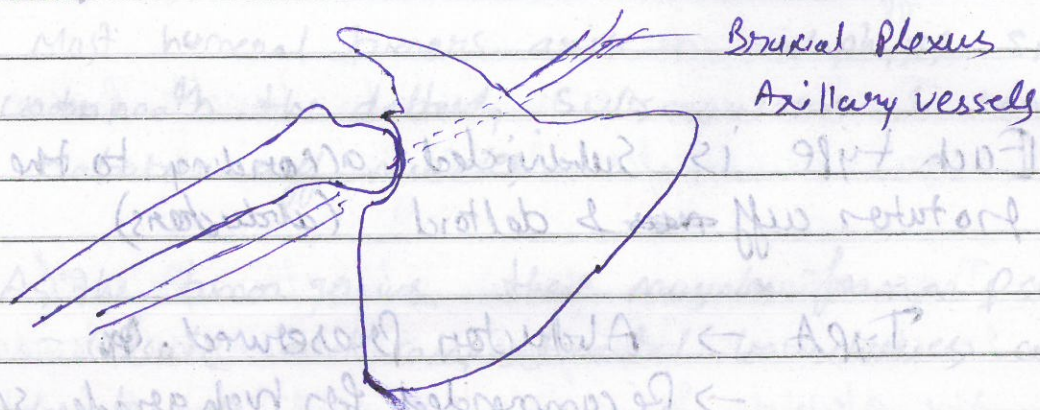
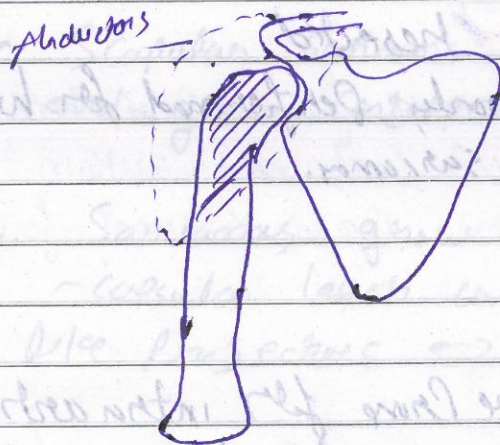


Shoulder Girdle Resections



Maulsner Classification System

1) Intra-articular Proximal humeral resection



Type A - Abductors retained (shown)

Type B - Abductors resected

2) Partial Scapular Resection

3) Intra-articular total Scapulectomy

4) Extra-articular total Scapulectomy and humeral head resection (classic Tikhoff-Linberg resection)

5) Extra-articular humeral & total glenoid-resection

6) Extra-articular humeral & total scapular resection.

Each type is subdivided according to the status of
rotator cuff ~~mus~~ & deltoid (abductors)

Type A → Abductor Preserved.

→ Recommended for high grade spindle cell
bone sarcomas that are intra compartmental
(contained within proximal humerus or
Scapula)

Type B → Abductor Resected

→ Most commonly performed for high grade
Spindle cell sarcomas.

* Shoulder joint is more prone for intra-articular
or peri-capsular involvement by high grade bone
Sarcomas

4 mechanisms of involvement

1) Direct capsule extension

2) Tumor along the long head of biceps

3) Fracture hematoma from
pathological fracture

4) Poorly planned biopsy

- * As a result, pt undergoing intra-articular resections are at a higher risk of recurrence.
- * Most humeral tumors arise in metaphysis, spread underneath the deltoid, subscapularis & remaining rotator cuff muscles.
- * As the tumor grows, these muscles form a pseudo-capsule and compartmental boundaries around the tumor.
- * Major neurovascular bundle is displaced by the tumor, and fascia over subscapularis muscle & axillary sheath protect the neurovascular bundle.
- * Scapular sarcoma arises from scapula neck and grow centripetally into soft tissue.
- * Sarcomas grow centripetally, the pseudo-capsular layer contains microscopic finger like projections $\rightarrow$ satellite nodules.
- * The anatomic boundaries form a compartment around the tumor. A sarcoma will fill the compartment in which it arises, and only rarely will a large sarcoma go beyond the compartmental boundaries.
- * Muscles provide fascial boundaries of the compartment and a "wide resection" of the tumor must remove the tumor with pseudo capsular layer.

- * The functional "compartment" around proximal humerus consists of deltoid, subscapularis, Rotator cuff, LD, brachialis & portion of triceps.
- * The main neurovascular bundle passes anteriorly to subscapularis & LD.
- * These Sarcomas grow along the path of least resistance and therefore, are directed towards the glenoid & scapular neck by rotator cuff & glenohumeral joint capsule.
- * When a large tumor protrudes through the rotator cuff, a wide excision involves the surrounding muscles, axillary nerve, humeral vessels & glenoid.
- * Scapular Sarcomas arise from scapular neck. Axillary nerve is not contained within the compartment and therefore can be spared from resection.

Indication for limb Sparing Surgery

- 1) High grade sarcoma & some low grade bone sarcoma
- 2) STS arising from shoulder girdle
- 3) Isolated mets with bony destruction
- 4) Benign aggressive tumours may need the Ht

Contra indications

Absolute contra indications:-

1) Tumor involvement of neurovascular bundle

2) Patient's inability to tolerate a limb sparing operation.

Relative CI :-

1) Chest wall extension

2) Pathological fracture

3) Lymph node involvement

4) Inappropriately placed biopsy scar that has resulted in a massive hematoma

Vascular involvement - If vessels are involved, then adjacent brachial plexus is also involved.

Then limb salvage is not possible.

Nodes → Bone sarcomas rarely involve adjacent lymph nodes, but axillary nodes should be evaluated & may require biopsy.

If involved, then amputation is always better.

Chest wall involvement → May involve chest wall, ribs, intercostal muscles if large enough.

It is not an absolute contraindication.
A limb sparing procedure with w/o of chest wall can be done.

Clinical evaluation - Imaging - MRI / CT

If there is intractable pain

Motor deficit

Venogram showing

obliterated axillary vein

Reliable in Predicting
Unresectable plexus invasion.

* Axillary vein, artery & lymphatic plexus travel together in a single axillary sheath. Major nerves & cords travel along the periphery of the sheath. So, complete obliteration of vein denotes direct tumor extension in & around the nerves and also indicates Secondary involvement of the Venous wall.

* Tumors that invade or encase the lymphatic plexus obliterate the axillary vein because of the vein's thin walls and low intraluminal pressure.

In these cases arteriography indicates displacement of axillary artery

Prosthetic Reconstruction

- * MRS proximal humeral prosthesis is used, with survival to be 95-100% at 10yr.
- * Soft tissue reconstruction is accomplished by a "static" repair (prosthetic stabilization) & a "dynamic" repair (soft tissue reconstruction).
- * Static methods of stabilization include heavy non-absorbable sutures, Dacron tapes or GORE Tex grafts, depending on the site of tumor resection & prosthesis being used.
- * Dynamic methods of stabilization include multiple muscle rotation flaps & muscle transfers.
- * Soft tissue reconstruction follows skeletal reconstruction & static stabilization.
 Tenodesis of short head of biceps to coracoid or clavicle or Pectoralis major is done.
- * In total Scapula reconstruction, Periscapular muscles are tenodesed to prosthesis using heavy, non-absorbable sutures.

Utilitarian Shoulder girdle incision (Pg 78, Malawen)

MRS. [Name] [Address] [City] [State] [Zip]

"[Name]" [Address] [City] [State] [Zip]

[Name] [Address] [City] [State] [Zip]

[Name] [Address] [City] [State] [Zip]

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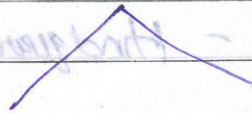
Total Scapulotomy

Type IV - Tikhoff-Linberg Procedure

- * It is an extra-articular en bloc resection of the Scapula, glenohumeral joint, humeral head & distal clavicle.
- * Incision - Utilitarian antero posterior incision
- * large posterior flap is elevated.
- * Rhomboids & trapezius are released from Vertebrae, LD muscle is mobilized but not transected.
- * Deltoid & trapezius, if ~~uninvolved~~ uninvolved, are reflected off the spine & a common to scapula.
 - * Classic Tikhoff-Linberg does not preserve these muscles
- * Osteotomy performed below the humeral head.
- * Extra-articular resection of scapula & glenohumeral joint is performed.
- * Scapular Prosthesis is fenestrated to ~~allow~~ permit ~~the~~ the muscles to ~~attach~~ tenodesis to themselves
- * Scapular Prosthesis is first sutured to rhomboid & a dacron tape, then LD is rotated over the body of prosthesis & sutured along vertebral bodies.

Hemipelvectomy (lecture)

M.C. tumors that metastasize to bone - Breast, thyroid, prostate, RCC.



External Internal hemipelvectomy
(limb preserving)

Indications - malignant bone tumors

- Benign bone tumors (GCT/ABC/osteosarcoma)
- Metastatic bone lesions
- Soft tissue sarcoma (with intralesional extension)

Metastatic lesion - usually done in RCC, or if it is # or painful.

Contraindication of limb salvage

- Resection not possible
- Resection too morbid

↳ Disease crossing midline
↳ Infiltration of sciatic notch
↳ Involvement of major blood vessels (iliac vessels) or sciatic (G)

Work up -> Xray - Defines bony architecture

-> MRI ± contrast - TO look for marrow involvement, involvement of muscles, neurovascular bundle, planes.

→ CT Scan - TO delineate bony architecture

→ CT angiogram - Evaluation of vessels going thru the tumor
 → PET CT - TO guide the site of biopsy in a large mass
 (take Bx from hottest part)

External hemipelvectomy - Hindquarter disarticulation

Two approaches → Anterior flap - when tumor is on gluteal aspect
 Posterior flap - Tumor is on femur

Internal hemi - Type 1 - Ilium bone

Type 2 - Acetabulum + proximal femur

Type 3 (extra-articular resection)

Type 3 - Ischium & Pubis

Type 4 - Resection of Sacrum.

Points to note for Planning Surgery

1) Iliac vessels - common / ext / internal

2) Ureter - Get it stented

3) Sciatic nerve - Preserve nerve. If involved, do external.

4) Visceral Organs - Bowel, bladder

5) Which bones involved?

Type 1 - Iliac bone resection

Utilitarian incision

Type 2 - Iliac bone resection

Reconstruction by Prolene mesh. Tie with head & remaining acetabulum.

Other reconstruction modalities

- Iliac femoral arthrodesis
- FCR & reimplantation of stabilized bone
- Prosthesis
 - ↳ Saddle Prosthesis
 - ↳ Customized Prosthesis

Type 3 - Iliac bone resection - No recon required.

Tobacco & Cancer

Classification of smokers

1) Current Smokers - Adult who has smoked two cigarette in his/her lifetime and who currently smokes

Every day Smoker Some day Smoker



Smokes at least 1 cig/day

2) Former Smoker → smoked at least two cigarettes but had quit smoking

3) Never Smoker → smoked < 100, and quit smoking

4) Quit attempt → Stopped for ≥ 1 day.

* First evidences of link → Doll & Hill
→ Ulynden & Graham

* Tha et al → HR for lung cancer in smokers

women	men
17.8	14.6

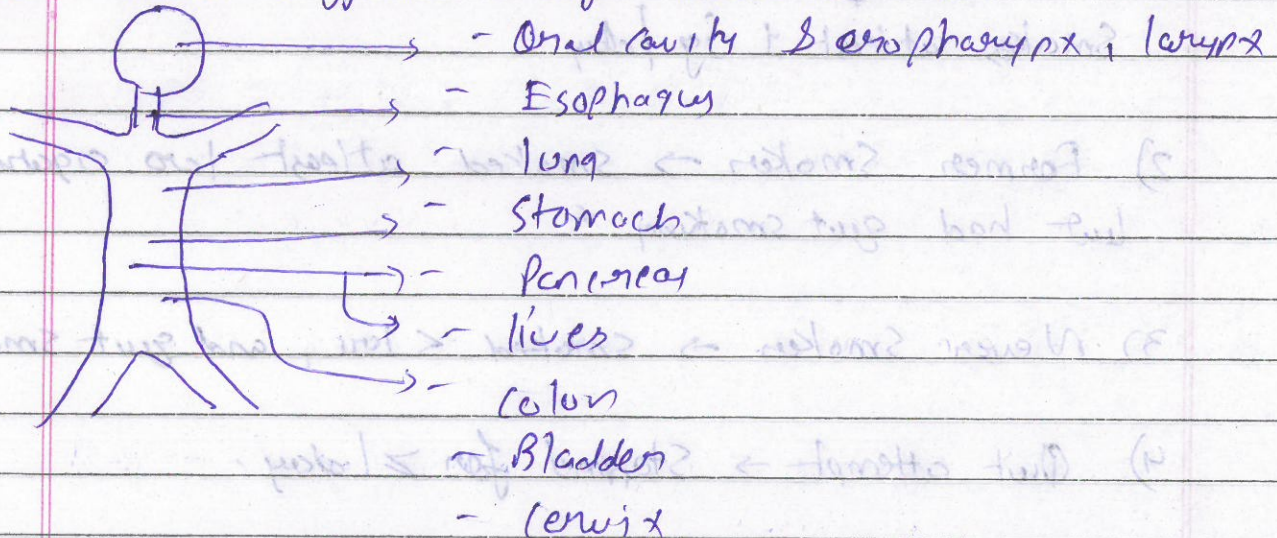
→ HR for cancers other than lung

women	men
1.7	2.2

- * Common index for risk of cancer & smoking is pack years.
i.e. number of packs smoked per day $\times$ no. of years.
- * Risk of cancer declines with quitting, but in most cases, doesn't approach that of never smokers.

Various cancers attributed to smoking

- ① Evidence sufficient to infer causal relationship



- ② Evidence suggestive but not sufficient - Breast
- ③ Inadequate evidence - Ovary
- ④ Evidence sufficient to infer NO causal relation $\rightarrow$ Prostate

- * The major primary driver of smoking behaviour is nicotine

Nicotine



Cotinine

↓ CYP2A6

* 3-HL (trans 3'OH cotinine)

- * Ratio of 3HL : Cotinine in plasma/saliva is a marker of CYP2A6 activity.

- * Ratio also predicts success in quitting & likelihood of quitting decreases as ratio increases.
∴ Slow metabolizers can quit more easily !!!

Historically, tar was believed to be the main contributor of smoking related disease.

So, low tar cigarettes introduced. But it has no significant benefit

Carcinogens in tobacco

- * IARC has classified cigarette smoke & smokeless tobacco as Group 1 carcinogens

Mainly, the N-nitrosamines are found to be carcinogenic, like Benzo(a)pyrene

1,3-butadiene

Aromatic amines

Cadmium

- * (i) Compound of particular concern → Benzo(a)pyrene (BaP)

② Aromatic amines in smoke → 2-amino naphthalene
4-amino biphenyl
Fluorens

③ Toxic metals → Beryllium
→ Cadmium
→ Lead
→ Polonium-210

④ N-nitrosoamines of cancer

NNK (formed by nitrosation of nicotine) NNN (nitrosation of nor nicotine)

- Both are formed during curing process of tobacco.
- * NNK - lung, nasal cavity, pancreas, liver
NNN - Respiratory tract, Esophagus
- * Smokeless tobacco also contains N-nitrosoamines.
- * PAH & N-nitrosoamines are involved in lung carcinogenesis
NNK - lung
- * Various biomarkers could be used to measure exposure to a specific carcinogen, for eg.
Monohydroxyl-3-hydroxy mercapturic acid → 1,3 lactones
Total NNN → NNN
4-amino biphenyl glucuronide → 4-amino biphenyl
5-phenyl mercapturic acid → Benzene

Mechanism of Carcinogenesis

- Carcinogen exposure leads to formation of carcinogen-DNA adducts

↓
mutations
↓
cancer

- A single cig has low levels of these carcinogens, but over decades of smoking, these accumulate.

- Cigarettes induces activity of Cyt. P450, which facilitates metabolic activation of carcinogens to electrophilic entities which bind to DNA.

- DNA adducts are crucial to cancer process & smokers tissues have higher number of adducts than do non-smokers.

- System involved in detox → UGT

- Glutathione-S-transferase.

1) NNN, NNK → α hydroxylation Activation Detox
UGT

2) PAH → Diol epoxidation MEH, GST, UGT

3) Benzene → Epoxide form. MEH, GST

4) 4-ABP → N-oxidation UGT, NAT

~~MEH~~ MEH → microsomal epoxide hydrolase.

- < Persistent DNA adducts on least misreading during DNA replication.
- < Mutations in KRAS, inactivation of p53 can occur due to these mutations
- < Nicotine is not a carcinogen in itself, but
 - it reduces apoptosis
 - Increases angiogenesis
 - Activates transformation process via NF- κ B.

IARC categories

- 1 $\rightarrow$ Carcinogenic to humans
- 2A $\rightarrow$ Probably "
- 2B $\rightarrow$ Possibly "
- 3 $\rightarrow$ Not possible to classify carcinogenicity in humans

Obesity & Cancer

• WHO categorizes obesity as $BMI \geq 30 \text{ kg/m}^2$

• In 2003, a landmark study by Calle EE et al demonstrated that obese men & women were upto 51% & 62% more likely to develop & die from cancer.

• Risk of cancer is increased with obesity in 13 different cancers:-

1) Meningioma RR 1.5

2) Thyroid RR 1.1

3) Breast RR 1.1

(Post menopause)

4) Esophagus (adeno) 4.8

5) Gastric (adeno) 1.8

6) Pancreas 1.5

7) Kidney 1.8

8) Liver 1.8

9) GB 1.3

10) Ovary 1.1

11) Uterine 7.1

12) Colo rectal 1.3

13) Myeloma 1.5

(Cancers not associated with obesity are after the ones which are strongly associated with smoking.)

* Breast Cancer → Obesity is associated with an increased risk of breast cancer specific & all cause mortality.

Obese women had 35% risk of breast cancer specific mortality. & 41% higher risk of all cause mortality.

Key meta-analysis → Chen et al

* Colorectal Cancer → Obesity is associated with increased risk of all cause mortality, cancer-specific mortality & recurrence.

Key meta-analysis → Dolener et al

* Prostate Cancer → Increased risk of biochemical recurrence & prostate cancer specific mortality.
Weight gain after diagnosis also associated. $\rightarrow$ ↑ risk

Key meta-analysis → Co U & Ma

* Endometrial Cancer → Obesity associated $\rightarrow$ ↑ risk in all-cause mortality, with obese women ($BMI \geq 40$)

Key meta-analysis → Sermond et al.

- Obesity is also related to increased of complications to chemo. more likely to undergo APR (than LAR).

Intervention

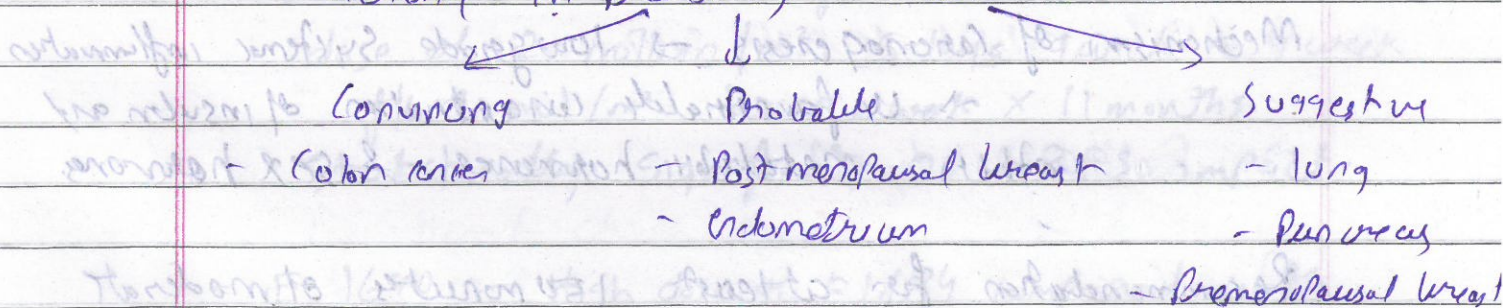
- PT undergoing bariatric surgery can have 27-59% lower risk of cancer [Adams et al]

- Intentional weight loss through diet & exercise is associated with 66% reduction in cancer risk.

- Ongoing trials → BWEL study - Breast Cancer Weight Loss study to determine efficacy of weight loss ~~on~~ on DFS among early stage breast cancer survivors with BMI ≥ 27 .

- Physical activity & cancer risk

World Cancer Research Fund study → Role of physical activity in preventing cancer



Pooled analysis by Moore et al showed that physical activity is associated with a risk of 13 different cancers.

Mechanism - Regulation of adiposity

- * In breast, colorectal & prostate cancer, physical activity is associated $\rightarrow$ lower risk of death.
- * In colorectal cancer, there exists a "dose-response" relationship, such that more the activity, greater the risk reduction. Same with prostate.

Ongoing trials

- 1) LIVES trial $\rightarrow$ Impact of physical activity & diet on PFS of advanced ovarian cancers.
- 2) CHALLENGE trial $\rightarrow$ Physical activity's impact on high risk stage II or stage III colon
- 3) INTERVAL trial $\rightarrow$ Prolongation of OS with exercise in metastatic (in prostate).

Mechanism of carcinogenesis $\rightarrow$ low grade systemic inflammation
 $\rightarrow$ unfavourable concentration of insulin and other metabolic hormones & sex hormones.

Recommendation for at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity per week.

Cancer Immunotherapy

(1) Interferon α

Functions & actions $\rightarrow$ * Antiproliferative & immunomodulatory

* Promote influx of infiltrating cells within tumor

* Stimulate antibody production

* Reduce Th1 cells in circulation

* Alter STAT1/STAT3 ratio in tumor infiltrating lymphocytes.

* Anti angiogenic effect.

Uses - 1) First approved for used in hairy cell leukemia

2) Malignant melanoma - Highest impact of IFN α -2b has been in resected high risk malignant melanoma

- E1684 $\rightarrow$ 1st RCT for IFN α -2b. Given at a dose of 20 million IU/m² 5 days a week $\times$ 4 weeks
 then 10 million IU/m² three a week $\times$ 11 months.

Statistically significant OS & RFS impact.

- E1690 - High dose of E1684 compared with low dose (3 million IU/m² twice weekly $\times$ 24w) and a third control arm with no therapy.

Highest RFS seen in high dose.

OS was similar in all three.

- E1694 → High dose IFN α 2b compared to a ganglioside vaccine [GMK vaccine]

Three arms — GMK + HDI (concurrent)
 — GMK + HDI (subsequent)
 — GMK alone.

Combined approach better.

- EORTC 18991 → Peg IFN α 2b vs observation.
 Improvement in RFS, but not OS.
 Not used outside USA.

- Mocellin et al metaanalysis → Significant improvement in RFS $\approx$ IFN, but modest improvement in OS.

3) Metastatic RCC — Showed modest improvement initially, but little use now with newer agents.

4) AIDS related Kaposi's Sarcoma

5) Follicular lymphoma

6) CMV

Toxicity — Dose limiting toxicity is fatal or life threatening neuropsychiatric, autoimmune, ischemic or infectious disorders.

Flu-like symptoms - Fever, headache, chills, myalgia, anorexia, diarrhea, alopecia

- Ischemic & hemorrhagic cerebrovascular accidents, hypotension, erythema, tachycardia, loss of vision, pneumonia, bronchiolitis obliterans.

(2) Interleukin 2

- * Predominantly produced by antigen stimulated $CD4^+$ T cells, but also by $CD8^+$ cytotoxic T cells, NK cells & dendritic cells.

- * Functions - 1) Maintenance of $CD4^+$ regulatory T-cell function
2) Promotes $CD8^+$ T-cell & NK cell cytotoxic activity
3) Modulates T-cell differentiation program in response to antigen.

Uses 1) High dose IL2 used in metastatic RCC

- 2) Biochemotherapy - Combining IL2 with conventional chemo drugs (cisplatin & dacarbazine) for malignant melanoma. But improvement in OS not seen.

When compared to IFN, biochemotherapy showed improved RFS, but no improvement in OS.

3) IL2 also tested for its effects on Treg cells in GVHD and has a favourable effect in steroid resistant GVHD.

③ Talimogene Laherparepvec

- * T-Vec is a genetically modified, oncolytic herpes virus, from JS1 strain.

- * It is only capable of replicating in cancer cells.

- * Gene encoding for infected cell protein is deleted & gene for GM-CSF is inserted in it. So, upon entering tumor cell, it causes increased local level of GM-CSF.

- * High GM-CSF promotes recruitment & maturation of dendritic cells, as well as macrophages into potent antigen presenting cells. It leads to priming of tumor specific T cells in tumor microenvironment.

↳ Main use in malignant melanoma.

- * In a phase II trial, 50 patients of unresectable, metastatic MM were given T-Vec.

8 CRs & 5 PR noted. Response lasted over 6 months.

* Phase III trial of stage IIIb/IV Malignant melanoma given T-vec Vs GM-CSF.

Durable responses higher in the T-Vec arm.

* T-vec can also be combined to other checkpoint inhibitors like ipilimumab or pembrolizumab.

Ongoing trial for intratumoral T-vec + pembrolizumab vs pembrolizumab alone → MASTERKEY 265.

* No dose limiting toxicity, but it should not be administered to immunosuppressed.

④ GM-CSF - Hematopoietic growth factor & immune stimulant

* Promotes development & maturation of dendritic cells & APCs.

* Supports activation & proliferation of T-cells

* Chemo attractant for neutrophils

* However, intra-tumoral GM-CSF can promote tumor growth & progression.

* In a phase II trial, ipilimumab + GM-CSF has better OS than ipilimumab alone. But no significant PRS benefit.

* No significant impact on survival when combined with peptide vaccines.

⑤ Tumor infiltrating lymphocytes (TIL)

- Presence of TIL has been associated with good outcomes in cancers of colon, breast & melanoma.
- Attempt made to culture TIL *ex vivo* & give them as adoptive cell therapy in melanoma.
- Number of factors associated with clinical response, including numbers of $CD8^+$ TIL that expanded quickly & recognized the tumor.
- With newer techniques, response rates as high as 72% & CR rates of 20% were observed.
- Currently used for uveal melanoma.

⑥ Checkpoint inhibitors - CTLA-4 & PD-1

- CTLA-4 is a negative competitor of CD28 that binds CD80 & CD86 with higher affinity & dampens T-cell response.

~~It's~~ Monoclonal antibody against it

- PD-1 is a receptor on activated T-cells. Upon binding with its ligands, it leads to apoptosis of T-cells. PD-L1 & PD-L2 are its ligands, found on tumor cells.

(3) Anti PD1 antibodies - Nivolumab (fully human)
 Pembrolizumab (humanized)

Anti PD L1A antibodies - Atezolizumab (humanized)
 Durvalumab (fully human).

Uses

1) Ipilimumab is used as an adjuvant treatment for malignant melanoma after complete resection & lymphadenectomy.

Melanoma 2) Pembrolizumab approved by FDA in 2014 for treatment of unresectable or metastatic melanoma based on results of KEYNOTE 001 & 002

KEYNOTE 002 compared Pembro with chemo in mPAs who had progressed on ipilimumab.

Significant improvement in DFS seen.

Nivolumab was approved for BRAF wild-type & BRAF V600E mutation positive unresectable, metastatic melanoma.

✓ Checkmate 066 → Nivolumab Vs Dacarbazine

✓ Checkmate 037 → Nivo Vs Dacarbazine / Pacli + carb

Combination of anti PD1 and anti CTLA 4 has proven to be more efficacious than either agent alone.

✓ Checkmate 069 → Nivo + Ipili Vs Ipili

Adjuvant Rx for stage III_a, III_b & IV is better with Nivo than Ipili (Checkmate 238)

NSCLC →

* Nivo approved in 2015 for treatment of NSCLC following progression on or after chemo with platinum agents or EGFR/ALK directed therapy.

* Pembrolizumab also approved for advanced NSCLC with ~~≥~~ >1% PD-L1 expression

Keynote 001 trial - Assessed safety, tolerability & antitumor activity of Pembro

Keynote 010 trial → Pembro vs Docetaxel to Pt 2 NSCLC who had received prior treatment & expressed ≥1% PD-L1 in their cells.

Keynote 024 → Pembro vs Platinum based chemo

In 2017, Pembrolizumab was + Permetrexed was approved as 1st line therapy for advanced or metastatic NSCLC, regardless of PD-L1 expression.

In 2016, atezolizumab was approved for metastatic NSCLC who had progressed on platinum chemo.

Durvalumab approved in 2018 as consolidation therapy in advanced NSCLC who did not progress on chemo/radiation. [PACIFIC trial]

(3) Mismatch repair deficient or MSIH cancers

Pembrolizumab approved for treatment of adults & children with MSI-H or dMMR solid tumours who had exhausted cell treatment options

Nivolumab approved for MSI-H or dMMR CRC pt who progressed on FOLFIRI

(4) RCC → Nivolumab approved for metastatic RCC in 2016. Significant OS benefit compared to Everolimus (Checkmate 025)

Combination anti CTLA4 & anti PD1 approved as 1st line therapy in advanced RCC in 2018.

(5) Head & neck SCC - Pembrolizumab approved for heavily treated recurrent or metastatic SCC. Nivolumab gained approval in 2016 for 1st line therapy in recurrent or metastatic HNSCC who progressed on chemo.

(6) Urothelial carcinoma - Atezolizumab approved for locally advanced or metastatic Ca Bladder which progressed on platinum based chemo.

In 2017 it was approved as 1st line therapy for pt who are ineligible for cisplatin based chemo.

Nivolumab is also approved for locally advanced or metastatic Ca Bladder.

Durvalumab approved in 2017 for locally advanced or metastatic urothelial carcinoma. (E)

Avelumab approved for the same, based on JAVELIN study.

(7) Merkel Cell Carcinoma - Avelumab for children ≥ 12 yrs with stage IV mCC

(8) HCC - Nivolumab (P)

Cancer Vaccines

1) BCG Vaccine - Given intravesically in 1st Bladder post TURBT

2) Sipuleucel-T $\rightarrow$ It is a dendritic cell vaccine that is designed to enhance the T cell response against Prostatic acid phosphatase

Patient derived dendritic cells are expanded in vitro and loaded with tumor specific antigen.

Approved in 2010 for treatment of castration resistant Prostate cancer with minimal to no symptoms (III IMPACT trial).

3) GvVAY → Whole cell vaccine composed of live irradiated prostate cancer cell lines that express GM-CSF to promote T-cell activation.

No survival benefit seen.

4) Gp 100 vaccine → Peptide vaccine with melanocyte differentiation antigen gp 100. When used in combination with IL2, in patients with melanoma it improved response rate & PFS.

↓
Causes vitiligo

Prophylactic Cancer Surgery

Cancers where it is being practiced / is applicable

- 1) Breast
- 2) Ovary & Endometrium
- 3) Thyroid
- 4) Colon
- 5) Stomach

Breast

High risk Patients $\rightarrow$ 1) lifetime risk $> 20\%$ as defined by models dependent on family history

2) Thoracic radiation before age 10-30 yrs $\rightarrow 20-25\%$ risk

3) 5yr risk of cancer $\geq 1.7\%$ on Gail model in pt ≥ 35 yrs.

4) LCIS/ALH or (ADH + 20% risk) $\rightarrow 10-20\%$ lifetime risk

5) Known genetic predisposition

6) Prior h/o (a Breast

Different risk Models

- 1) Gail model - Age, family history, Age at menarche, age at 1st child birth, number of previous live births
- 2) Claus Model → Number of first & second degree relatives with breast or ovarian cancer
- 3) Tyrer Cuzick → Most comprehensive inventory of family history
- 4) BRCAPRO → Predicts the probability of carrying BRCA mutation & developing Ca Breast - It can only predict risk of IDC.

Tyrer Cuzick & Claus can predict risk of DCIS as well.

EMRACE study → Risk of developing breast, ovarian & contralateral breast cancer in BRCA 1/2 mutations by age 70

	BRCA1	BRCA2
Breast	60%	55%
Ovary	54%	16.5%
CBCTD	83%	62%

Noninvasive management → Read "Breast Cancer Screening".

Chemo prevention

STAR trial $\rightarrow$ Compared to Placebo, Tamoxifen & Raloxifene reduces risk of IDC by 50% & 38% resp.

Pre-menopausal $\rightarrow$ Tamoxifen

Post menopause $\rightarrow$ Tamox, Raloxifene, Exemestane.

Invasive option — Risk reduction mastectomy & Risk reduction Salpingo-oophorectomy.

PROSE study $\rightarrow$ RRM reduces risk of Ca Breast in BRCA1/2

by 94% if oophorectomy done

90% if ovaries intact

In another study, RRSO reduces Ca Breast by

37-56% in

BRCA 1

46-64% in

BRCA 2

For RRM, skin sparing or nipple sparing mastectomy can be done.

Timing of Surgery $\rightarrow$ As close to ~~child~~ completion of child bearing as possible.

less benefit of RRSO after 40 yrs age.

③ Stomach - Hereditary diffuse gastric cancer.

Hereditary diffuse gastric cancer is defined by

- 1) ≥ 2 cases of DGC in 1st or 2nd degree relatives at least one diagnosed before age of 50 ym.
- 2) ≥ 3 cases of DGC in 1st or 2nd degree relatives independent of age of onset
- 3) 1 case of DGC before age of 40
- 4) Family with h/o DGC & lobular carcinoma before age of 50 ym.

Average age of onset $\rightarrow$ 38 years

Pattern of inheritance $\rightarrow$ AD.

* Germline CDH1 mutations are associated with increased risk of lobular carcinoma.

* Penetrance of DGC in patients carrying CDH1 mutation is $\sim 70\%$.

CDH1 $\rightarrow$ localized on 16q22.1

$\rightarrow$ Encodes Calcium dependent cell adhesion glycoprotein E-cadherin

$\rightarrow$ Acts as tumour suppressor gene.

$\rightarrow$ Germline CDH1 mutation is a truncating mutation

Recommended screening criteria for CDH1 mutation

- 1) Families with one or more case of DGC.
- 2) Individuals with DGC before the age of 40 yrs without a family history.
- 3) Families or individuals with cases of DGC (one case ≤ 50 yrs) and lobular carcinoma in situ.
- 4) Cases where pathologists detect in situ signet ring cells or pagetoid spread of signet ring cells adjacent to DGC.

* Genetic counselling should take place prior to genetic testing & should involve geneticist, gastroenterologist, surgeon & oncologist.

* Testing first performed on a family member with HDGC or on a tissue sample if no relative around.

If a mutation is identified, asymptomatic family members may proceed with testing, preferably by age 20 yrs.

* Screening is difficult in these patients bcoz cancer grows underneath normal mucosa, so they are difficult to identify on UGIScopy & biopsy.

* 5 yrs survival with developed cancer is 10%.

* Hence, Prophylactic total gastrectomy recommended.

* Most specimens found to have foci of cancer even if surgery done prophylactically.

* Specimen must include the entire stomach & transection be done at esophagus. Lymph node dissection not required.

Risks of Prophylactic gastrectomy

- 1) 2-4% mortality
- 2) Nearly 100% morbidity of dumping syndrome
- 3) 15-20% pt have no cancer in final HPR.

Non operative Surveillance

- 1) Biannual endoscopy with multiple biopsies acc to Cambridge method, beginning 10 yrs before the youngest case in family
- 2) Any endoscopically visible lesion is to be targeted
- 3) Random biopsies taken from antrum, transitional zone, body, fundus, cardia (6 each)
- 4) Women should undergo annual mammogram & biannual breast MRI.

(3) Hereditary Ovarian Cancer - BRCA1/2

- * Most BRCA related cancers arise from fimbriae of the fallopian tube.
- * BRCA1 mutations are twice as common as BRCA2 and together they amount for 15-20% of these cancers.
- * Lifetime risk of ovarian cancer in:-
 - 1) General Population - 1-1.5%.
 - 2) BRCA1 $\rightarrow$ 30-50%.
 - 3) BRCA2 $\rightarrow$ 15-25%.
- * Avg age of onset $\leftarrow$ BRCA1 - 35-40 yrs
BRCA2 - 45-50 yrs.
- * Testing is performed on affected family member, but if that is not possible, then unaffected individuals are tested. If a disease causing mutation is identified, then "cascade-testing" for that single ~~mutant~~ mutation is performed in other family members.
- * It is recommended that all ovarian cancers undergo BRCA testing, and reflex blood testing done if a mutation is found, to check whether it is germline.

- * OC pills reduce risk of cancer in general population by 30-60%. & has similar effect in BRCA mutation too.

- * Ovarian cancer risk in BRCA1

Before 40 yr $\rightarrow$ 2-3%.

50 yr $\rightarrow$ 10-21%.

70 yr $\rightarrow$ 40%.

So, appropriate time for RRSO is after childbearing is completed

For BRCA2, risk is slightly lower, so surgery can be postponed to 40-45 yr.

- * Several studies have shown benefit of RRSO.

- RRSO reduced risk of ovarian cancer by 96%.

- 2-3% chance of primary peritoneal carcinoma remains.

- * High grade serous cancers in uterus can also arise, but prophylactic hysterectomy not advised yet.

- * Post operatively, estrogen replacement therapy in the form of tablet or cream can be given to pre menopausal women.

- * RRSO reduces risk of 2nd breast by about half in BRCA 1/2 carriers (Kauff et al)

Steps of RRSO in Ca Ovary topic

④ Hereditary Endometrial Cancer (Lynch Syndrome)

- * Ca endometrium is the second most common cancer in women with Lynch syndrome
- * M.I. mutated genes $\rightarrow$ MSH2, MLH1
- * Risk of ovarian carcinoma is also significantly increased
- * Tumor tissue to be analyzed for presence of mutation
- * OC pills can be considered for chemo prevention of Ca endometrium

Screening modalities - USG to look for endometrial thickness. Low PPV.

CA 125 - no proven value.

- * Pt can be educated about symptoms & endometrial biopsy done if symptoms +ve.
- * Risk reducing hysterectomy has not shown to reduce mortality in L.S, but can be considered due to high incidence of Ca endometrium.
- * Not recommended before age of 40 yrs.

- * Concomitant BSO ~~not~~ can also be done if/when increased risk of an ovary in these pt.

⑤ MEN Type 2

- * The constellation of Syndromes in MEN type includes

MEN2A - multifocal, bilateral MTZ
Pheochromocytoma

Hypen parathyroidism

Hirschsprung disease

MEN2B - Multifocal, bilateral MTZ

- Phro

- mucosal neuromas, megacolon

FMTZ - Multifocal, bilateral MTZ.

- * Most Severe. is MEN2B, where age of onset is in infancy. Most common germline mutation in codon 918 ($ATG \rightarrow A(G)$).
other mutations described in codon 883, 922.

- In MEN2A, codon mutation is 634, 618.

Some patients do extremely well for years.

Others keep having debilitating symptoms.

- * In FMTZ, pts only have MTZ & are cured by thyroidectomy alone.

Ulcer to Per form?

These levels of risk have been described

Level I $\rightarrow$ lowest risk

$\rightarrow$ MEN2A Codon 768, 790, 791, 804, 891

$\rightarrow$ FMTZ
 $\rightarrow$ Surgery at 5-10 years.

Level II $\rightarrow$ Intermediate risk / High risk

$\rightarrow$ MEN2A Codon 634, 620, 618, 611

$\rightarrow$ Surgery < 54n age

Level III $\rightarrow$ Very high risk

$\rightarrow$ MEN2B, esp Codon 918

$\rightarrow$ Surgery < 14n age.

* Parathyroids can be removed & auto-transplanted.

* Pre op Calcium & lymph node:-

< 20 pg/ml $\rightarrow$ Only thyroidectomy

20 - 50 pg/ml $\rightarrow$ Ipsilateral (CND) & LND.

50 - 200 pg/ml $\rightarrow$ Contralateral (CND)

> 200 pg/ml $\rightarrow$ Contralateral (LND)

Post op, lifelong thyroid supplementation given & calcium + Vit D for several weeks until parathyroid function recovers.

② FAP & HNPCC → Ca Colon topic

Adenomatous polyps are precancerous lesions of the colon and rectum. They are characterized by the presence of dysplastic epithelial cells. The risk of progression to colorectal cancer increases with the number and size of polyps.

Adenomatous polyps are classified into three types based on their morphology: tubular, tubulovillous, and villous. The risk of malignancy increases with the size of the polyp. Polyps greater than 1 cm have a 5-10% risk of malignancy, while polyps greater than 2 cm have a 25-40% risk.

Total Score for all 13 questions is 100
 x11 - 112.0 → 112.0

Adenomatous polyps are precancerous lesions of the colon and rectum. They are characterized by the presence of dysplastic epithelial cells. The risk of progression to colorectal cancer increases with the number and size of polyps.

- 1) Adenomatous polyps are precancerous lesions of the colon and rectum.
- 2) They are characterized by the presence of dysplastic epithelial cells.
- 3) The risk of progression to colorectal cancer increases with the number and size of polyps.
- 4) Adenomatous polyps are classified into three types based on their morphology: tubular, tubulovillous, and villous.
- 5) The risk of malignancy increases with the size of the polyp.
- 6) Polyps greater than 1 cm have a 5-10% risk of malignancy.
- 7) Polyps greater than 2 cm have a 25-40% risk of malignancy.
- 8) The risk of progression to colorectal cancer increases with the number and size of polyps.
- 9) Adenomatous polyps are precancerous lesions of the colon and rectum.
- 10) They are characterized by the presence of dysplastic epithelial cells.
- 11) The risk of progression to colorectal cancer increases with the number and size of polyps.

Cytoreductive Surgery & HIPEC

- * Cytoreductive Surgery with Peritonectomy & visceral resections are being used for various GIT & gynecological malignancies.

An adjunct to it is a form of intraoperative Chemo either HIPEC, or EPIC (Early Post Op Intraperitoneal Chemo) or NIPEC-LT (Normothermic Intraperitoneal Chemo - long term).

- * Pre op CT Sensitivity
- | |
|------------------|
| 0.5 cm - 11% |
| 0.5 - 5 cm - 37% |
| > 5 cm - 94% |

Concerning Radiological features

- 1) Non mucinous ascites
- 2) obstruction
- 3) Clumped up mesentery
- 4) Tumor along leaves of small bowel mesentery
- 5) Gastric outlet obstruction
- 6) CT PCF > 20
- 7) > 5 cm mass on Jejunum or lesser omentum
- 8) Invasion of seminal vesicle or vagina
- 9) Rectal stenosis
- 10) Hydronephrosis
- 11) Psoas muscle infiltration

How to calculate PCI?

	Rt		left	
13 regions	1	2	3	9 - Upper Jejunum
	8	0	4	10 - Lower Jeju
	7	6	5	11 - Upper ileum
				12 - Lower ileum

PC 1 $\rightarrow$ lesion < 0.5 cm

PC 2 $\rightarrow$ $0.5 - 5$ cm

PC 3 $\rightarrow$ > 5 cm.

Total Score in all 13 regions is PCI.

Peritoneal ~~and~~ Surface Disease Severity Score

3 components $\rightarrow$ Clinical features (0, 1, 6)

PCI (0, 1, 3, 7)

Biology (1, 3, 9)

Clinical features — No features — 0

— Mild — Mild pain, $< 10\%$ wt loss,

asymptomatic ascites — 1

— Severe — Severe pain, $> 10\%$ wt loss, ascites — 6

0-10 $\rightarrow$ 1

10-20 $\rightarrow$ 3

> 20 $\rightarrow$ 7

PCI

Well diff — 1

Biology Moderately — 3

Poorly — 9

Pathophysiology of Peritoneal Dissemination

In gastric cancer, one can have low density seeding or high density seeding.

Low density seeding implants into peritoneal nodules over small bowel serosa.

High density deposits over resection margin as fusiform layers of cancer cells.

Biologic aggressiveness as measured by histopathology

- 1) Good prognosis $\rightarrow$ Low grade, multicystic.
- 2) Intermediate $\rightarrow$ Epithelial, Papillary
- 3) Poor $\rightarrow$ Sarcomatoid, cellular.

Completeness of cytoreduction (CC) score

- CC0 $\rightarrow$ No grossly visible tumor
- CC1 $\rightarrow$ Minute nodules, total < 2.5 mm
- CC2 $\rightarrow$ Gross nodules left behind - 2.5-2.5 cm
- CC3 $\rightarrow$ > 2.5 cm.

Role of diagnostic laparoscopy

- It lacks sensitivity to detect lesions < 1 cm.
- So, direct laparoscopic visualization is useful to save a pt from unnecessary laparotomy.
- Most appropriate is colorectal peritoneal mets in a pt $\bar{c}$ poor performance status, age > 70 y.

Components of CRS

- 1) Anterior peritoneal peritonectomy
- 2) Left upper quadrant peritonectomy
- 3) Rt upper quadrant peritonectomy
- 4) Pelvic peritonectomy
- 5) Omental wedge resection
- 6) Mesenteric peritonectomy

Most common locations of peritoneal deposits

Maximum deposits occur where bowel is tethered to retroperitoneum

- Rectosigmoid
- IC Junction
- Gastric antrum.

These sites often need to be resected during peritonectomy.

- * Peritonectomy in the absence of ~~HP~~ HIPEC will lead to cancer cells being implanted beneath peritoneal layer of abdomen / pelvis

Position - Modified lithotomy.

Steps - Abdomen opened from midline, from xphi to pelvis.

- * Skin retraction done by suture, passed over a self retaining retractor.
- * Ball point cautery is used, with wire cut at high voltage.
- * Since a large volume of smoke is generated, a smoke evacuator is used.

① Xiphoidectomy - If right or left subdiaphragmatic resection is needed, then xiphoidectomy should be done beforehand.

- * Epigastric fat pad is released and self retaining retractor is used to expose the xiphoid.
- * After exposing xiphoid, electrocautery is used to demarcate the line betⁿ xiphoid & sternum & bleeders coagulated.
- * Bone is fractured with minimal downward pressure.
- * Xiphoid is released & base is caught with a Kocher's clamp.
- * Attachments to diaphragm are divided as it is peeled off.

② Anterior parietal peritoneotomy

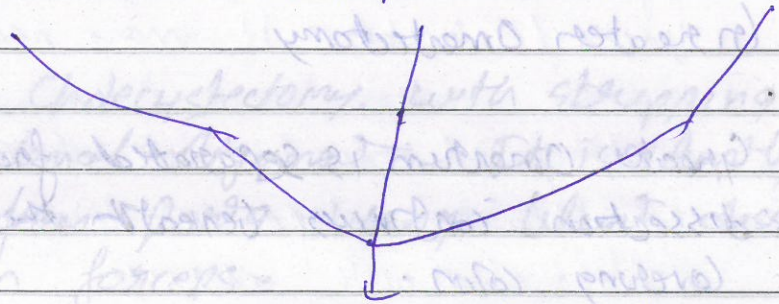
- * Single point entry made in peritoneum
- * Peritoneum dissected away from posterior rectus sheath
- * Peritoneum from undersurface of hemidiaphragm is stripped off
- * Dissection blends in with R & left subdiaphragmatic peritoneotomy Superiorly & pelvic peritoneotomy inferiorly.

Adhesiolysis → It is a must. Otherwise, cancer cells may get trapped in adhesions and intraperitoneal chemo is not effective. This is the Tumor cell entrapment hypothesis

Serosal invasion
+ Surgical Trauma

Lymphatic invasion
+ Lymphatic transection

Venous invasion
+ H/Age



Free intra peritoneal tumor emboli

↓
Fibron entrapment

↓
Inflammatory cell infiltrate

↓
Growth factor Stimulation

↓
Cancer implant

(3) Left Subphrenic Peritonectomy

- * Epigastric fat pad & peritoneum at the edge of incision have been stripped off.
- * With strong traction, tumor is separated from diaphragmatic muscle, left adrenal, superior half of perinephric fat.
- * Splenic flexure of colon is severed & moved medially to proceed dissection along the line of Toldt.
- * Once completed, the stomach is reflected medially by ligating numerous branches of gastro-epiploic arteries. Left adrenal, tail of pancreas & left perinephric fat should be seen.

(4) Greater Omentectomy

- * Greater Omentum is separated from colon, & dissection continues beneath the peritoneum covering colon.
- * Peritoneum covering the tail of pancreas, if involved, is separated bluntly & splenectomy performed.

(5) Right Subphrenic Peritonectomy & Separation of tumor from Glisson's Capsule

- * Peritoneum is stripped off the right hemidiaphragm.
- * It is continued till bare area of liver is encountered.
- * Tumor on superior surface of liver is electrovaporated and a layer of tumor is lifted off liver by dissecting below Glisson's capsule.
- * Isolated patches on liver surface are electrovaporated with distal 2cm of ball tip cautery bent in hockey stick configuration.
- * Upon completing it, anterior branches of phrenic artery & vein can be visualized, with pt hepatic vein, subhepatic space including pt adrenal & perinephric fat.

⑥ Next step is Cholecystectomy with stripping of hepatoduodenal ligament. It is bluntly separated from porta using blunt dissection & Russian forceps.

Further, resection of lesser omentum is done.

⑦ Stripping the floor of omental bursa is done by retracting the caudate lobe & visualizing the entire omental bursa. Peritoneum from liver to IVC is divided and bluntly stripped off using Russian forceps.

⑧ Mesenteric peritonectomy is needed in case of ~~mesenteric~~ peritoneal mesothelioma. It starts at root of small bowel & continues in a centripetal manner to the peritoneal reflection on to the surface of small bowel.

⑨ Liver wedge over umbilical ligament (Port-hepatic) has to be divided in order to resect umbilical ligament.

⑩ Pelvic peritonectomy

- In continuation with stripping of peritoneum of rectus sheath, peritoneum over bladder is removed.

- If the tumor is invading seminal vesicles & base of bladder, it may need to be resected.

- Rectosigmoid resection is done, vaginal cuff is transected and entire cul-de-sac is removed en bloc along with uterus.

- Rectosigmoid may be preserved in low tumor bladder, less aggressive histologies. The procedure is called: Cul-de-sacectomy.

Before intraoperative chemo, vaginal cuff is closed, otherwise it will cause leakage of solution. But before that, entire abdomen is thoroughly irrigated.

- * Colonic anastomosis & stoma created after chemo instillation.

Small bowel mesentery involvement

→ often involved in mucinous appendiceal neoplasm.

Type 1 - non invasive nodules - Resected by scissors

Type 2 - Small invasive nodules on anti mesenteric border → partial thickness bowel resection & closure

Type 3 - Moderately sized invasive nodules on anti mesenteric border → Full thickness bowel resection & anastomosis

Type 4 - Small nodule at Junction of bowel & mesentery → Resection of bowel + mesentery
 J16 HIPEC J16 anastomosis

Type 5 → large nodules

All anastomosis in bowels done after HIPEC.

Techniques for HIPEC

① Open Technique → After Surgery, a Tenckhoff catheter & closed suction drains are inserted through abdominal wall & fixed tightly.

→ Skin edges are elevated & smoke evacuators are placed

→ During 90 minutes of perfusion, all anatomic structures are uniformly exposed to heat & chemo. Intra peritoneal temp is $41-46^{\circ}\text{C}$.

② Closed technique / Coliseum technique / Lindgren technique

→ Abdomen is closed by a plastic Sheath & access is taken by a cruciate incision in the lower half of the Sheath.

③ Totally closed technique

→ Surgery is done, abdomen irrigated, anastomosis & closure done, tubes inserted then chemo given.

All drugs except Melphalan can be given by both techniques. Melphalan is to be given only by closed. coz it's a nitrogen mustard & with moderate heat, it may escape into environment.

Role of CRS & HIPEC for different organs

Level 1 evidence in - Gastric cancer (PCI < 13, complete CRS possible, no mets).

- Ca Ovary (first line)

Level 3 evidence for - CRC

- Appendiceal neoplasms

- Peritoneal mesothelioma.

Appendiceal neoplasms

Biology of appendiceal neoplasms divide them into 3 types

1) Disseminated peritoneal adenomucinosis

2) Peritoneal mucinous (carcinoma)

3) Peritoneal (carcinoma (non mucinous)

Survival is highest in DPAM & lowest in PC with CRS.

Surgical learning curve $\rightarrow$ 130 procedures

Sugarbaker reported a 5yr OS of 86% in low grade tumors undergoing CRS

* CRS + HIPEC are now the standard of care for pseudomyxoma peritonei arising from appendiceal neoplasms.

Colorectal Cancer

* Peritoneum is the second most common site of recurrence following curative resection.

* Around 10% have PM at presentation & 25% develop it after treatment of primary.

Studies

1) Elias et al → CRS + HIPEC vs Systemic Chemo

Median OS → 30 months

Syn OS → 29%

5Yr DFS → 10%

2) Verwaal et al → CRS + HIPEC vs Systemic Chemo
± Palliative Surg.

Median OS → 22.3 months vs 12.6 months

In a subgroup analysis, it was shown that patients with > 5 affected sites fare poorly despite CRS + HIPEC.

3) PRODIGE 7 → pt aged 18-70 yrs, with PCr < 25,
ECOG 0-1 ~~received systemic~~

~~HIPEC~~ CRS

↓
Observation

→
HIPEC

Oxaliplatin was delivered as HIPEC & systemic.

5 FU + Folinic acid delivered IV 20 mins before HIPEC.

Primary end point was OS.

	CRS	CRS + HIPEC
Median OS	41.2 month	41.7
Adverse events	32%	42%
Grade 3 adverse events		None.

So, in a color, CRS alone is standard. Role of HIPEC under investigation.