid cartilage

- Impaired mobility/flexity of vocal cord
- Impaired mobility of BOT
- Invasion of B/L arytenoids
- Involvement of anterior & posterior commissure.

Extension to glottis

Technique - * Resection includes removal of whole of epiglottis, false cords, AE fold, Pre-epiglottic space & upper half of thyroid cartilage & hyoid bone.

* After lifting flaps, thyroid cartilage is exposed & perichondrium is reflected down to infrahyoid muscles.

* ~~Infrahyoid~~ Inferior constrictor is separated from lateral & postero superior margins of thyroid cartilage, releasing the pyriform sinus.

* Thyroid cartilage is divided along an oblique line towards its superior corner.

* If hyoid is uninvolved, it is preserved.

* Pharynx entered at the level of valleculae.

AE fold on uninvolved side is transected anterior to arytenoid.

* Reconstruction is done by suturing BOT on to thyroid cartilage.

Laryngeal remnant is positioned anteriorly & superiorly as much as possible.

Complications - Aspiration - mild to moderate.
 - Prolonged may need T-tube ± PEG.

- long term failure to develop physiological deglutition may require esophageal laryngectomy

(3) Supracricoid laryngectomy (SCP2) & Crico-hyoid-epiglottopexy (CHE)

also known as subtotal laryngectomy

Principle - Traditionally, glottis is deemed as the functional unit of larynx, but the driving force for phonatory function is a mobile & sensate Crico-Arytenoid-Unit (CAU).

CAU

Cartilage - Cricoid ring
 - Arytenoids (+ corniculate / cuneiform)

Muscles - Posterior Cricarytenoid
 - lateral Cricarytenoid
 - Interarytenoids

Nerves - RLN

- SLN

* In SCL, membranous vocal cords, false cords & paraglottic space is excised, along with entire thyroid cartilage.

* Pre epiglottic space & epiglottis is also removed (unless union (H&P) is done).

* Compared to VPZ, SCL provides a more comprehensive resection of paraglottic space.

Indication

- 1) T_{1a} / T₂ / T₃ glottic / subglottic cancer
- 2) Selected T₄ carcinoma & limited invasion of thyroid ala without extension to outer thyroid perichondrium.

3) Salvage after RT failure

Contraindication - Involvement of retroarytenoid space, posterior commissure, mucosal involvement of B/L arytenoids

- Fixed arytenoids

- Subglottic extension > 10 mm anteriorly or > 5 mm post.

- Extra-laryngeal spread, invasion of hyoid bone, invasion of pre-epiglottic space.

Repair methods

1) CHEP → Done when incision of thyrohyoid membrane is just above thyroid cartilage

2) CHP → Transvallecular pharyngotomy done.

Reconstruction - Arytenoids need to be resuspended as they tend to fall posteriorly

It is crucial to create a T-shaped valve that will close against epiglottis/BOT

Cricopharyngeal myotomy is placed if hypertension is detected.

The 'Pexy' is performed by placement of 3-5 Impaction sutures 8-10 mm above

Inverted funnel shape of PFS is important for swallowing.

Physiological aspects - Speech is generated by periodic mucosal wave on the anterior aspect of arytenoid cartilage where it abuts epiglottis.

Hydrophobic membrane is used above

(c) 118 There is no other information

1. 1980

- non achievement of phagocytosis.

Outcome: All class members

Conductomics = European Longitudinal Society classification

II - Sublingual gland - Epithelium, Rente's SP

+ vocal ligament

III → Transmuscular - proceeds through the vocalis muscle

IV $\rightarrow$ Total Cardiology

Da $\rightarrow$ Extended conditioning that encompasses the contralateral vocal field & anterior commissure (Ac)

Da - Extended cordectomy that includes arytenoids

$D_c \rightarrow$ that encompasses Schrodt

$D_d \rightarrow$ vertices

Effect of temperature on rate of reaction

Ca Maxilla [Read Sinusnasal drainage Pg 268 Myers]

Anatomy * It is a pyramidal cavity in the body of maxilla

- * Base is formed by the lateral wall of nasal cavity
- Alex formed by zygomatic process
- Roof or orbital wall is ridged by a infra-orbital canal
- Floor is formed by alveolar process of maxilla. It is usually 1-4 mm below the level of floor of nose.
- * Ostium is partially covered by unguate process & communicates with the lower part of hiatus semilunaris.

Infratemporal fossa → * Irregularly shaped space, below & medial to zygomatic arch

- * Anteriorly bounded by posterior surface of maxilla
- superiorly by greater wing of sphenoid & squamous part of temporal bone
- medially by lateral pterygoid plate
- laterally by ramus of mandible.

contains → Temporalis muscle

- Internal maxillary vessels
- Mandibular (D₃) nerves including inferior alveolar, lingual & auriculotemporal

- * Foramen ovale & spinosum open on its roof
- * Inferior orbital & pterygomaxillary fissures communicate with it & may act as routes of spread of cancer.

- * Also contains upper carotid sheath, including internal carotid artery, IV, V & IX, X, XI, XII nerve.

Pterygo palatine fossa

- Small Δ space, behind maxilla & in front of pterygoid plates, beneath apex of orbit.

- * Communicates with orbit via inferior orbital fissure. & with nasal cavity via sphenopalatine foramen. & with ITF via pterygomaxillary fissure.

Five foramina open into it

- | | |
|--------------------|--|
| Posterior wall | Medial wall |
| - Foramen Rotundum | - Sphenopalatine foramen |
| - Pterygoid canal | - Superior surface of pterygopalatine canal. |
| - Pharyngeal canal | |

- * Contains maxillary nerve, sphenopalatine ganglion, terminal part of internal maxillary artery.

- * Most common malignant tumor of nasal cavity is SCC
Most commonly involved sinus $\rightarrow$ Maxilla.
Ant. skull base invasion most frequently seen with
nasal cavity or ethmoid sinus ~~involvement~~ cancer.

Spread

- (1) Local is Most common route of local spread is direct extension.

Spread of Ca maxilla

Anteriorly $\rightarrow$ Soft tissue of cheek

Superiorly $\rightarrow$ Orbit, leading to Proptosis

Inferiorly $\rightarrow$ Oral cavity

Posteriorly $\rightarrow$ Pterygomaxillary space, where it may spread branches of V₂.

It may also erode into pterygopalatine fossa, from where it may extend into pterygomaxillary fissure, infratemporal fossa or into middle cranial fossa via foramen rotundum.

- (2) Perineural spread & Tumors that have considerable propensity to spread along nerves are called neurotropic tumors.

* Tumors of paranasal sinuses may use this route for intracranial spread or spread to skull base.

They may also spread in contiguous fashion & along the involved nerve & its branches.

* Cancers with a greater propensity for perineural spread are Adenocarcinoma (Maximum), SCC & Sinusoidal undifferentiated cancers.

(3) Regional mets → Regional mets from Paranasal Sinus are relatively uncommon

* Regional disease is evident on initial presentation in ~ 10% of patients & further 15% will develop it later.

(4) Distant mets → Distant mets is rare, but most common sites are lung & bone.

Clinical features - Early features are of Sinus obstruction like

- Nasal congestion

- Nasal discharge

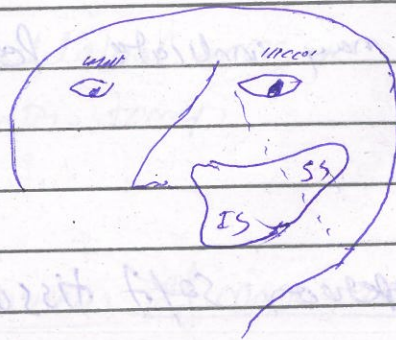
- Anosmia

- Sinus Pain

The symptoms are often not relieved with medication & are unilateral.

- Features of local spread.

Ohngren's line $\rightarrow$ Imaginary line joining medial canthus of eye to angle of mandible.



Part of maxilla superior to it is "suprastructure" & part inferior to it is called "infrastructure".

* In infrastructure lesions, symptoms develop early and tumors are readily amenable to surgical resection.

* Tumors in suprastructure ~~are~~ present late, have a higher propensity to spread & less amenable to surgical resection.

Imaging CT scan $\rightarrow$ Coronal images best delineate the involvement of orbital walls.

Axial images are best for demonstrating tumor extension thru post. wall of maxillary sinus & thru PPF & ITF.

Sagittal images are useful for evaluating extension thru cribriform plate.

* main advantage of CT scan is to delineate the architecture of bone, esp in the "bony window".

* Bony destruction & soft tissue invasion indicates a malignant lesion

* Widening of foramina may indicate perineural spread

MRI → MRI has superior soft tissue contrast.

~ Obliteration of fat planes, in PPT, ITF, or nasopharynx indicates spread along those regions

* Dural thickening or enhancement is an indicator of tumor involvement

~ PNI is better detected on MRI

~ Useful to differentiate recurrent secretions from growth.

~ Monitoring patients post op.

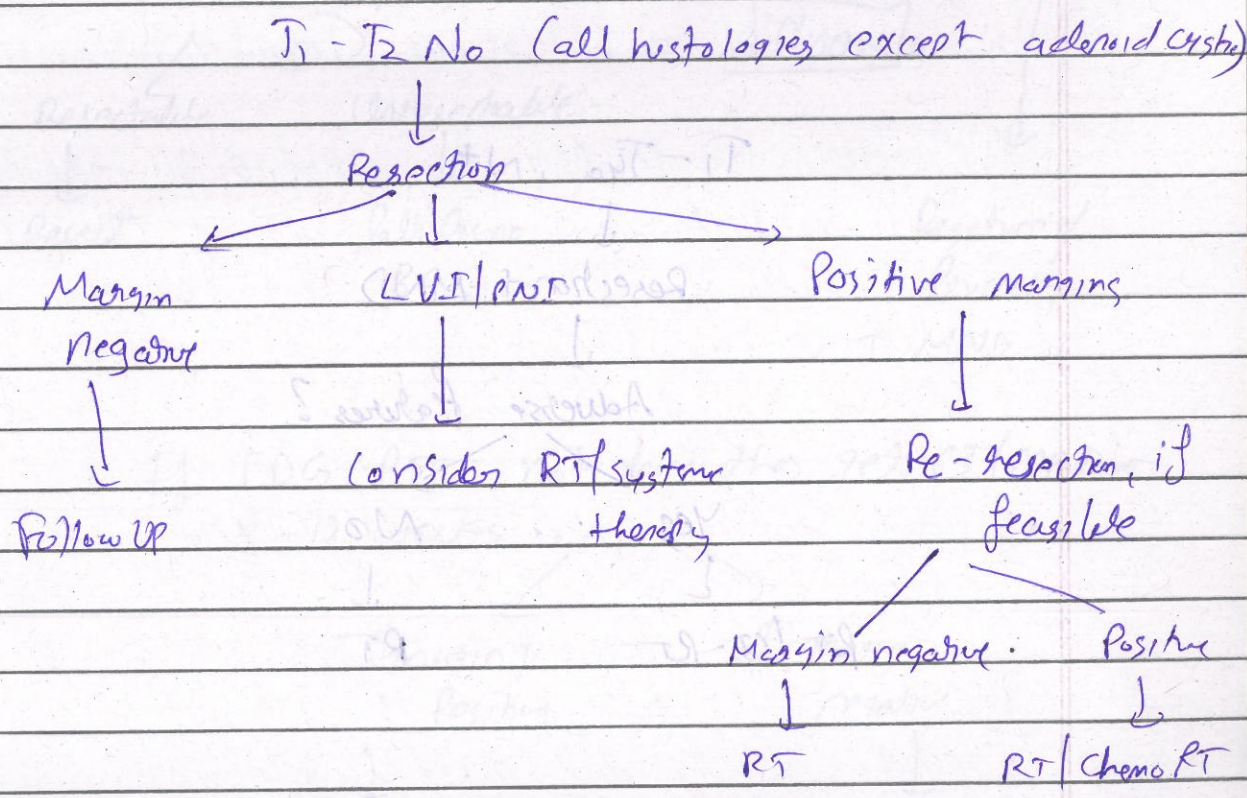
PET CT → Useful for post op monitoring

→ Evaluation of disease post CT-RT

Biopsy → Endoscopic approach by creating a wide antrostomy in the region of natural ostium

→ Sublabial incision in canine fossa via antrocyano antrostomy.

Overview of management



Adenoid cystic → Resection → RT (Preferred)

Observation if margin -ve
No PM.

T3 - T4a No

Resection

Adverse features

RT / CT-RT

No adverse features

RT to Primary

T1 - T4a, N+

Resection + MND

Adverse features?

Yes

RT / CT-RT

No

RT

T4a No-3 Mp

Performance Status

Concurrent CT/RT

Induction chemo f/ RT

RT

Concurrent CT-RT

Rel. RT

Full chemo

Clinical assessment after 4-8 weeks

Residual Primary

Persistent disease

Progression

Response seen

FDG PET at 12 weeks

Assess the extent of
disease by CT/MRI

Negative

Positive

Observed

Resectable

Unresectable

Resect

Pall. Chemo

BSC

Rejection of
Primary

+ MND

If FDG-PET not done then get CT/MRI at
8-12 weeks

Imaging

Positive

Imaging

Negative

FDG PET or Surgery

Observed

Surgical Management of Maxillary Cereus

Approach $\rightarrow$ 1) Weber Fergusson incision.

* A modified Weber-Fergusson incision is based on nasal & facial subunits, resulting in superior aesthetic & functional outcomes.

* Incision divides the upper lip in the midline through the philtrum of the upper lip upto columella.

Then turns laterally & cephalad to enter the floor of nasal vestibule along the crest of columella, takes a 45° turn & exits the floor of nasal cavity, remaining in the groove of the lateral aspect of ala.

Follows alar subunit all the way upto lateral aspect of nose.

Proceeds cephalad along the lateral aspect of nose till medial canthus of eye.

Can be given subciliary extension

Types of Maxillectomies

- 1) Medial Maxillectomy
- 2) Infrastructure maxillectomy
- 3) Subtotal maxillectomy
- 4) Total Maxillectomy.

Surgical anatomy

Vasculature → The only significant vein encountered here is the angular vein at medial canthus.

Blood supply to maxilla & PNS originates from both ECA & ICA systems

- 1) Facial / external maxillary artery
- 2) Internal maxillary artery (IMA) → ICA passes thru pterygo maxillary fissure to enter pterygopalatine fossa (PPF)

Branches of IMA

Greater Palatine

- Infra-orbital artery

- Sphenopalatine

- Posterior septal artery

2) Branches of ICA of significance

- Anterior & posterior ethmoidal.
- ophthalmic artery

Medial Maxillectomy - Entails resection of lateral wall of nasal cavity (medial wall of antrum & orbit), ethmoidal sinuses & medial part of orbital floor.

- Used for tumors involving lateral wall of nose, lacrimal sac & ethmoids.

Steps → 3 main stages

- 1) Soft tissue dissection / Bone exposure
- 2) Bone resection
- 3) Closure / Reconstruction.

① Soft tissue dissection

* ~~It~~ Can be done by midface degloving or lateral rhinotomy approach

* Soft tissues of face are lifted off, flush to bone

* Identify medial palpebral ligament, anterior lacrimal crest, lacrimal sac in lacrimal fossa & posterior lacrimal crest.

* Elevate lacrimal sac & transect it as distally as possible.

* Expose medial & inferior orbit. Periosteum is stripped from the nasal bone. Strip the orbital contents in ~~subperiosteal~~ extra periosteal plane from lamina papyracea.

* Identify frontoethmoidal suture line. Ligate & cut the anterior ethmoidal artery. It is not necessary to cut posterior ethmoidal artery.

* Strip along orbital floor in an extra periosteal plane.

* Free the soft tissues from the bone upto anterior free marginal nasal aperture.

* Retract the nasal ala & incise lateral wall of nasal vestibule to expose ipsilateral nasal cavity & inferior turbinate.

② Bone Resection — Osteotomies are done as under

* Along inferior orbital rim

~ Connecting antriotomy with nasal vestibule

* Across frontal process of maxilla

* Along orbital floor

* Along floor of nose

* Through lacrimal bone, lamina papyracea & anterior ethmoid

* Vertical posterior osteotomy through posterior ethmoid, post wall of antrum & PPF.

(3) Closure - Wound is irrigated, nasolacrimal duct is started.

↳ Maxillary antrum is packed & packing brought out through nares

- Medial canthal ligament is sutured back to a drill hole made in the nasal bone

- Remaining nostril is closed in two layers

Post op care - Nasal Packing is removed after 5-6 days

- Vigorous nasal irrigation & provision of humidity is required.

Inframaxillary Maxillectomy

Steps → a Incision is made in the mucosa of GBS and that of hard Palate with satisfactory mucosal margins

• Mucosal incision is extended through the soft tissue up to the bony anterior wall of maxilla to hard palate intra-orally.

• Osteotomy is made through the marked incision.

* Lower half of maxillary antrum is removed superiorly.

* If oral mucosa has chronic inflammatory changes, it needs to be curetted out & replaced by STSG.

Subtotal maxillectomy → Removal of entire maxilla except the orbital floor

* After giving incision, cheek flap is raised in the infra-orbital region, exposing the infra-orbital nerve. If only the lower half of maxilla is to be resected, then nerve should be preserved.

* Anterior wall of maxilla is divided just below the infra-orbital foramina.

* Line of transection is continued anteriorly through nasal process of maxilla & posteriorly upto zygoma.

* Then, transection through alveolar process is carried out.

* Mucosa of hard palate is then cut.

* Mucosa of maxillary antrum should be completely curetted.

* STSG is now used to line the undersurface of the cheek flap.

* Skin graft is applied to bony surface of antrum & is covered with dressing.

* Palatal defect is closed by dental obturator.

Post op → Oral hygiene etc.

→ One week later, dental obturator is removed by cutting the wires. An interim obturator is then placed.

After 3 months, a permanent obturator is placed.

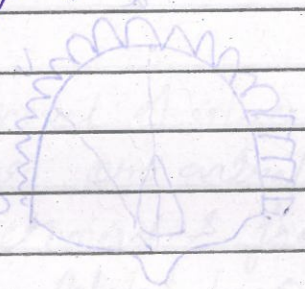
Total maxillectomy

- * Weber Ferguson incision & Subiliary extension is Placed.
- * Upper cheek flap is raised by a mucosal incision through upper gingivolabial & upper gingivobuccal sulcus. Raised till 1cm lateral to lateral canthus.
- * Then the Subiliary incision, skin of lower eyelid is elevated superficial to orbicularis muscle to preserve nerve & blood supply to that muscle.
- * Subperiosteal dissection in orbital plate is done which is Superior margin of surgical specimen.
- * Using a Periosteal elevator the orbital plate is lifted off.
- * In the oral cavity, mucosal incision is placed betⁿ canal & lateral incisor.

The incision is extended posteriorly till junction of hard & soft palate, then it turns laterally towards GBS.

- Entry is made in the nasal cavity by opening the vestibule.
- All soft tissue attachments are divided, nasal process of maxilla is divided.
Superiorly, maxilla is separated from zygomatic arch & inferiorly through the alveolar processes.
- Once all osteotomies are done, the bone is separated using periosteal elevator.
- Defect is closed by a dorsal osteotomy.

~~Maxilla~~



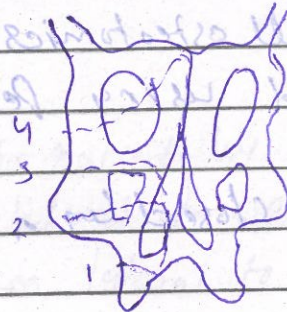
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Maxillectomy defects & Reconstruction

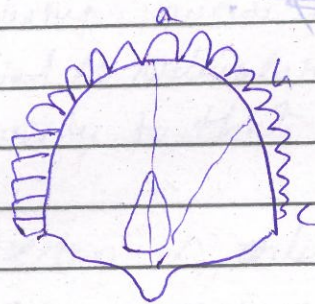
James Brown Classification of Maxillectomy defects
(AKA Liverpool classification)

The surgical defect is classified according to vertical dimension, which relates to involvement of orbit & skull base and the resultant mainly aesthetic deformity; and a horizontal or palatal aspect of the maxillectomy. Horizontal component relates more to functional & dental outcome.

Vertical component →



Horizontal →



Horizontal component applies to vertical components
2, 3 & 4. Not 1.

Vertical Component

Class 1 → Maxillectomy with no oro-entrat fistula

Class 2 → low maxillectomy

Class 3 → High maxillectomy

Class 4 → Radical maxillectomy

Horizontal Component

a → Unilateral alveolar maxilla & hard palate resected
Not involving nasal septum, not crossing midline

b → Bilateral alveolar maxilla & hard palate,
crosses midline, including nasal septum

c → Entire alveolar maxilla & hard palate.

Explanation,

Class 1 → Removal of alveolar bone, not leading to
oro nasal or oro entrat fistula [upper alveolotomy]
Resection of ethmoid & frontal sinus tumors
Resection of palatal bone.

Class 2 → Alveolus & entrat walls, but not
orbital floor & rim

Class 3 → Including floor of orbit, with or without
peri-orbital or skull base resection.

Class 4 $\rightarrow$ Class 3 + orbital extension.

Choice of reconstruction

Local flap (~~temporoparietal~~) $\rightarrow$ Class 1

Pedicle flap (temporals) $\rightarrow$ Class 1, 2a

Obturator $\rightarrow$ 1, 2a, 3a. Problematic for 4, C on class 4.

Soft tissue free flap $\rightarrow$ Same as obturator

Composite free flap $\rightarrow$ Class 2 a/c

3 a/c

4 a/c

Reconstruction by Class

Class 1 $\rightarrow$ local flaps or pedicle flaps

Central Palatal defects can be obturated.

Class 2 $\rightarrow$ Defect is created at the level of maxillary sinus and the nasal cavity

2a defect can be successfully obturated w a dentate maxilla

Pedicle flap can be used for 2a

Full thickness buccal bone can be brought into oral cavity and vascularised on temporalis flap.

In more extensive defects (b, c) obturation will be more difficult. Some methods as 2a will be adequate as long as sufficient bone is made available for implants.

Class 3 → Vascularized iliac crest with internal oblique provides method of closing large fistulas and providing sufficient bone to support denture & cheek & implant-retained prosthesis.

Composite radial forearm flap can also be used.

Class 4 → DCIA ± internal oblique is required to seal the cranium, obliterate the dead space and close the coronal fistula.

Other Classification

① Cordeiro Classification →

Type 1 → Limited maxillectomy - One or two walls are removed, with preservation of palate. Recon ± nonvascularized bone or Radial forearm free flap

Type 2 → Subtotal → 5 out of 6 walls are removed, preserving orbital floor,

Recon → RFFF or osseocutaneous RFFF

Type III $\rightarrow$ Total Maxillectomy

IIIa $\rightarrow$ Orbital contents preserved

IIIu $\rightarrow$ Orbital Exenteration done.

Type II $\rightarrow$ Orbito-maxillectomy

IIIa is repaired by nonvascularized bone graft, sandwiched betⁿ flap (Temporalis & Rectus abdominis)

IIIu repaired with rectus abdominis flap

* No mention of use of obturators in this

Colorectal Cancer Screening

Average Risk - Age ≥ 45 yrs

- No h/o adenoma / sessile serrated polyp / CRC
- No h/o IBD
- Negative family h/o CRC or advanced adenoma or advanced SSP.

Colonoscopy

Stool based
testing

Flexible
Sigmoidoscopy

CT
colonography

- * CRC Screening is recommended for age 45-75 yrs with life expectancy >10 yrs. Beyond that it should be individualized.

Colonoscopy - If no Polyps seen, then rescreen with any modality in 10 yrs.

If Polyp seen, then Polypectomy should be done.

Hyperplastic Polyp
< 1 cm in size

↓
Rescreen with any
modality in 10 yrs

- Adenoma any size

- SSP any size

- Hyperplastic Polyp > 1 cm

↓
(PTV)

In case a polyp found at colonoscopy, it is classified as low risk or high risk

Low risk adenoma $\rightarrow$ ≤ 2 polyps $\rightarrow$ Repeat colonoscopy in 7-10 yrs

If negative, repeat in 10 yrs
- If positive, repeat colonoscopy all to findings

Low risk SSP $\rightarrow$ No dysplasia $\rightarrow$ Repeat Scopy in 5 yrs
 ≤ 2 polyps
 < 1 cm

High risk - Traditional serrated adenoma
- HGD

- Villous or tubulovillous histology $\rightarrow$ Repeat Scopy in 3 yrs.

- Betⁿ 3-10 adenomatous polyps

- Adenoma or SSP > 1 cm

Hyperplastic polyp > 1 cm

If negative, repeat in 5 yrs.

See later

≥ 10 adenomatous polyps or SSP $\rightarrow$ Consider Polyposis syndrome

② Stool based testing

- 1) Fecal occult blood - If negative, repeat in 1 yr.
If positive, colonoscopy.
★ High sensitivity guaiac based, non-oxidized, 3 successive samples.
- 2) Fecal immunochemical testing (FIT) → Same as above.
- 3) multitargeted stool DNA based testing
If negative, rescreen in 3 yr.

FIT has superior sensitivity to FOBT, but FOBT is shown to reduce mortality & can be used as an alternative to FIT.

③ Flexible sigmoidoscopy. → If no Polyps seen, rescreen with any modality in 5-10 yr.

If seen, same pathway as colonoscopy.
In PLCO trial, 21% ↓ in CRC incidence & 26% ↓ in CRC mortality with two sigmoidoscopies, done 3-5 yr apart.

④ CT colonography [CTC]

- 1) Polyp 6-9mm $\begin{cases} 1-2 \rightarrow \text{CTC in 3 yr} / \text{colonoscopy} \\ > 3 \rightarrow \text{colonoscopy} \end{cases}$

- 2) Polyp $\geq 10\text{mm}$ → colonoscopy

- 3) No Polyps → Re-screen in 5 yr.

Management of large colorectal polyp ($\geq 1\text{cm}$)

① Pedunculated polyp $\rightarrow$ No invasive cancer $\rightarrow$ colonoscopy in 3yrs
 cancer $\rightarrow$ Manage as per staging

② Sessile polyp $\rightarrow$ High risk features for submucosal invasion

- NICE type 3
- Kudo type V
- non lifting sign
- size $\geq 4\text{cm}$
- Intraluminal bleeding
- HGD
- macroscopic tissue alterations

NO

YES

No high risk features $\rightarrow$ Complete resection

1) No invasive cancer or unfavourable risk factors like

- Size $\geq 4\text{cm}$

- Intraluminal bleeding

- HGD

- Macroscopic tissue alterations

Colonoscopy in 1-3yrs

If no recurrence, colonoscopy in 3yrs.

If recurrence, repeat scope or resection

2) No invasive cancer but unfavourable factors (+) or piecemeal excision.
 colonoscopy in 6 months

If no recurrence, then within 1yr,
 then in 3yrs.

3) Invasive cancer → Manage as per stage.

~~High risk endoscopic features~~

→ In complete resection

No cancer



Refer to higher centre

Cancer



Manage as per stage

High risk features →

No invasive cancer

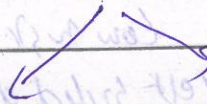
Invasive cancer

Increased Risk

(1) Due to personal history of CRC



Routine testing for Lynch syndrome (MMR deficiency) for pt of CRC



MMR proficient

MMR deficient



~~Refer~~ manage as per

Colon / Rectum guideline

Guideline for Lynch Syndrome

② Due to Inflammatory Bowel Disease

↓
8YA after onset of symptoms

↓
Colonoscopy with

- Chromoendoscopy & extensive sampling of structure or masses
- 2 biopsies from every bowel segment OR
- High Defⁿ white light endoscopy with random & targeted biopsies every 10cm with ≥ 32 total biopsies.

Evaluation findings:

1) Invisible dysplasia → If confirmed, refer to IBD expert

If no dysplasia

Low risk

High risk

- Left sided disease
- No chronic inflammation

PSC,
Extensive colitis
F/H of CRC

↓
Scope 2-3 yrs

↓
Annual scope.

2) Non resectable Polypoid lesion → Surgery refer.

3) Resectable lesion → Complete resection done

Low risk

High risk



Scopy 2-3yr

Annual Scopy

Incomplete resection → Surgical refer
→ Expert refer

4) Stricture → Transversal stricture

Low risk

High risk

Annual Scopy

High center

Annual Scopy

Non Transversal → Surgery refer

③

③ High risk based on positive family history

- 1) ≥ 1 first degree relative $\pm$ CRC at any age
 - Begin Scopy @ 40 yrs or 10 yrs before earliest age of onset in family
 - Repeat every 5 yrs.

2) 2nd & 3rd degree $\pm$ CRC at ages

- Scopy @ 45-50 yrs
- Perform every 10 yrs.

3) 1st degree relative $\pm$ confirmed adenomatous polyps or advanced SSP

↓
Same as (1)

Emerging options

① The methylation status of septin 9 (sept 9) gene has been shown to distinguish CRC tissue from normal surrounding tissue. Circulating methylated sept 9 DNA is a biomarker for CRC.

Paris Classification of Superficial neoplastic lesions

- $I_p \rightarrow$ Pedunculated
- $I_s \rightarrow$ Sessile
- $II_a \rightarrow$ Slightly raised
- $III_a \rightarrow$ non Polypoid, flat
- $II_c \rightarrow$ non Polypoid, slightly depressed
- $II_d \rightarrow$ non Polypoid, excavated.

Kudo Pit Patterns

- $I \rightarrow$ Round pits - non neoplastic
- $II \rightarrow$ Stellar or Papillary pits $\rightarrow$ non neoplastic
- $III_s \rightarrow$ Small, tubular, rounded pits $\rightarrow$ neoplastic
- $III_c \rightarrow$ Tubular or rounded pits $\rightarrow$ "
- IV - Branch like pits
- $V_s \rightarrow$ Irregularly arranged pits $\rightarrow$ invasive neoplastic
- $IV_n \rightarrow$ non structural pits $\rightarrow$ Massively submucosal invasion.

Minnesota Cancer Control Study

- * ~~First~~ First trial to utilize FOBT in screening.
- * Three arms - Annual FOBT
 - Biennial screening
 - Usual care
- * At 13 yr follow up, annual screened arm had 33% relative reduction in mortality
- * At 18 yr follow, 48% reduction in biennial group - 21% annual group - 20%
- * Reduced cancer specific deaths but NOT overall mortality

Surgical Management of Ca Colon

Colonoscopic resection of Polyp done



- Complete resection
- Favourable histological features

→ Grade 1, Grade 2

→ NO LVI

→ Negative margin > 2mm

Pedunculated Polyp

cancer [T1/T2/T3]

observer

Sessile Polyp

cancer

observer

Colonoscopy

General Principles

- * Lymphatic Capillaries are primarily located in submucosal & subserosal layers of bowel wall.

The extent of resection depends on the location of primary tumor

- * Lymphatic flow is primarily circumferential in the colon with longitudinal spread of 1cm in each direction, hence 5cm normal bowel on each side is sufficient to avoid recurrence.

- * length of terminal ileum resected does not influence risk of recurrence.

Regional lymph node drainage

Four main groups of nodes → Epicolic

→ Paracolic

→ Intermediate

→ Apical

~~D1~~ D1 → Epicolic & Paracolic nodes with 5cm of tumor

D2 → Epicolic & Paracolic nodes from 5-10cm from tumor

Intermediate nodes

Right colic nodes

Middle colic nodes

WORLD Trial
D3 increases nodal yield compared to D2

D3 → All nodes for D1 & D2 plus lymph nodes at the roots of ileocolic, R colic & middle colic arteries

D4 → D1, D2, D3 + Removal of central nodes

Vessel ligations needed for each colectomy

Right colectomy → Ileocolic

R colic

R branch of middle colic

Extended Rt hemicolectomy → vessels of Rt colectomy
(till transverse) middle colic.

Extended Rt colectomy → Above + left colic
(till splenic flexure)

left hemicolectomy → left branch of middle colic
left colic.

Complete mesocolic Excision

- (ME + Central Vascular Ligation [CVL] proposed by Hohenberger et al.

Imp points from Hohenberger paper

* Except in very advanced cases, the lymphatic spread follows the lymph drainage along major arteries.

• Mesocolon is covered by visceral fascia from both sides like envelope.

• CME is sharp dissection of visceral plane from parietal plane (retroperitoneal); aiming to avoid any breach in visceral fascia.

- * With this procedure, colonic arteries are well exposed and tied at base. It is associated with improved survival.
- * Discuss arteries / vessels ligated in various resections.
- * Median number of nodes harvested $\rightarrow 32$ [2-169]
- * 5yr OS $\rightarrow 85\%$.

Laparoscopic Colon Resection

Three Significant trials

- 1) Clinical Outcomes of Survival Therapy [COST]
- 2) CLASSIC trial
- 3) Colon Cancer (lap or Open Resection [COLOR] trial

COST trial $\rightarrow$ Sample size - 872

length of stay $\rightarrow$ 6 day (open) $\rightarrow$ Significant
5 day (lap)

No difference in mortality rates

Operative time is significantly less in open

Conversion rate to open $\rightarrow 21\%$

Significantly less analgesic requirement in lap.

All analgesic outcomes are equivalent
(OS, DFS) in 3yr & 5yr follow up

2) CLASSIC trial - Sample Size $\rightarrow$ 794

- * No difference in length of stay
- * No difference in mortality
- * Shorter operative time with open
- * No diff in complications
- * 25% conversion rates

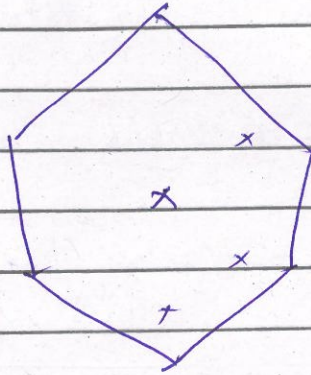
* No diff. in OS or DFS in 3yr & 5yr follow up.

3) COLOR trial $\rightarrow$ 329 Patient included

Similar rate of OS, DFS

$\rightarrow$ Significant decrease in analgesic requirement = 10%

Post Placement for Rt hemicolectomy



← Pt is in Trendelenburg position, Rt side tilted upwards

Role of CRS + HIPEC in Colorectal Peritoneal mets

PRODIGE 7 - ACCORD 15 trial →

IASO Guidelines - Lung

* Multidisciplinary team is mandatory.

Biopsy? - Biopsy is preferable, do when possible.

Clinical history is an important component of decision making.

Prehabilitation → Smoking cessation x Quik

→ Bronchodilators

→ Chest PT, Spirometry

→ Nutritional Rehab.

Staging

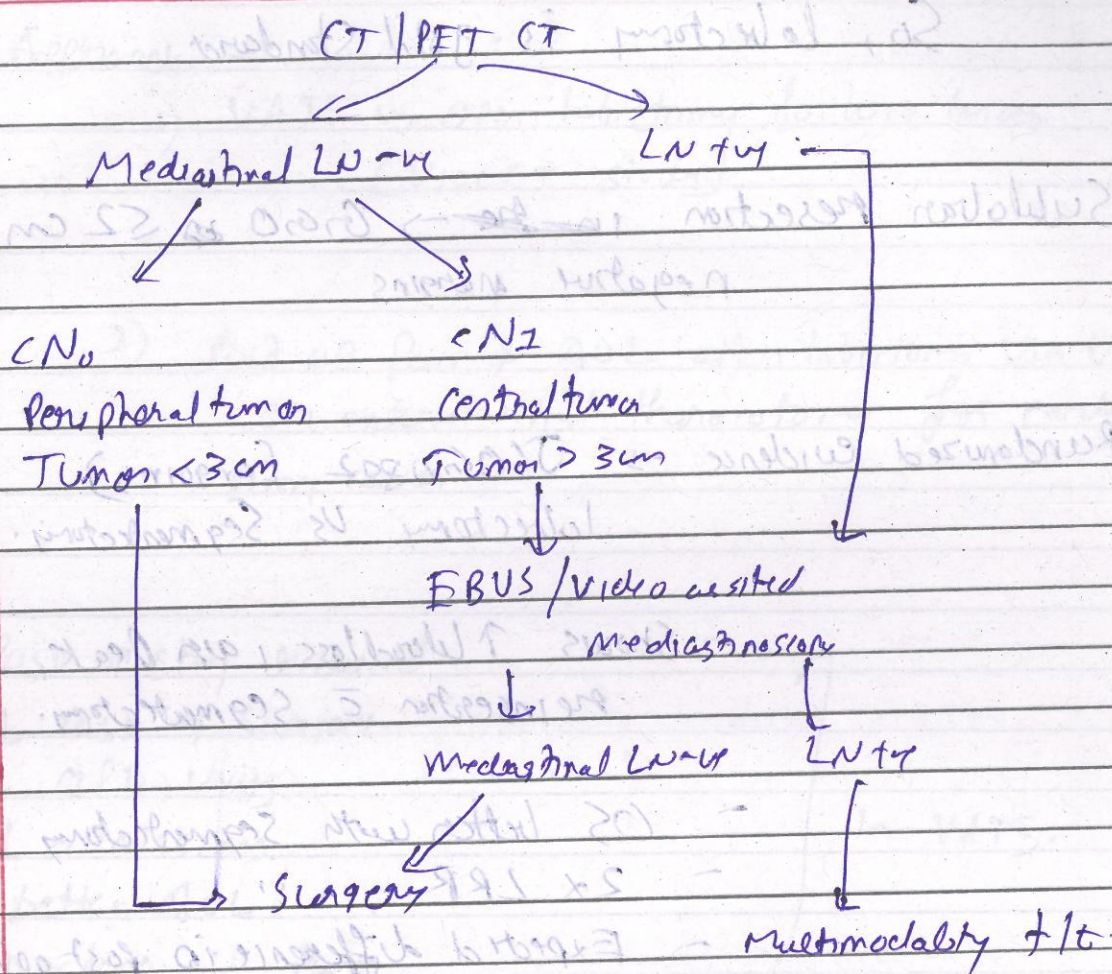
→ PETCT - not perfect though.

Positive predictive value for nodal evaluation is 53.8% (TMH study).

~~ESTS~~ guideline

~~CT/PETCT~~

~~Medic~~



Functional evaluation - Effort tolerance

6 min. walk test

PFT / DLCO > 30%.

Further evaluation - Perfusion scan

Stress echo

If medically unfit → SBAT

Extent of resection → Total at lobectomy VS sublobar resection [Lung Cancer Study group]

3x rate of LK

30% increase in mortality

} in Sublobar resection

So, lobectomy is gold standard

Sublobar resection is ~~not~~ → GGO $\leq$ 2 cm with negative margins

Randomized evidence → JCOG0802 (ongoing)
lobectomy vs Segmentectomy.

- Shows ↑ Wound loss, air leak, TCD reinsertion in Segmentectomy.
- OS better with Segmentectomy
- 2x LRR
- Expected difference in post op lung fn is only 3.5%.

Mediastinal lymph node dissection?

ALC0606 20030 → LN sampling is equivalent to LN dissection, but most patients in this trial were T₁/T₂ [82%]. So in most scenarios, systematic mediastinal LN dissection is mandatory.

Approach $\rightarrow$ search for - report - investigation

1) VATS vs Open lobectomy for lung cancer
[VIOLET study]

2) Post op Pain & QOL after lobectomy via VATS
or anterolateral thoracotomy for early
lung cancer

- * Post op stay reduced
 - * ↓ Cost of Surgery
 - ↓ CPD loss
 - ↓ admissions
 - Better QOL
 - Decline in pain
 - LN upstaging 6.2% Vs 4.8%
 - Rx resections 97.8% Vs 97.4%
- In VATS.
- $\therefore$ VATS $>$ open.

Multifocal VATS vs Unilateral $\rightarrow$ MVUVLC Trial
(ongoing)

Neoadjuvant therapy $\rightarrow$ N2 disease

$\rightarrow$ Downstage primary to avoid pneumonectomy

Single station N2 < 3 cm

* Induction ~~chemo~~ therapy

- NACT

- NACT-RT

More evidence favouring NACT

Surgery $\rightarrow$ Lobectomy + Mediastinal LN

* Neoadjuvant TCI $\rightarrow$ Not standard of care.

Multistation discrete N2

$\rightarrow$ Chemo radiation $>$ Surgery

Incidentally detected N2 $\rightarrow$ Proceed to resection

R_0

R_1/R_2

- Adjuvant Chemo

$\pm$ Sequential CRT

Adjuvant CRT

Check in
Devita

Post op RT

Lung ART trial

Port C trial



No improvement in OS = PORT
So, not standard of care for Rn resections.

Adjuvant chemo $\rightarrow T > 4cm$
N+

ZACE meta-analysis $\rightarrow$ Increase survival by 3% in
-5yr

Osimentinib $\rightarrow$ ADORE trial

can be given $\times 3yr$

DFS benefit, but no OS benefit shown
yet.

Surgery in Oligometastatic NSCLC

Types $\rightarrow$ Synchronous

Metachronous

Oligo recurrence - limited to 3-5 sites

Oligo progression - >1 of a ~~total~~ limited number
of mets recur while systemic

therapy controls other sites

Local Consolidative vs Maintenance Therapy in
oligometastases

49 pts; 2 oligomet

Randomized to maintenance / oligomet
vs local therapy

Surgery where feasible (Brain / lung)
Local Rx at other sites (Bone / Lu)

Pts ideal for Surgery → Brain / lung / adrenal / mets

→ No disease

→ Small T1

→ longer DFI

→ Younger age

→ Adenoma (Driven mutation)

Genetics of CRC

- Broadly, three pathways for evolution of cancer

~~Defective tumorigenes~~

1) Classic Chromosomal instability.

- Chromosomal instability or CIn was proposed by Vogelstein

- First step - inactivation of Wnt signalling pathway.

- It is followed by activating mutations in KRAS, CDC4, PIK3CA

- It is followed by disruption of TGF- β signalling

- Final step for conversion to cancer - p53 mutation

- Genetic alteration in Wnt pathway begins by biallelic inactivation of APC gene, which removes the protein regulating intracellular conc. of β catenin.

- β catenin is a growth promoter, that turns on growth program & it is also involved in intracellular adhesion complex that holds adjacent epithelial cells together

Genetics of CRC

* Broadly, three pathways for evolution of cancer

~~1) Proto-oncogenes~~

1) Classic Chromosomal instability.

2) Chromosomal instability or CIN was proposed by Vogelstein

* First step $\rightarrow$ inactivation of Wnt signalling pathway.

* It is followed by activating mutations in KRAS, CDC4, PIK3CA

* It is followed by disruption of TGF- β signalling

* Final step for conversion to cancer $\rightarrow$ p53 mutation.

* Genetic alteration in Wnt pathway begins by biallelic inactivation of APC gene, which removes the protein regulating intracellular conc. of β -catenin.

* β -catenin is a growth promoter, that turns on growth program & it is also involved in intracellular adhesion complex that holds columnar epithelial cells together

- The median age of first adenoma in FAP $\rightarrow$ 16 yrs
in CRC $\rightarrow$ 39 yrs

2) CpG island methylation phenotype [CIMP]

- * Inactivation of tumor suppressor genes through hypermethylation of gene promoters.
- * It is usually a normal process that becomes accelerated through a process not completely understood.
- * The hypermethylated sequences are CpG dinucleotide pairs, which are infrequent in the genome, except gene promoters. They occur in clusters called CpG islands.
- * When there is excess of promoter methylation in the cancer genome, this is called CpG island methylation phenotype.
- * CIMP often occurs with BRAF (V600E) mutation & that is associated with more aggressive CRCs.
- * Tumors in CIMP pathway begin as sessile serrated adenomas & it has been called serrated carcinogenic pathway.
- * Occur predominantly in proximal colon.
- * Genes that commonly undergo hypermethylation are p16, CDKN2A, MLH1.

3) Microsatellite instability

* This is a secondary consequence of either CIN (in Lynch Syndrome) or CIMP

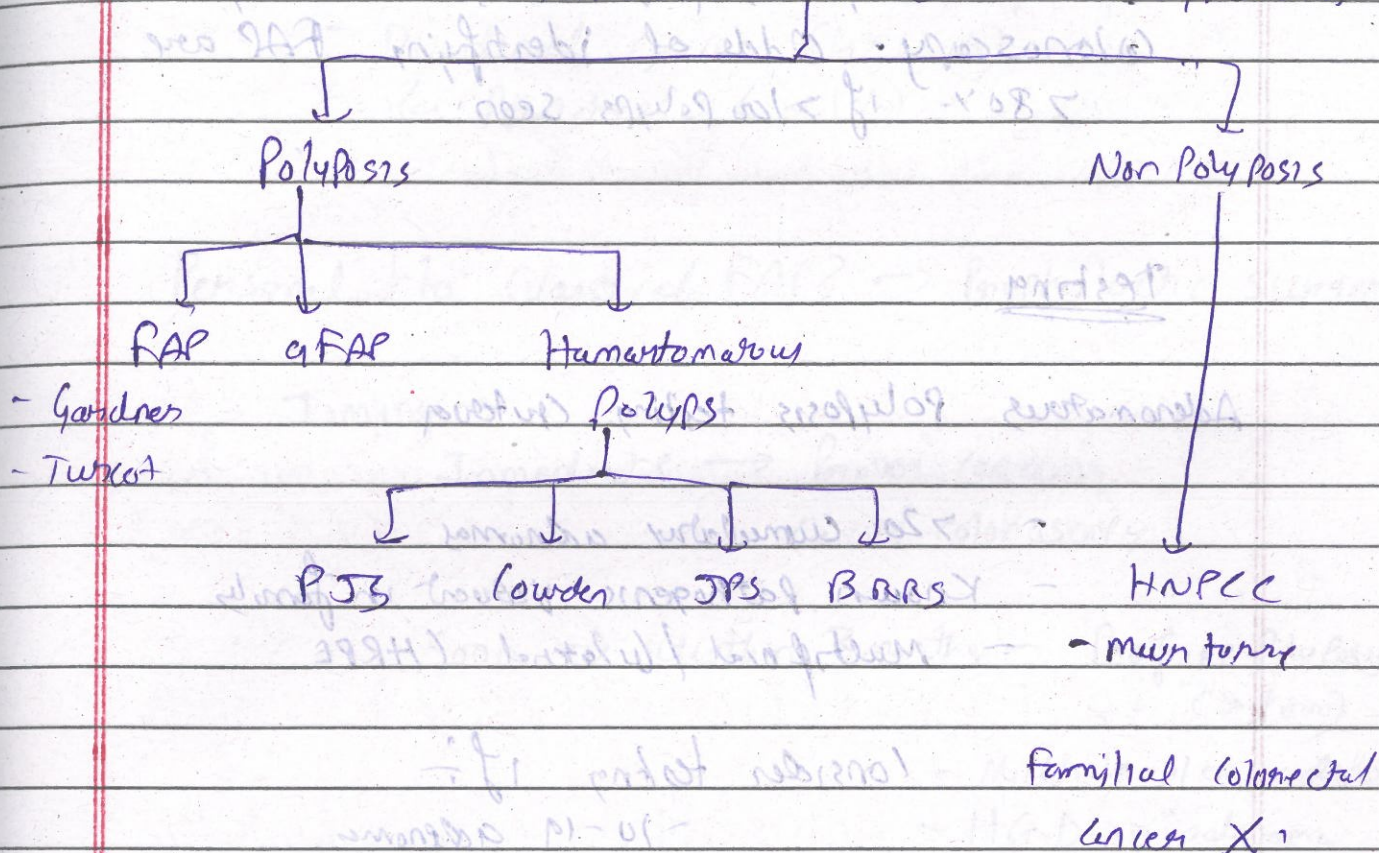
* DNA mismatch repair (MMR) is mutated.

* During DNA replication, the DNA polymerase is prone to errors & this MMR system helps correct those errors.

CRC with MSI can occur in three circumstances

- 1) 12% of all CRC begin as CIMP tumors but when methylation occurs at both alleles of DNA MMR gene (like MLH1), MSI ensues
- 2) 3% of CRC occur in setting of Lynch Syndrome, of which most have MSI.
- 3) Small proportion of CRC begins in CIMP pathway & develop biallelic mutations in MMR genes, after which MSI ensues. This is called "Lynch-like" Syndrome.

Inherited Colorectal Cancer Syndromes



Polyps Syndromes

Familial Adenomatous Polyposis

* Incidence $\rightarrow 1/10,000$

Diagnosis $\rightarrow$ * Inherited AD, 100% Penetrance

* Children of an affected parent undergo genetic testing at puberty, and if affected, start colonoscopy at that time.

* Testing in infancy is needed to rule out possibility of hepatoblastoma, a rare manifestation of germline FAP.

- * Clinical diagnosis of FAP is made by colonoscopy. Odds of identifying FAP are $>80\%$ if >100 polyps seen.

Testing

Adenomatous Polyposis testing criteria

- >20 cumulative adenomas
- Known pathogenic variant in family
- Multifocal / bilateral CHRPE

Consider testing if:

- 10-19 adenomas
- Cerebroid macular PTC
- Desmoid
- Hepatoblastoma
- Unilateral CHRPE

Classical FAP - Germline APC variant

- >100 cumulative adenomas (clinical suspicion)

- AD inheritance
- Additional findings like

→ CHRPE

→ Osteoma, Supernumerary teeth

→ Duodenal adenomas

→ Gastric fundic polyps

- ↑ risk for medulloblastoma, PTC,
- Duodenal cancer (4-12%)
- Ca Pancreas (<1%)

Personal h/o Classical FAP? → Prophylactic Surgery

Timing →

Immediate → Proven cancer

(x of colonoscopy)

Soon → Within 3 months - Profuse Polyposis (→ poor)

- Multiple >1cm adenomas

+ HGD in adenoma

Sometime → On yr by year → 100-1000 Polyps

→ Socioeconomic factors

Defen → High Comorbidity

→ High risk of desmord.

Surveillance → * If IRA done, endoscopic evaluation of ~~the~~ rectum every 6-12 months.

* If total procto colectomy ± IPAA, then endoscopic evaluation of ileal pouch & rectal cuff at 6 months.

* If TPC ± end ileostomy done, then ileoscopy

~~Broadband Cancer~~

Asymptomatic, at risk family members?

↓
APC gene testing recommended

↙
If positive,
follow APC gene pathway
written about

↘
If negative,
average risk
CRC screening,

Surgical options for Colon / Rectum

1) Ileorectal anastomosis → Contraindicated in
rectal cancer

→ Can be done in <20 rectal adenomas
<1000 colon adenomas

2) IRAA → Higher complication rate

→ Ileostomy needed

→ Risk ATZ cancer

→ Can be done in >20 rectal adenomas
rectal cancer.

3) Proctocolectomy + end ileostomy

→ safest

→ least complication

- High ligation & CMF should always be practiced.
- If ATZ & low rectum are covered by adenomas, then microsectomy & hand sewn anastomosis should be done in IPAA.

Chemoprevention → Most tested drug is Sulindac

Other agents → DFMO

→ Celecoxib

→ Enterochol i Sulindac in duodenum.

None of them are standard as of now.

Desmoids in FAP

- Desmoids are found in 30% FAP patients
- Overall, 12% regress, 7% are lethal & rest never disappear but remain asymptomatic.
- Risk factors -
 - 1) Females
 - 2) Family h/o desmoid
 - 3) Extra colonic manifestation of Gardner
 - 4) Mutation at 3' end of codon 1400.

have more severe disease
- Desmoids in FAP are to be managed non operatively as long as possible, esp in mesentery

Church et al Staging System

Stage	Size	Symptom	Growth
I	< 10cm	none	none
II	< 10cm	mild	< 25% in 6 months
III	11 - 20cm	Moderate	25 - 50%
IV	> 20cm	Severe	> 50%

Treatment & surveillance are to stage

I → Nothing, or Sulindac 150-200mg BD
→ Repeat Scan in 1yr.

II → Sulindac 150-200mg BD
+
Rabaxolone 60mg BD

→ Repeat Scan in 6 months.

III → Methotrexate / Vincristine
or Sofagene

→ Repeat Scan in 3 months.

IV → Doxorubicin, Adriamycin

→ Repeat Scan in 3 months.

Duodenal Polyps in FAP

- * Duodenal cancers are the third most common cause of death in FAP, after CRC & desmoid.
- * Screening to begin with side view OGDscopy at 25-30 yrs age.



(Classify polyp as per Spigelman Grading)

Spigelman Staging

Characteristic	1	2	3
Polyp number	1-4	5-20	>20
Polyp size	1-4mm	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	low	moderate	high

Stage I → 1-4 → Survey in 5 yrs.

II → 5-6 → Survey in 3 yrs

III → 7-8 → 1 yr

IV → 9-12 → 6 months

IV → 9-12 → Consider Surgery.

Groves et al → 36% of stage IV develop carcinoma.

Pancreas preserving duodenectomy or Whipple can be done.

Extra-colonic manifestations

What physical defects you look for in (a colon it?)

- 1) Gardner Syndrome → Osteoma
→ Epidermoid cyst
→ Extra teeth
→ Desmoids.

- 2) PTZ is 7x more common in FAP.
Circumferential-mucosal PTZ is an indication for APC gene testing.

- 3) Adrenal adenomas

- 4) Turcot Syndrome → Brain tumor (medulloblastoma)
→ hereditary CRC.

Attenuated FAP [aFAP]

- * < 100 synchronous adenomas
- * Present at older age
- * Develop CRC 10-20 yrs later
- * Mutations tend to be at an extreme of the gene

* In 3' extreme mutation, there can be hereditary desmoid without CRC.

* Surgery is almost always total colectomy + IRA.

Mut YH Associated Polyposis

NTHL1 Associated Polyposis

* Mut YH & NTHL1 are genes involved in DNA Base excision repair

* < 1% of all CRCs.

* Phenotypically resembles a FAP with < 100 Polyps

* Young age of onset of Microsatellite stable CRC.

* Polyps can be adenomatous or serrated.

* Classically, progressive inheritance seen but sometimes dominant pattern is seen.

Extra colonic manifestations → Most are similar to that of classical FAP

* Gastric & duodenal adenomas, Small bowel carcinoma, Dermoid tumors, thyroid carcinoma

Surgery → Colectomy + IRA for uncontrolled polyposis or CRC

Hamantomatous Polyposis Syndromes

① Juvenile Polyposis Syndrome

Diagnosis → * Any juvenile polyp in family history of juvenile polyposis

* > 4 Synchronous Juvenile Polyps in large intestine

Incidence ~ 1/50,000 - 1/100,000

* Germline mutations in SMAD4 & BMPRIA genes.

* Autosomal dominant with variable penetrance

Clinical features * Polyp growth begins in 1st decade of life.

* Polyps are all across GIT tract, but most commonly in Colon.

Sachatello et al divided JPS into three categories

- 1) Juvenile Polyposis of infancy → Extremely rare
 - Entire GIT is affected
 - Bloody diarrhea, intussusception, protein losing enteropathy
 - Death within 2yr of life.

2) Juvenile Polyposis coli (rare)
→ Polyps limited to colon & rectum

3) Generalized JPS - From stomach to rectum.

* M.I. Symptom → Rectal bleeding.

Others → Hypoproteinemia
Hypokalemia
Clubbing

Extraintestinal morphologic features

- * Macrocephaly
- * Mental retardation
- * Abetal & Ventricular septal defects
- * Pulm. Stenosis
- * Meckel diverticulum

Malignant potential?

→ Most common malignancy is CRC

→ Others - Stomach, Pancreas, duodenum, Small bowel.

Mean age of onset → 35 yrs.

Screening & Surveillance → In a known mutation,

Screening colonoscopy to begin at 12-15 yrs.

If $\emptyset$, then repeat in 2-3 yrs

If Polyp seen → Polypectomy & HPR & follow accordingly.

Ultrasound starting age 15-25 yrs.

Surgery → Correction of anemia, electrolyte disorder, hypoprotecemia etc first

→ For children & Juvenile Polyposis,
↓ protein, anemia, failure to thrive
are indication for Sx

→ For any dysplasia or cancer

→ Prophylactic colectomy done in case of
multiple polyps that cannot be removed
endoscopically or adenomatous elements in
polyps, as when f/h/o CRC.

Choice of Surgery → Colectomy + IRA / IPAA.

* Total Procto Colectomy may be done in case of
Involvement of rectum.

* But unlike FAP, number of rectal polyps is
not an indicator for need of TPC

* Ultrasound should be done before surgery!

② Petz-Jeghers Syndrome.

Diagnosis $\rightarrow$ (Clinical Criteria) $\rightarrow$
 ≥ 2 Peutz-Jeghers polyps anywhere in GI

OR

At least 1 intestinal PJ Polyp in a pt &
 family h/o PJS

OR

(Classical Mucocutaneous Pigmentation.

In the absence of polyps, diagnosis can be made
 based on family history & Pigmentation.

* Autosomal dominant, Gene $\rightarrow$ STK11

* Diffuse hamartomatous polyposis seen, most
 commonly in small intestine. (75%).

Peutz-Jeghers Polyp $\rightarrow$ Smooth muscle bundles
 within the lamina propria of the stalk & head of
 polyp.

$\rightarrow$ Do not have dilated cystic spaces Pathognomonic
 for Juvenile Polyps.

* Characteristic melanin macules, m.c. on
 lips & perioral region

Symptoms → Small bowel obstruction due to intussusception

→ Abdo discomfort & distention

→ Anemia due to on/off bleeding

Cancer risks → Colon (36%)

Pancreas (39%)

Stomach

Small bowel

Breast (54%)

Ovary (21%)

Lung

Uterus

Unusual tumors → Adenoma malignum of cervix

→ Ovarian sex cord tumor with

Annular tubules (SCTAT)

→ Testicular SCTAT

Surveillance → • Upper GI scopy & Small bowel evaluation every 2 yrs, starting age 10.

• Colonoscopy every 2-3 yrs, starting age 25.

• Capsule endoscopy is better than

Small bowel radiographs

- * Symptoms of polyposis, Or Polyps $> 1-1.5$ cm should undergo laparotomy.

Intra-op enteroscopy is needed to locate lesion.

Colonoscopy polyp > 1 cm should be removed endoscopically.

Extra-intestinal screen,

1) Annual testicular, age 10 onward

2) Annual Pelvic exam & Papanicolaou, starting age ~~20~~ 18-20

3) 6 monthly breast exam, annual mammogram

4) EUS/MRCP & CA 19-9 every 12 m starting age 25-30 yr.

(2)

PTEN Hamartoma Tumor Syndromes

Cowden Syndrome

Bannayan-Riley-Ruvalcaba Syndrome

- * PTEN is a tumor suppressor gene that encodes a phosphatase in PI3K/AKT pathway.

Both are AD inherited

Cowden Syndrome

Major diagnostic criteria → Ca Breast

→ FCT

→ Macrocephaly

→ Ca endometrium

→ Lhermitte Duclos disease

Minor criteria → Benign thyroid changes

→ Mental retardation

→ Hamartomatous Polyps

→ Fibrocystic changes in breast

→ Lipoma, Fibroma

→ Gastrointestinal lesions

Diagnosis → Macrocephaly / Lhermitte Duclos
+

Any one major

→ One major + 3 minor

→ Four minor.

Risk of cancer → Breast (50% lifetime risk)

10% lifetime risk for Ca Thyroid

Colorectal Polyp may occur

Screening → Physical exam → 18 yr or
5 yr before earliest cancer in family

Annual breast exam starting 18 yr
Mammo age 30 yr, or 5 yr before

Thyroid USG every 1-2 yr
starting age 18

Colonoscopy every 1-3 yr starting

UGIScopy every 3-5 yr starting

Pelvic exam for endometrium
starting age 35-40

Bannayan-Riley-Ruvalcaba Syndrome

- Macrocephaly
- Hamsteroidous colorectal Polyp
- Pigmented macules on glans penis
- Histiocytosis
- Mental retardation.

No increased risk of cancer.

Other PTEN mutation syndromes

1) Proteus Syndrome (Elephant man)

2) Gorlin Syndrome (nevoid BCC).

Hereditary Non-Polyposis

Colorectal Cancer

[HNPCC] / Lynch syndrome

HNPCC is defined by Amsterdam II criteria

- 1) At least 3 relatives with HNPCC associated cancer (CRC, endometrial, small bowel, ureter)
- 2) At least two successive generations
- 3) At least one case before age of 50y.
- 4) FAP should be excluded
- 5) Tumours should be verified histopathologically.

* Accounts for upto 3% of CRC

* < 100 colorectal polyps, most often in Rt colon

* Accelerated rate of development of CRC in these polyps. Mean age of onset of CRC $\rightarrow$ 43y.

HNPCC Type 1 $\rightarrow$ CRC

Type 2 $\rightarrow$ Extracolonic tumours in
Stomach, endometrium, Small bowel,
renal pelvis

Lifetime risk of CRC $\rightarrow$ 80%.

(ca endometrium $\rightarrow$ 50-60%).

* Autosomal dominant inheritance $\approx$ 80% penetrance

* Mutations in mismatch repair genes, most commonly
MLH1 or MSH2.

Testing & Surveillance

1) If Known Lynch variant in family

Gene testing for the pathogenic variant

Positive for
variant

Negative

Aug. risk CRC
Screening

Manage according to
the involved gene.

2) No Known pathogenic variant

Multigene testing

If gene identified

Follow surveillance
according to
gene

If not

Individualized
Management

Revised Bethesda Criteria

- 1) Colorectal cancer diagnosed in a patient age ≥ 50
- 2) Synchronous, metachronous colorectal, or other HNPCC associated tumors, regardless of age
- 3) Colorectal cancer with MSI-H, diagnosed age < 60 y
- 4) Colorectal cancer in one or more first relatives, with an HNPCC related tumor
One of the cancers being diagnosed < 50 y
- 5) CRC in 2 or more first- or second degree relatives, with HNPCC related tumors, regardless of age.

- 6) Sigmoid type CRC before age 45 yr
- 7) Adenoma before age 40.

MMR Predictive models → MMR Pro
MMR Predict
PREMM.

Surveillance & Prevention Strategies

- 1) Colon Cancer → Colonoscopy at 20-25 yr, or 5 yr before the youngest case.
Repeat every 1-2 yr.

(APP2) → Daily aspirin 60mg/day x 2 yr found to decrease likelihood of incidental CRC in
MLH1 / MSH2 / MSH6.

- 2) Endometrial → Risk reducing hysterectomy
→ Endometrial biopsy every 1-2 yr starting at 30-35 yr.
TV-USG - not recommended as a screening tool.

- 3) Gastric → Baseline UGI study at 40 yr
Repeat every 3-5 yr.

4) No recommended guidelines for RCC? (d)
Breast
Ovarian (F)

5) Pancreatic Cancer Screening at 50 yA, with
MRI/MRCP and/or EUS.

Management → Total colectomy + TRA is
recommended.

→ Risk of metachronous rectal cancer is
3-12% at 10 yA.

→ Annual surveillance proctoscopy to be done.

→ Primary rectal cancers in Lynch syndrome
occur in 20-30% patients. Surgical options
include LAR or APR.

Various of Lynch Syndrome

1) Muir-Torre Syndrome → Skin sebaceous gland
neoplasms
→ Kerato acanthomas

2) Turcot → CRC & brain tumor (glioblastoma)

3) Constitutional Mismatch Repair Deficiency → Biallelic
inheritance of MMR genetic variants.

→ Develop CRC < 20yr age, café au lait spots, hematologic malignancies, brain tumor.

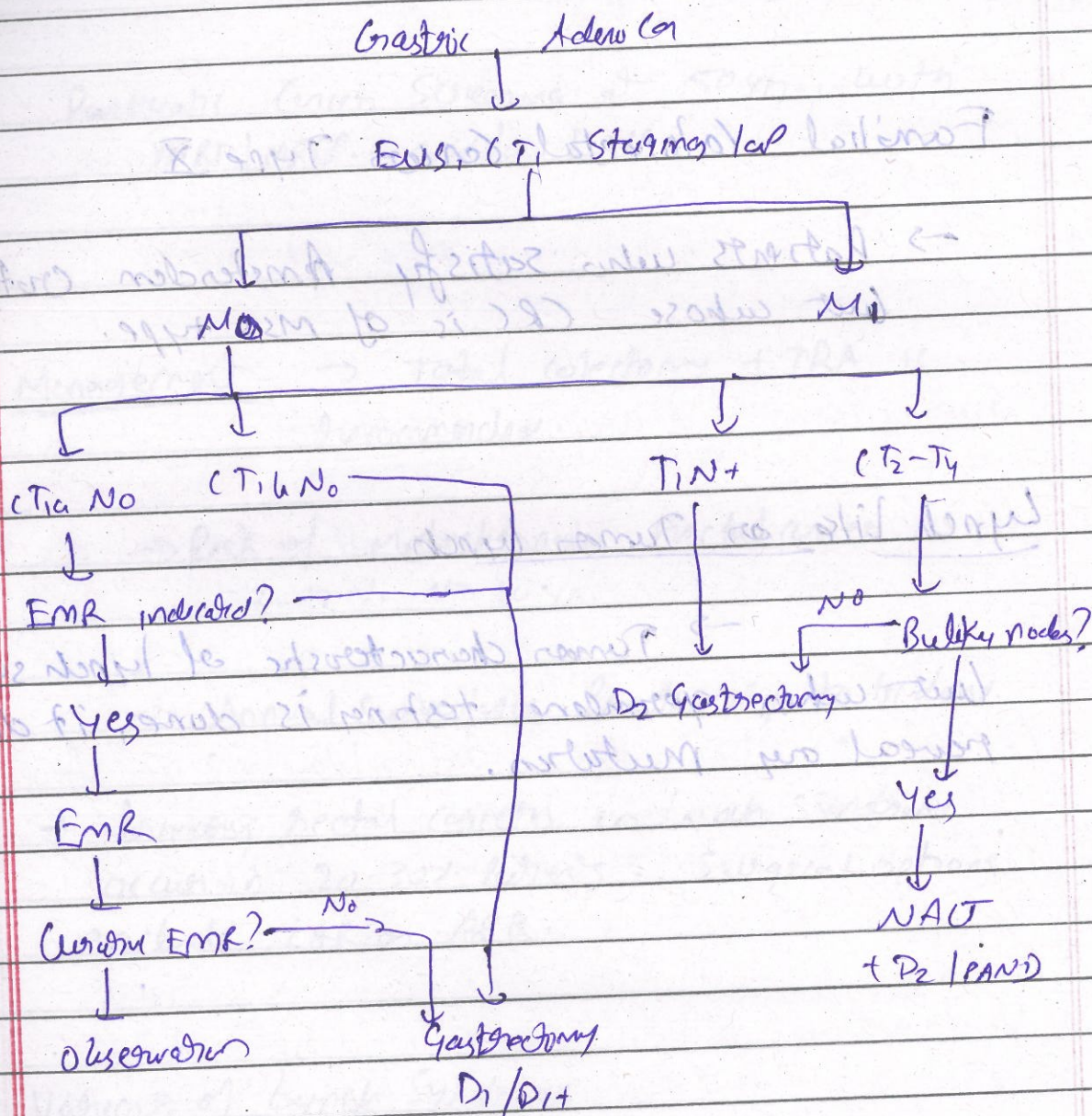
Familial Colorectal Cancer Type X

→ Patients who satisfy Amsterdam criteria but whose CRC is of MSS type.

Lynch like or Tumor Lynch

→ Tumor characteristic of Lynch syndrome but when germline testing is done, it doesn't reveal any mutation.

Gastric Adenocarcinoma - Japanese Guidelines



Types of gastrectomy

- 1) Total
- 2) Distal $\rightarrow$ Stomach resection including pylorus.
less than $\frac{2}{3}$ stomach resected
- 3) Pylorus preserving gastrectomy
- 4) Proximal gastrectomy - Cardia & Oesoph
- 5) Segmental gastrectomy
- 6) Local resection.

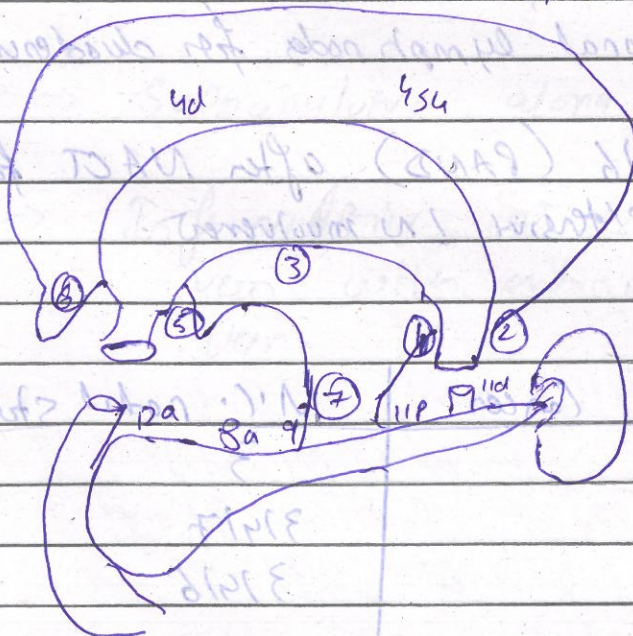
Lymph nodes

Total gastrectomy $\rightarrow$

$D_1 \rightarrow 1-7$

$D_{1+} \rightarrow D_1 + 8a, 9, 11p$

$D_2 \rightarrow D_1 + 8a, 9, 11p, 11d, 12a$



Distal $\rightarrow D_1 - 1, 3, 4sa, 4d, 5, 6, 7$

$D_{1+} \rightarrow D_1 + 8a, 9$

$D_2 \rightarrow D_1 + 8a, 9, 11p, 12a$

Proximal

$D_1 \rightarrow 1, 2, 3a, 4sa, 4sd, 7$

$D_{1+} \rightarrow 8a, 9, 11p$

When should D_{1+} dissection be done?

- $\rightarrow$ Dissection of No. 10 (splenic hilum) without splenectomy for cancer of the upper stomach invading greater curvature
- $\rightarrow$ Dissection of 14v for cancer of distal stomach extends to level 6
- $\rightarrow$ Dissection of no. 13 for cancer invading duodenum
No. 13 are regional lymph nodes for duodenum.
- $\rightarrow$ Dissection of no. 16 (PAND) after NACT for cancer with extensive LN involvement.

Location of Cancer	M.C. nodal station
Upper $\frac{1}{3}$	3
Middle $\frac{1}{3}$	3/4/7
Lower $\frac{1}{3}$	3/4/6

Lymph nodes in (a) stomach

Perigastric LN

1 → Rt Paracardial - Along first anastomosis of ascending L/A LGA

2 → left Paracardial → Along Cardiac esophageal L/A left inferior phrenic vessel.

3 → lesser curvature → Along descending L/A LGA

4 → Greater curvature → They are divided into two groups separated by Von Gaster Point where Rt & left gastroepiploic arteries meet

4s → left group

4d → Right group. → Along Rt gastroepiploic.

4s → 4sa → Proximal part along short gastric

4sda → Distal part along left gastroepiploic

5 → Suprapyloric, along Rt gastric artery

6 → Infrapyloric, at confluence of Rt gastroepiploic ven with ant. inferior pancreaticoduodenal Ven.

Regional / Second tier LNs.

7 → left gastric, betⁿ its origin & its ascending curves

8 → Common hepatic

8a → Anterior

8p → Posterior

9 → Celiac trunk nodes

11 → Splenic artery

11p → nodes about halfway betⁿ origin & pancreatic tail end

11d → From halfway till end of pancreatic tail

Third tier nodes

10 → Splenic hilum

12 → Hepatoduodenal ligament

12a → left hepatoduodenal ligament along proper hepatic artery

12u & 12p → posterior hepatoduodenal ligament, along bile duct & portal vein, betⁿ confluence of pt & left bile ducts & superior border of pancreas

13 → Retroperitoneal nodes

14 → Superior mesenteric

14v → SMV

14a → SMV

15 → Middle colic

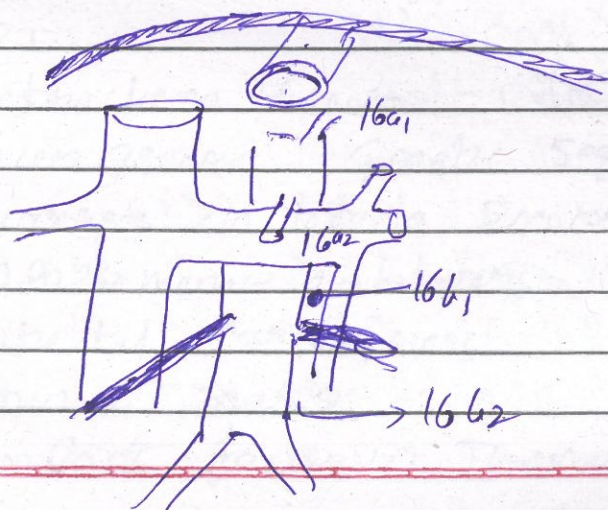
16 → Para-aortic.

16a1 → Around diaphragmatic aortic hiatus, from the inferior hedge of the hiatus to upper border of renal artery.

16a2 → Anterior surface of aorta, from renal artery to lower border of left renal vein.

16b1 → From lower border of left renal vein to upper border of origin of IMA.

16b2 → betⁿ upper border of origin of IMA & aortic bifurcation.



17 → Nodes along anterior surface of pancreatic head

18 → Along inferior border of pancreatic body

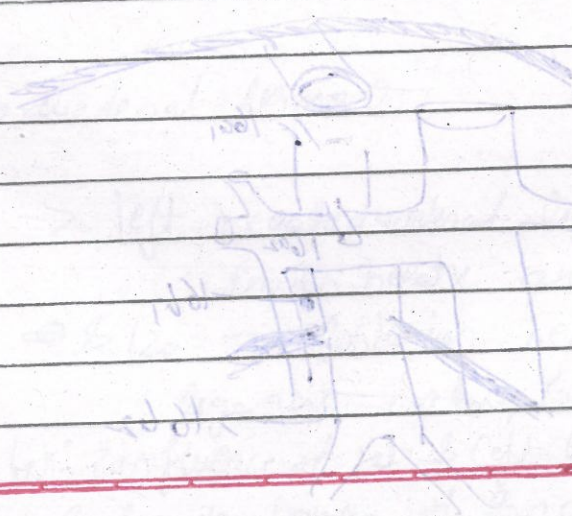
19 → Infradiaphragmatic

20 → Pariesophageal

110, 111, 112 → Lower thoracic (110)

In supradiaphragmatic space, separate from esophagus (111)

Post. mediastinum (112)



Paper Analysis [2014-2020]

General Onc

- 1) Role of HBV virus in Cervical cancer & HBV Vax
— Devita, Video
- 2) Lead time bias
- 3) Phase IV clinical trials
- 4) Dose density & Dose intensity (Chemo)
- 5) Principles of concurrent CT-Ra (Chemo)
- 6) Hallmarks of cancer (Molecular)
- 7) Oncogenic virus
- 8) Recent advances in field of Radiation Onc
- 9) Type of Clinical trials, Phase of Trials
- 10) RECIST
- 11) Prophylactic Cancer Surgery
- 12) Surgical Safety Checklist
- 13) Genetic Counselling
- 14) Isolated limb perfusion
- 15) HPPC
- 16) ILG in Cancer Surgery
- 17) IORT
- 18) Electorchemo therapy (Chemo)
- 19) Cancer genome, Genetic Sequencing
- 20) Carcinogens in Tobacco Smoke
- 21) Topoisomerase inhibitors (Chemo)
- 22) Colorectal Carcinogenesis
- 23) Survival analysis
- 24) Impact factor in Journals

- 25) mTOR inhibitors, ALK inhibitor (Chemo)
- 26) SVC syndrome
- 27) Quality of life
- 28) Trastuzumab (Chemo)
- 29) Immunotherapy in Cancer (Chemo) ||
- 30) Artificial intelligence — ?
- 31) Cell cycle (Molecular)
- 32) Role of inflammation in cancer ||
- 33) Radiation biology (RT)
- 34) Alkylating agent (Chemo)
- 35) ~~From~~ Tobacco in Cancer
- 36) Microsatellite instability
- 37) Cancer Pain [part II]
- 38) Lung Cancer Screening (also in 2021)
- 39) Radio Surgery (RT)
- 40) Intra cavity chemo
- 41) Autologous stem cell transplant
- 42) Female Germ cell cryopreservation
- 43) New taxonomy of tumors — notes
- 44) Role of Radiation therapy
- 45) meta-analysis
- 46) Kinase inhibitors
- 47) Cancer Stem cells
- 48) Fast neutron therapy
- 49) Trans Oral Robotic Surgery
- 50) Aromatase Inhibitors (Chemo)
- 51) ~~Leptin~~ PFT ||
- 52) Lap & Robotic Surgery
- 53) ~~Obesity~~ obesity & Cancer

- 54) Molecular epidemiology
- 55) Cell cycle
- 56) Cancer Screening
- 57) Lapatinib, Imatinib (Chemo)
- 58) Capecitabine
- 59) Nicotine replacement therapy
- 60) Clinical trial
- 61) Modular Prostheses (ortho)

HPB [2012-2020]

- 1) Borderline resectable Pancreas 11
- 2) Surgical anatomy of liver & Hepatectomies → Fischer
- 3) Etiological factors for cholangiocarcinoma
- 4) /a GIB 11
- 5) Regional therapies of unresectable liver mets → Blum
- 6) RFA → Blum
- 7) Mx of hepatic mets from CRC → Shaky
- 8) Non surgical Mx of HCC → Blum
- 9) Adjuvant Rx in pancreatic cancer → Notes
- 10) Non function PNET → Notes.

Breast

- ✓ 1) Gene expression assays in Ca Breast - NCN
— Oncoplastic book
- 27 LIPAR flap
- ✓ 5) Screening methods & guidelines II — NCN
- ✓ 6) Mx of Screen detected non palpable lesions
- ✓ 5) SLNB & tricals — Devita / Fischer
- ✓ 6) Mx of LABC — Devita
- ✓ 7) Phylloids — Notes + Kuehn
- 8) AJCC Classification & how survival alters i stage
- 9) Adjuvant hormonal therapy II — Devita
- ✓ 10) BCT — indication, Contra indication, risk factor for LR
- 11) Oncoplastic Breast Surgery
- ✓ 12) Molecular Classification of Ca Breast — Devita
- ✓ 13) Mx of axilla in Ca Breast
- 14) Screening Mamma
- ✓ 15) Ductal Carcinoma in Ca Breast

JP

Gene Expression assays

1) Oncotype DX is node negative, HR+ve, Her2-ve

" 21 gene recurrence score is useful in predicting locoregional & distant recurrence

(8-1) Predicting distant recurrence

Trials $\rightarrow$ Trans ATAC study & NSABP B20

The assay has also been validated to predict benefit from adding adjuvant chemo to adjuvant hormonal therapy for HR+ve, Her2-ve, node-ve.

Among pt $\bar{c}$ T1u1c & T2 No H+ve Her2-ve,

RS $\rightarrow$ 0-10, there is no benefit of chemo & hormonal R can be given.

For RS ≥ 31 , there is high risk of

recurrence & chemo should be given.

For RS 11-25, the ~~Railor~~ TAILORx trial

of post menopausal women (n=6711) showed similar DFS at 9yr in those who received chemo flg HT & those who received HT alone.

In a subset analysis, women ≤ 50 yrs age with RS 16-25 had lower recurrence & chemo.

Chemo offered to those with RS 16-25

2) Oncotype DX in node positive?

* West German Plan B study, Node +ve, HR +ve and $RS \leq 11$ were found to have 57% DFS 94.4% with HT alone.

So, in pt with limited nodal positivity (1-3) & a low RS, the benefit of chemo is very small.

Ongoing trial $\rightarrow$ SWOG Rx Ponder for 1-3 positive nodes, HR +ve Her2 -ve with $RS \leq 25$, randomized to HT alone, with or without chemo.

3) 70 gene assay (MammaPrint) +

Trial $\rightarrow$ MINDACT trial

Demonstrated that 70 gene assay can identify a subset of patients who have a low likelihood of recurrence despite high risk clinical features (based on tumor size, grade, nodal status).

21% pt had 1-3 +ve LN, 79% No. All underwent risk assessment clinically by Adjuvant! online & by 70 gene assay.

pt with low risk acc to both criteria were not given chemo & those at high risk acc to both were given chemo.

PT $\bar{c}$ discordant results - randomized to Chemo or no chemo group.

5yr survival in PT $\bar{c}$ high clinical / low genomic risk who did NOT get chemo $\rightarrow 94.7\%$.

High clinical, low genomic risk, who received chemo $\rightarrow 95.9\%$. OS
who did not receive chemo $\rightarrow 94.4\%$.

No significant difference seen PT $\bar{c}$ low clinical, high genomic risk who did or did not receive chemo.

$\therefore$ MammaPrint does not provide evidence for making recommendation in low clinical risk

- 4) PAM 50 $\rightarrow$ 50 gene assay risk of recurrence (ROR) score stratifies PT $\bar{c}$ HR+ve disease into high, low risk & medium risk.

In a study from Danish Breast Co-operative group database, PT $\bar{c}$ low ROR had distant recurrence risk of 5%. & high ROR had a risk of 17.8%.

In PT $\bar{c}$ 1-3 positive nodes, HR+ve, Her2-ve, low ROR score, distant recurrence risk was $< 3.5\%$ at 10yr $\bar{c}$ HT done.

- 5) ^{Helps identify} 12 gene assay $\rightarrow$ Subgroup of PT $\pm$ ER+ve, Her2+ve tumours $\rightarrow$ very low risk of recurrence without adjuvant chemo

~~Based on~~ Trials $\rightarrow$ ABCSG 6
ABCSG 8.

In these studies, the PT $\pm$ low ROR had a risk of distant mets of 2% in 10y

The prognostic value of this risk score is independent of clinicopathological factors.

- 6) Breast Cancer Index $\rightarrow$ It is a combination of two profiles - HoxB13 to I217BR (H:I)
- Molecular Grade Index

Compared with other factors, the H:I ratio is found to be prognostic in the setting of tamoxifen monotherapy.

In a secondary analysis of ATAC trial, BCI was prognostic in No patients for both early & late recurrence.

Breast Cancer Screening

* Performed in pt without any signs or symptoms of breast cancer.

* Components of a screening programme depend on

- Age
- Medical history
- Family history

* Clinical breast exam $\rightarrow$ Sensitivity 54%
Specificity 94%.

Clinical encounter in asymptomatic (non palpable)

Average risk

Increased risk

Age 25-40

Age > 40

Clinical exam
every 1-3 yrs

Annual breast exam
Annual mammo

ACS Breast Cancer Screening Guidelines

* Women should undergo regular screening mammo, starting at age 55 yr.

45-54 yr, should be screened annually

> 55 yr, should have biennial screening

* Can begin screening betⁿ 40-49 yr if they wish.

* Should continue screening mammo as long as overall health is good & life expectancy is ≥ 10 yr.

Increased risk

- 1) - Life time risk $> 20\%$. as defined by models dependent on family history (Claw, BRCAPro, Tyrer-Kuzick)
- 2) - Thoracic RT betⁿ 10-30 yrs.
- 3) - 5yr risk of cancer $\geq 1.7\%$ in pt ≥ 35 yrs (Gail model)
- 4) - LCIS/AUT or (ADH $\pm 20\%$ risk)
- 5) - Known genetic predisposition.
- 6) - Given h/o breast cancer.

- (1) - CBE every 6-12 months, to begin when identified as being at risk, but not before 21 yrs
- Annual Screening Mamm
- to begin 10 yrs before youngest age of onset in family or age 40 yrs, whichever is first
- Annual breast MPT
- Risk reduction strategies

(2) $\rightarrow$ Age ≥ 25 yrs - Annual CBE

$\rightarrow$ start 8 yrs after RT

$\rightarrow$ Age > 25 yrs - CBE 6-12 monthly, 8 yrs after RT

- Annual Screening mamm 8 yrs after

Annual MPT, 8 yrs after

(3) - CBE every 6-12 months, to begin when identified as high risk

- Annual memo

- Risk reduction strategies

(4) Same as above.

Breast imaging

1) Mammogram - BIRADS score

- Technical details

- Effect of dense breast

2) Screening USG - Useful in dense breasts

- Sensitivity of mammo alone in dense breast is 50%.

Sensitivity of mammo + USG is 77%.

- Routine use of screening USG in women

at average risk is not recommended by NCCN.

3) Screening MRI - Sensitivity higher than mammo but lower specificity, so higher false +ve.

Recommeneded for high risk.

Guideline from American Cancer Society } → mammography
USP TF guidelines after 40 yrs

UK AGE trial - non significant ↓ mortality
at 10 & 17 yrs follow up

Patients who are symptomatic during clinical encounter.

(1) Palpable → Age ≥ 30 yrs → Mammography

USG

1) If mammography BIRADS 1-3 - Bx if suspicious
no mass on USG

- If low suspicion, CBE
every 6-12 months.

2) Mammography BIRADS 1-3

mass / complex cyst on USG

- If BIRADS 3, then observe if low
clinical suspicion

- Biopsy if suspicious

- If complex or cystic mass, & BIRADS 4-5,
Biopsy

- If complicated cyst, go for screening or
aspiration.

If mass persists on aspiration, go for biopsy.

Cytology $\swarrow$ negative $\rightarrow$ Back to routine Screening
 $\searrow$ Positive $\rightarrow$ Surgical Hx

Age < 30 yr $\rightarrow$ USS least Preferred

$\rightarrow$ If low suspicion, then observe for 1-2 cycles.

② Nipple discharge, no palpable mass

1) Non spontaneous or $\rightarrow$ Age < 40 - observe
 mult duct $\rightarrow$ > 40 - Mamm.

2) Persistent, Single duct, $\rightarrow$ $\rightarrow$ Clear or bloody

Age < 30 yr - USS + Mamm

Age > 30 - Mamm + USS

BIRADS 1-3

BIRADS 4-5

MRI

Ductogram

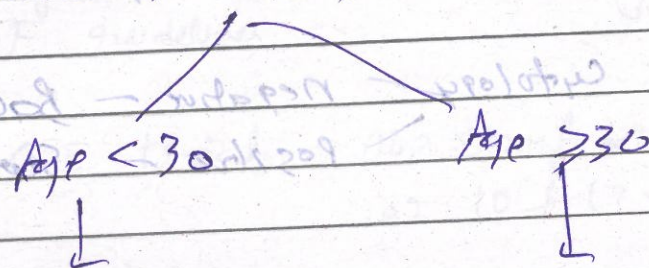
Biopsy

BIRADS 1-3

BIRADS 4-5

Duct Excision

(3) Asymmetrical thickening or nodularity



USG ± Mamm

Mammo + USG

BIRADS 1-2 — Observe

BIRADS 3 — Biopsy or Observe

BIRADS 4, 5 — Biopsy

(4) Skin changes — peau d'orange

- Erythema
- Nipple excoriation
- Edema

Prob Sign thickening

- Suspicion of Paget

Mammo

BIRADS 1-3

BIRADS 4-5

consider MRI

Punch biopsy

Skin biopsy

core biopsy

(5) Breast Pain — Cyclical & acyclical mastalgia

(6) Axillary masses — Bilateral *
Unilateral

Bilateral — Evaluate for systemic disease

— If systemic disease, then mammo + USG

Unilateral — Mammo + USG

In both, if suspicious, then do biopsy.

If malignancy — Breast origin — Mx as per Breast
non Breast — Mx as per Primary

Follow up for core needle biopsy

1) Benign & image concordant — follow up

2) Indeterminate / image discordant / ADH / pleomorphic LCIS /
ALH → Excision.

3) Malignant — As per Ca Breast

Non Surgical ~~Regional~~ Therapies for HCC (2)

(1) RFA - Radiofrequency ablation (3)

- * Destroys tissue by generating enough heat to denature cell protein & cause cell death.
- * Electric generator propagates a rapidly alternating radiofrequency current ranging from 300-500 kHz.
- * Resistive heating is generated by intense friction.
- * If tissue impedance is low, an expanding spherical zone of ablated tissue is created.
- * When temp. reaches $45-100^{\circ}\text{C}$, irreversible coagulative necrosis destroys the tumor, but not tissue architecture.

Scheme of RFA - High freq. Alternating current
 ↓
 Ionic vibration & heat generation
 ↓
 45°C - Protein denaturation
 70°C - Thermal coagulation
 100°C - Tissue desiccation

Procedure

* Pre Procedural metastatic work up

- Can be done by laparoscopy, laparoscopy or percutaneous.

* Each ablation should create a zone of 5mm margin of treated normal parenchyma to ensure tumor destruction.

- Ablation of large tumors should begin at most posterior aspect.

* Between ablations, the probe should wait centrifurcally in 2cm increments

* Percutaneous approach may not be appropriate for larger tumors proximal to vessels > 4mm (heat sink) or near major bile ducts (complications)

* Percutaneous RFA is more cost effective for very early HCC (< 2cm) and 2-3 nodules (< 3cm)

* During open RFA, Pringle maneuver can be done to reduce heat sink effect.

* RFA can be combined with formal surgical resection in unilateral liver mets.

RFA for CRC mets - Multiple studies & RCT shows that resection is superior to RFA for DFS & OS, but many patients are poor candidates of ~~RR~~ Surgery.

RFA is a good alternative.

- Chen et al showed that RFA was as effective as surgical resection in treatment of solitary HCC $\leq 5\text{cm}$ in terms of OS & DFS.

- Huang et al showed that Surgery $>$ RFA in terms of local recurrence rate. But OS was not significantly different.

- Feng & Liang showed similar efficacy of RFA & surgery (HCC $\leq 4\text{cm}$).

- RFA can produce equivalent results with lower morbidity in cirrhotics.

- In recurrent HCC, RFA is an effective therapeutic modality, esp in pt with impaired hepatic function.

- RFA can be used as a bridge to transplantation in recurrent HCC, however the impact on OS is less clear.

* Response rates vary from 48-98% across studies.

Success rate was lower for infiltrating versus non infiltrating HCC.
No significant difference with approach to RFA.

* Elective Cholecystectomy is recommended to prevent heat sink.

Complications

- Biloma
- Biliary fistula
- Hepatic insufficiency
- Hepatic abscess
- Pain
- Hemorrhage
- Hydro pneumothorax

* One series compared patients who received RFA vs Chemo therapy after laparotomy revealed unresectable disease. Non significant trend towards improved OS in ~~resection~~ RFA.

* Another trial had non resectable CRC mets on Chemo (FOLFOX + Bevacizumab) vs RFA + Chemo. Median OS higher in combination.

② Microwave ablation

- Achieves tissue destruction through active & passive heating
- Heating process of microwave ablation requires the presence of water to function
- MW antennae have a frequency to length relationship
- It has lower propensity for heat sink effect

Advantages over RFA - Lesser heat sink

In RFA, if the target temperature of over 100°C is reached too quickly then the intracellular content vaporizes and carbonizes, causing an insulative effect.

MWA does not have such adverse effects because energy is broadcast uniformly.

• Approach can be open, percutaneous or lap.

• If MWA is the sole modality of treatment, the lap is preferred.

* lesions located anteriorly can be treated percutaneously

(3) Irreversible ~~RF~~ electroporation

- non thermal injury, relatively technology that uses multiple short pulses (70-90 μ sec) at high voltage (2750-3000 V)

- Induces permanent electroporation of tissue

- Since its non thermal based, it can be used near major vascular pedicle.

- But it needs Gd.

Tumour location

Non perivascular

Perivascular

Proximity to

vital structures

<3cm

3-5cm

RFA

MWA

IRE/PEF

(4) Cryoablation - Cryotherapy destroys tissues by
by extreme cooling.

- Three overlapping zones of injury are created
in the liver.

Rapid tissue freezing occurs closest to
the probe.

Rate of freezing decreases in proportion
to the distance from the probe, creating zones
of intermediate & slow cooling.

Rapid cooling rate $\rightarrow -50^{\circ}\text{C/min}$

Intermediate $\rightarrow 1-10^{\circ}\text{C/min}$

Slow $\rightarrow <1^{\circ}\text{C/min}$

Further damage to tissue occurs in thawing process
and varies according to rate of thaw.

In slowly thawed tissue, extracellular ice melts to
water, flows down osmotic gradient & causes
cell lysis to occur.

Complications - 1) Cracking the ice ball $\rightarrow$ Bleeding
can occur after a sizeable freeze when a fair
extent of capsule is frozen.

2) Myogalactorrhoea & AKI

3) Generalized hypothermia

4) Hemorrhage

5) Bile fistula & collection

6) Cryoshock - complex multisystem organ failure, renal failure, DIC, and is potentially lethal. Responsible for 18% of deaths after cryo.

Likely related to systemic release of TNF, IL1, IL2, IL6.

7) Mortality ~ 1.5%.

* 54% OS of HCC treated w Cryo is 30%.

★ Portal Ven thrombosis is contraindication for TACE & HAE.

Page No.:

Date: | |

Regional Therapies for liver tumors

① Hepatic Artery Infusion of Chemotherapy

Rationale — * Liver metastases are perfused almost exclusively by hepatic artery.

So, injection of chemo drug inside HA leads to 15x more concentration of drug in tumor cells.

- Use of drugs that are largely extracted by the liver during first pass metabolism results in high local concentration with minimal systemic toxicity.

- Drugs with steep dose response are more useful when given by intrahepatic route.

- Drugs with a high total body clearance are more useful for hepatic infusion.

- Concept of stepwise pattern of metastatic progression states that hematogenous spread first occurs via portal vein to liver, then liver to lungs. Aggressive treatment of liver mets can check this spread.

For delivery of the drug, hepatic artery pump needs to be placed.

VS HAI = PUDR → T survival & response rate is HAI

* GDA is the preferred conduit for drug delivery and is most reliable

* Blechur cholecystectomy should be done prior, to prevent cholecystitis

Steps - Hepatic artery & its branches are circumferentially dissected.

- GDA runs parallel to & lies to the left of CBD.
It is advisable to start dissecting CHA, to avoid injuring bile duct

- Right gastric artery is ligated & divided.

- It is imp to mobilize full length of extrapancreatic GDA. Suprapyloric side branches of GDA are to be ligated.

- Should be ensured that no vessel to Pancreas, Stomach or duodenum remains.

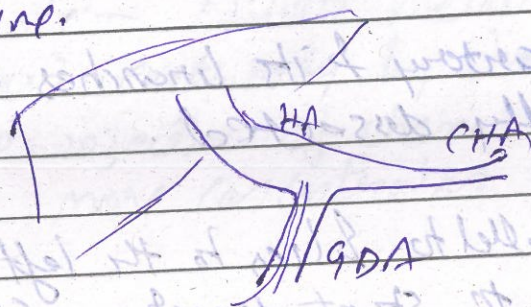
- GDA should be temporarily occluded to with Palpation of CHA to rule out critical retrograde flow to the liver through GDA.

- Pump Pocket should be created in the lower abdomen so that the pump lies below the waist

- Transverse arteriotomy is made in distal GDA and catheter is inserted up to, but not beyond the Junction of GDA & HA

- Secure the catheter & test liver perfusion by infusing 2-3 ml of half strength fluorescein dye.

- After perfusion test it is flushed & heparinized saline.



Complications —

1) Extrahepatic Perfusion - Small branches of hepatic artery to stomach, duodenum or pancreas can be missed on pre op angio.

Perfusion of small bowel with FUDR will lead to severe GI pain & ulceration.

2) Incomplete hepatic perfusion

3) Gastro duodenal ulcers - Subtle extrahepatic perfusion via small branch to lesser curve.

4) Arterial or catheter thrombosis

5) Infection

6) Hemorrhage

7) Biliary Sclerosis.

(2) Transarterial chemoembolization →

* Lipiodol solution of doxorubicin is prepared and injected into hepatic artery

* Lipiodol is preferentially accumulated in tumor due to hemodynamic diff. b/w tumor & normal liver.

* When tumoral sinusoidal spaces are filled, any additional lipiodol may flow back into the portal vein.

* Once inside tumor cells, it is retained for a long time due to absence of Kupffer cells.

* Allows slow release of chemo drug.

* Ischemic damage by embolization potentiates absorption of chemo.

* Asute is a ~~poor~~ relative contraindication.
Most common indication - Unresectable HCC.

Typically recommended in Child Pugh A/B & ECOG 0-1.

- Spontaneous rupture of HCC is an indication for emergency TACE.

- Neoadjuvant therapy or bridge awaiting Transplant

* micro catheter is advanced via femoral artery to tumor feeding vessels (identified beforehand by arteriography).

RCT for TACE

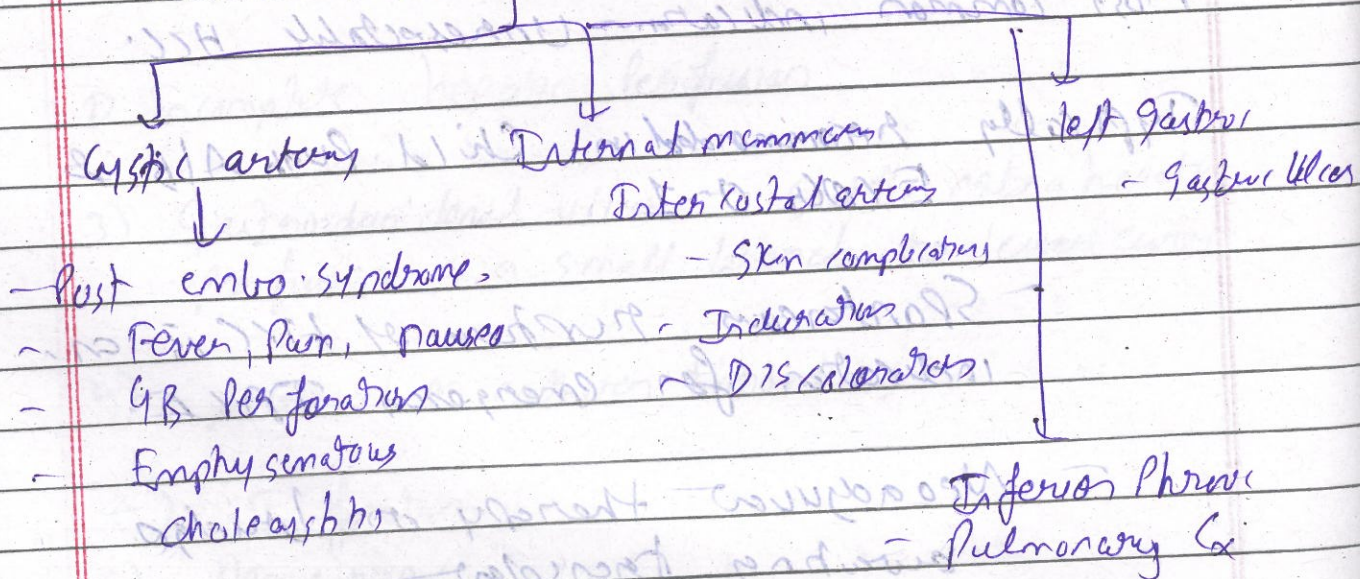
- | | |
|------------------|------------------------------|
| 1) Barcelona | } TACE → conservative
T/E |
| 2) Hong Kong | |
| 3) Lo et al | 5) Becker et al |
| 4) Llovera et al | |
- Established for intermediate stage tumors in BCLC

Complication — Post embolization Syndrome

— Liver abscess

— Liver failure

— Extrahepatic non targeted embolization



(3) other techniques of embolotherapy

1) Bland embolization - microspheres using PVA granules

2) TACE - drug eluting beads (DEBs)

i) PVA based microspheres

ii) supersolvent based microspheres

PRECISION - v trial failed to demonstrate diff. betⁿ DEB-TACE & conventional TACE

3) DEBIRI - Drug Eluting Beads - Irinotecan for colorectal liver mets

(4) Radioembolization - ^{90}Y is the radioactive element most commonly used in TARE.

- Pure β emitter - $t_{1/2}$ of 64.2 hr.

- Patients with ECOG 0-1 can be taken

- Pre treatment diagnostic mesenteric angiography, Patency of portal vein & Presence of arterio-portal shunting is noted.

Coil embolization of non target vessels may be needed. (Inf. esophageal, accessory left gastric, Supraduodenal, Retroduodenal).

- ^{99m}Tc -MAA scan is used to assess splenic & pulmonary shunting.

- Lung Shunt fraction is used to calculate dose delivered to lungs.

Available devices - TheraSphere

- SIR spheres

Uses - Bridge to transplant

- Patients beyond transplant criteria, for downstaging

Complication

1) Post-radioembolization Syndrome
- Fatigue, nausea, vomiting, anorexia, fever, cachexia.

2) Radiation induced liver dysfunction - typically occurs after 4-8 weeks

3) Biliary injury

4) Radiation pneumonitis

5) GI ulcerations

Phase II trial of TARE vs TACE



↑ PFS, ↑ time to progression

↓ diarrhea, hypoalbuminemia

OS not changed.

IASO Webinar - Larynx

Causes of hoarseness except larynx

- Thyroid malignancy
- Locally advanced Ca lung
- Idiopathic RLN Palsy.

What cannot be seen on IDL?

- Apex of PPS
- Post cricoid

Higher risk of thyroid cartilage injury, lesser exposure
Poorer voice quality Post op, for AC lesions after
laser excision.

When to go for surgery in larynx?

Ideal pt for TLM - T₁, midglottic cancers
- Adequate mouth opening

Recurrence after concurrent CRT?

- Better to go for Salvage TL
- Higher risk of fistula formation.

Additional Precautions for Salvage surgery

- Tension free closure
- Patch pharyngoplasty

Flaps - PMMC

- Supraclavicular flap

Primary TEP on Secondary TEP?

* Primary TEP to be inserted if surgery is done upfront.

* If it is irradiated beforehand, Secondary TEP

Diff betⁿ TORS & TLM?

* TORS used for supraglottic cancer

* TORS has more degrees of freedom & 3D view.

* CO₂ laser used in TLM.

* ~~works by~~ Lasers have higher precision
Lasers can be coupled with operating microscope
lessen post op inflammation.

Total laryngectomy in recurrence

> Narrow field laryngectomy (not addressing neck)

but before planning, assess for neck node by USG.

Do TFTs ~~Post~~ pre op, and 6 monthly post op

PET CT in larynx?

Post op exam if we see edema?

If edema is persistent, then we can go for PET CT or MRI.

How to diff. Recⁿ disease & Post RT changes in PET?

Biopsy = Deep core biopsy.

Transoral Laser Microsurgery

Mx options for early laryngeal cancer

1) Open Partial laryngectomy

2) RT

3) TLM

Advantage of TLM - Single day treatment

- No need for T-tube or Feeding tubes.

CO₂ lasers Used.

Chemoradiation for oropharyngeal preservation in T3 lesions.

- Veterans Affairs trial
- RTOG 91-11

IMRT → In AC lesions, the visibility is impaired, it is often understaged.

With conventional RT, the dose delivery to AC was insufficient. So, earlier, AC lesions would be taken for surgery.

With IMRT, the dose distribution is adequate to AC & they can be treated.

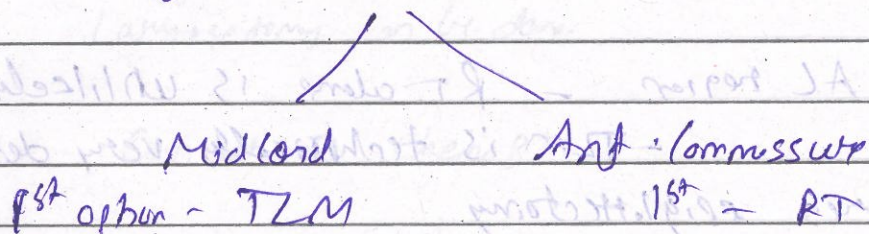
Treatment options in laryngeal cancer

- Benign lesions - * No role of RT in larynx.
- Cord stripping; excise the patch if localized
 - Can be done with laser or knife.
 - lift mucosa using saline injection & use laser to remove it
 - Counsel pt to quit smoking.

Cord Stripping Vs RT - Cosury et al Study

Summary - Surgical excision is best option

- No gold standard tool to assess
- Steel or laser > monopolar cautery
- RT should be offered in those circumstances for patients where there is a very high risk of conversion to malignancy & surgical resection is not possible due to patient or tumor factors

2) T₁ glottic cancer

2nd - RT 2nd - TLM

3rd - Open Partial laryngectomy 3rd - OPL

Recurrence after TLM can be

Salvaged by RT

Recurrence after RT generally

Needs TL

OPL in early (a larynx is preserved for cases where surgery is preferred mode, but TLM is not possible, like

1) Vegetative carcinoma

2) Very young pt

3) Previous RT

4) Non squamous pathology

If exposure is not good, then TLM should not be done.

3) T₂ glottic cancers.

Factors in decision making - Bulk of lesion
- location (midcord or AC)
- Impairment of cord mobility

non bulky lesion in mid-cord → RT (better voice)
→ TLM

Bulky, AC region - RT alone is unlikely to work
- TLM is technically very demanding
requires epiglottectomy

- Open partial laryngectomy is a safer option [Supracord laryngectomy + CHEP]
But surgery can be offered only to young fit patients.

- If pt is not fit, Chemo-RT should be given in bulky T₂ disease of AC.

4) TLM for early Supraglottic cancer

TLM can be done, if a neck dissection

Case selection - Marginal Zone Cancer
- Epiglottectomy can be done.

5) T3 laryngeal cancer

* If hemilarynx is fixed, then Supra-glottic laryngectomy cannot be done.

Upper border of cord is lower border of larynx preservation surgery.

* If cord fixed, but arytenoid is mobile, Supra-glottic laryngectomy can be done.

* Concurrent ChemorT

- SCPL + CHER / CTR

* Total laryngectomy.

6) Post RT recurrence & edema - Observe, until there is obstruction to airway.

- Core biopsy can be used instead of punch.

7) T4 larynx - Total laryngectomy + Adj. RT / CTR

Any role of MACT?

* RTUG 91-11 has shown that concurrent CRT is better.

* Can be used for "bridge" - If PT can respond well to chemo, PT can be sent to Chemo RT - If it doesn't respond, PT can be taken for Surgery (SCLL or TL)

TORS

- * Transoral robotic surgery is used to treat oral, throat & skull base cancers using a minimally invasive robotic approach.
- * It allows deeper access & dissection of suspicious lesions & neoplastic growths.
- * Robotic surgery allows the surgeon to operate in tight spaces without a large incision.
- * TORS was approved by the FDA in 2009 for benign & malignant disorders of throat & larynx.

Technical aspects

- * Composed of a surgeon console, a patient cart & robotic arms, robotic instruments and a mobile tower cart equipped with high definition monitor system.
- * Surgeon console allows the surgeon to visualize anatomic structures in three dimensional high definition, with upto 10x zoom.
- * Patient cart, referred to as "robot" consists of articulating robotic arms. One arm is dedicated to holding the camera. These arms can rotate 360° ~~and~~ & have upto seven degrees of freedom.

* These instruments allow more freedom of motion than laparoscopic instruments, scaled reduction of surgeon's hand movements and filtration of hand tremors.

* Mobile tower cart is equipped with image-processing equipment and a wide screen high definition monitor. It also stores additional surgical equipment such as electrosurgical unit generator.

Patient Selection :- TORS is restricted for use in benign & cancerous tumors in otolaryngology procedures T1 & T2 stage & for BOT lesions.

Contraindications - Unresectable / Locally advanced tumors
- Invasion of tumor into mandible
- Advanced BOT lesions requiring >50% tongue resection
- Advanced pharyngeal tumors requiring >50% resection of post. wall.
- Vertebral involvement

Advantages - No disfiguring of lip split incision

- No large external incisions on patient's neck

- No malocclusion or malunion of jaws

- No need for separate procedure done for hardware, plate & screw removal etc. after mandibular split.

- Potential absence of decreased duration of tracheostomy
- Decreased duration of NBI tube
- More rapid Swallowing rehabilitation
- Preservation of lingual artery
- Decreased blood loss
- Lesser pain
- Decreased hospital stay & faster return to daily activities

Disadvantages - High cost of robot, instruments & robot specific supplies

- Surgical procedure is challenging & requires training

- loss of tactile sensation.

- Potential Patient injuries like

→ lip & dental injury

→ Mucosal injury

→ Facial lacerations

→ Mandible fracture

→ Cervical spine injury

→ Ocular injury

* De Almeida et al showed that 2yr locoregional Control rate was 92%, disease specific survival 94.5% & OS was 91%

* Meta-analysis by de Almeida et al OS $\pm$ TORS $\rightarrow$ 82-94%

OS $\pm$ IMRT $\rightarrow$ 84-96%

Long term gastrostomy rates were 157. Morbidity & Mortality

Page No.:

Date: | |

Preparation for TORS

- In addition to the surgeon, a surgical assistant operates at the bedside.
- * The bedside assistant positions the arms on the patient cart, inserts robotic instruments, suctions, cauterizes & monitors movements of the arms.
- * Patient positioning may vary depending on the facility. Low patient is generally supine, both arms secured at the side & to the surgical table.
- * Patient can also be seated.
- * After intubation, OR bed is rotated 180° which allows for the patient cart to be properly positioned with access to the surgical site.
- * Positioning & draping is done. Protective eye goggles can be given to patient to protect eyes.

Applications of TORS - Base of tongue

- Tonsil

- Palate

- Pharyngeal wall

- Retro-molar pad

- Supraglottis

- Glottis

- DFS

- Studies have shown that QOL is adversely affected by RT & IT treated with TORS alone have highest QOL, & those ~~at~~ treated with triple modality have the lowest.
- Sharma et al demonstrated that survival is similar betⁿ TORS & IMRT, but gastrostomy tube rate at 3y vs 11% at 1y.

TASO Stomach

clc → Vomiting and ~~ab~~ its ODP

H/o acid peptic disease?

Prosechite / non Prosechite

Aggravating / relieving factors

CGAAs

Bilious / non bilious

Asso. e nausea?

Genetic Syndromes asso. e it.

CDH1 testing guidelines.

Grading of gastric outlet obstruction.

look for signs of dehydration.

How to look for visible gastric Peristalsis?
Comment on VGP!

What to look for in UGIscopy?

Characteristics of malignant growth on UGIscopy?
↳ Borrmann's classification.

Accuracy of Staging

EUS

CT

PETCT

Role of PETCT?

How to do peritoneal lavage?

* Conversion therapy

Management of positive peritoneal cytology - Controversial

If done via D-lap,
then do staging, given NAC
then re-do peritoneal cytology
(conversion therapy)

If laparotomy done
already, then
Proceed with
surgery if pt is
young & fit.

Post gastrectomy Syndromes.

Grade 1 - 2/7
2 - 13/47
3 - 15/40

N/A.
28.57
27.66
37.5%

- 1) Mean age
- 2) Most common T stage
- 3) T-stage wise correlation with SNB +ve
- 4) Rate of identification $92/94 = 97.87$
- 5) Mean no. of sentinel nodes 13.39
- 6) ~~Positive cases~~ ^{No %} Cases with SNB positive 31.91%
- 7) Correlation of ER/PR +ve with node positive (ER OR PR)
- 8) % of Her2+ve with node positive
- 9) Rate of individual complications
- 10) ~~% of PT + PNE~~
- 11) Mean duration of procedure 71.46 min
- 12) Sensitivity, Specificity, PPV, NPV
- 13) % clinical / Radio node neg were SNB +ve
- 14) % PT +ve h/o lymphoma $17/94 = 18.08\%$
- 15) No. of PT +ve BCS 21/94
No. of PT +ve mastectomy 73/94
- 16) Concordance

Significant

Big topics $\rightarrow$ GI $\leftarrow$ Digestive tract
 $\rightarrow$ Head neck $\leftarrow$ Non digestive tract
 Neck, oral cavity
 Thyroid, larynx, other
 therapy stuff.

$\rightarrow$ Uro
 $\rightarrow$ General 1
 $\rightarrow$ General 2

Small ~~and~~ / medium $\rightarrow$ Breast
 $\rightarrow$ Thorax
 $\rightarrow$ Gynec
 $\rightarrow$ Ortho
 $\rightarrow$ Skin
 $\rightarrow$ Endocrine

Pairs $\rightarrow$ GI 1 (Digestive) + Lung / Thorax
 $\rightarrow$ GI 2 (non digestive) + Breast
 $\rightarrow$ Head & Neck 1 + Gynec
 HN 2 + Ortho
 Uro + Skin + Endocrine.
 General 1 + General 2



6 weeks