RHABDOMYOSARCOMA: AN OVERVIEW

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ETIOLOGY & EPIDEMIOLOGY

- Most common soft tissue sarcoma in children
• 3% to 4% of all cases of childhood cancer
• More common in males and Caucasians
• Median age at diagnosis is 5 yr with 2/3rd pts <10 yrs
- Associated with various congenital anomalies (upto 32% on autopsies) and syndromes like:
• Costello syndrome
• Beckwith-Wiedemann syndrome
• Neurofibromatosis type I
- Other etiologies include Germ-line P53 mutations, parental use of cocaine & marijuana & radiation exposure

Pathology and Molecular Biology

International Classification of RMS

1. Embryonal RMS (65-70% incidence & favorable)

a. Botryoid (10%)

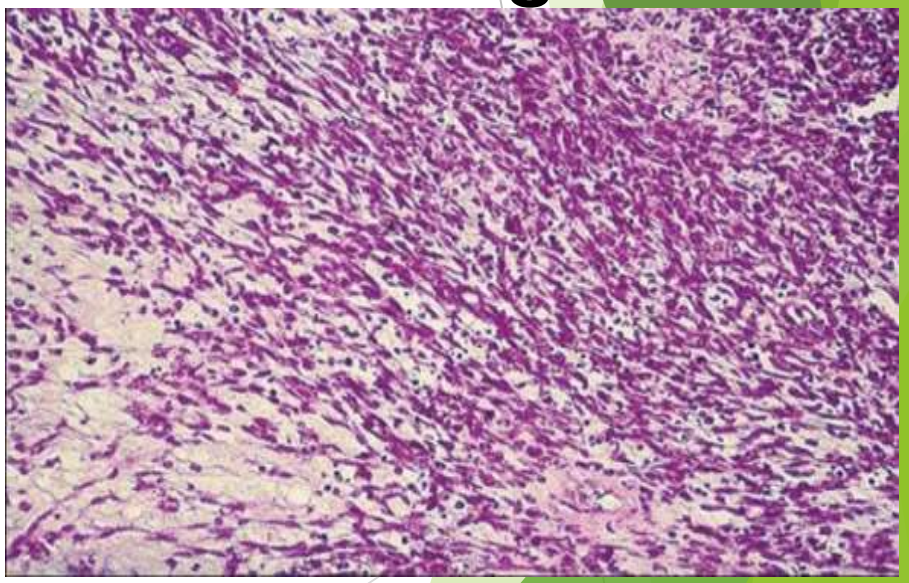
b. Spindle cell

2. Alveolar RMS (20% incidence & unfavorable)

3. Undifferentiated / pleomorphic sarcoma (unfavorable)

EMBRYONAL RMS

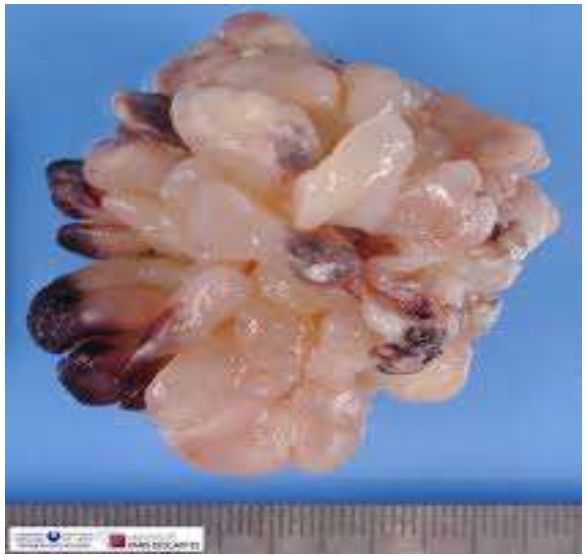
– Favorable clinical outcome with 5-year OS of 82%
– Affect younger patients
– Most commonly arise in head, neck & GU regions
– High background mutation rate and chromosomal anomalies
– LOH at chr 11, presence of EGFR & chromosome 8 gains (74%) are highly specific

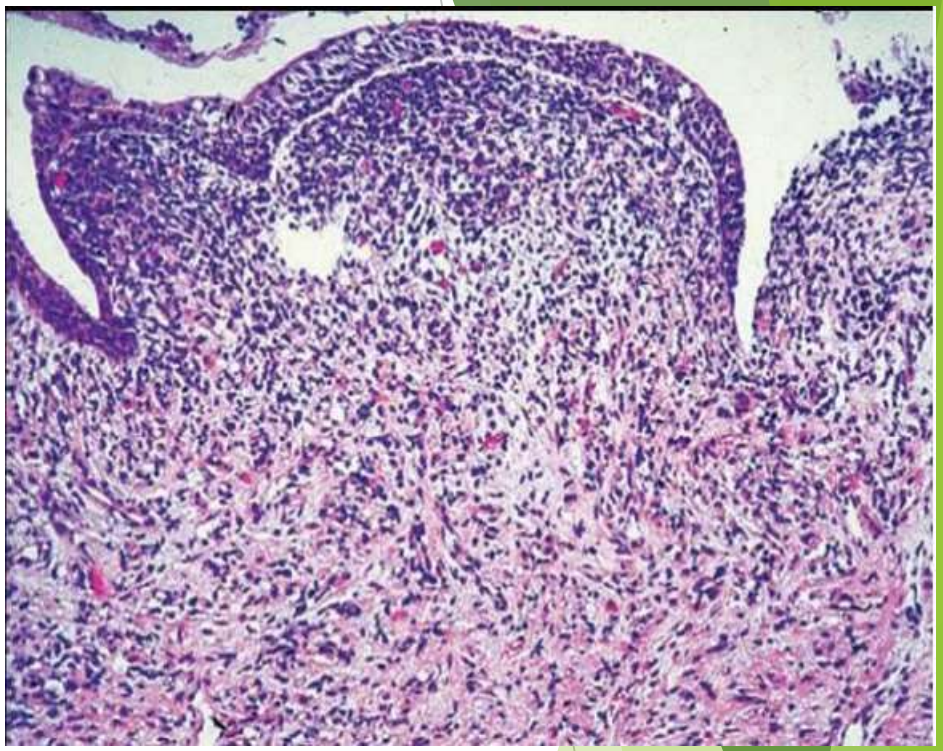


- Exhibit all cellular phases of myo-genesis with dense condensations of rhabdomyoblasts amid foci of loose myxoid stroma.
- Share features of other embryonal neoplasms of childhood like Wilms tumors, hepatoblastomas & neuroblastomas

BOTRYOID TYPE

- Subtype of Embryonal
- Superior Prognosis

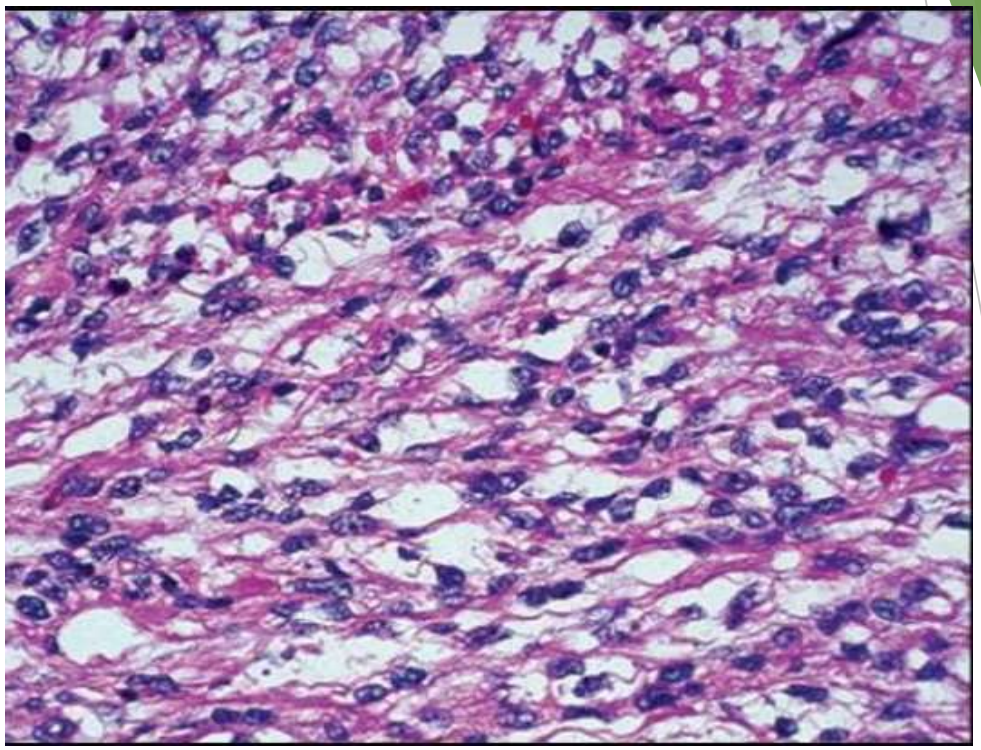




- Most commonly arise in mucosa of hollow visceral organs like Vagina, Billiary tree, Bladder, Nasopharynx etc with grape like masses projecting in the lumen
- Scattered malignant cells in myxoid stroma with subepithelial condensation of tumor cells

SPINDLE CELL

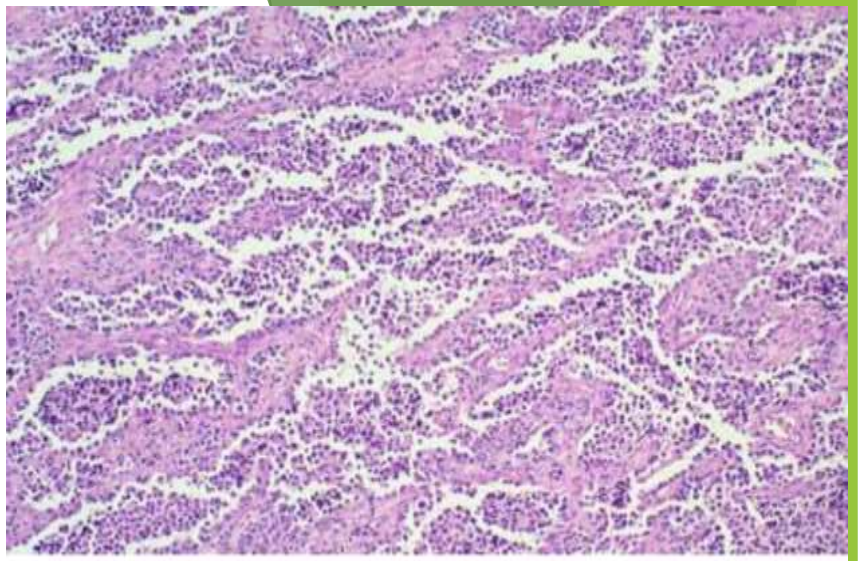
- Subtype of Embryonal
- MC site is Paratesticular
- Superior Prognosis



Relatively differentiated spindle cells having cytologic features reminiscent of smooth muscle tumors.

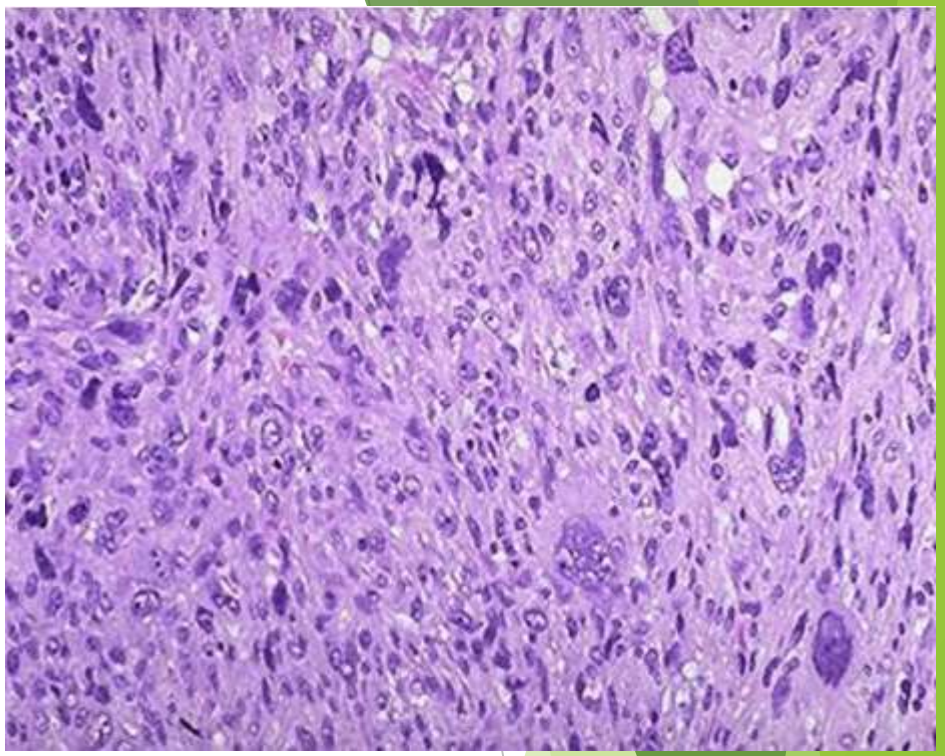
ALVEOLAR

- Extremities, trunk, perianal, perineal
- Aggressive with high metastatic potential
- *Characterized by a t(2;13) or t(1;13), where PAX3 gene on chr 2 or PAX7 gene on chr 1 is fused with FOXO1 gene on chr 13 (80% cases)*



- PAX/FOXO1 fusion gene is key determinant of clinical behavior & led to adoption of “fusion positive” or “fusion negative” molecular classification for risk stratification
- RMS 2005 showed 5-yr EFS of 43% (fusion +ve) vs 74% (fusion –ve)
- Fusion-negative alveolar RMS behave more like embryonal tumors
- Fibrous septa with loose clusters of rounded cells in center alveolar pattern

UNDIFFERENTIATED



- Diagnosis of exclusion
- Previously called Pleomorphic
- Rare in children
- Commoner in adults (30-50 yrs)
  & skeletal muscles of older people

- Marked pleomorphism
- Irregularly arranged cells with multi-nucliated giant cells with enlarged, pleomorphic, hyperchromatic nuclei

Natural History

- RMS is a locally invasive Tx often with a pseudo-capsule.
- Potential for local spread along fascia, muscle planes, lymphatics & blood.
- Overall risk of lymphatic spread is 15%-25% including
  - H&N: 15% (highest NPx, lowest orbit)
  - Paratesticular: 25%,
  - Trunk & extremities: 25%
- LN involvement depends on tumour invasiveness & size
- Distant mets at diagnosis seen in 15% (truncal/extremity Tm)
- MC sites for spread are Lungs, BM & Bone.

Clinical presentation

- Depend upon the site of primary tumor
- Head & neck (35% of all cases)

– Proptosis, ophthalmoplegia, nasal d/s or obstruction, headache, nerve palsies, dysphonia, dysphagia & adenopathy.

- Genitourinary tumors (25% of cases)

– Hematuria, dysuria, hydronephrosis, abdominal mass, vaginal d/s etc

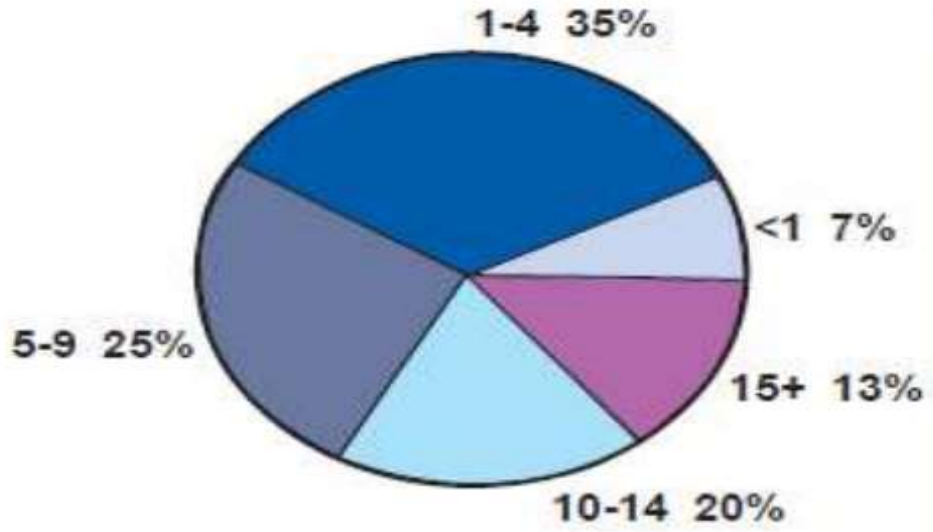
- Extremities (20% of cases)

– Swelling, palpable adenopathy or pain.

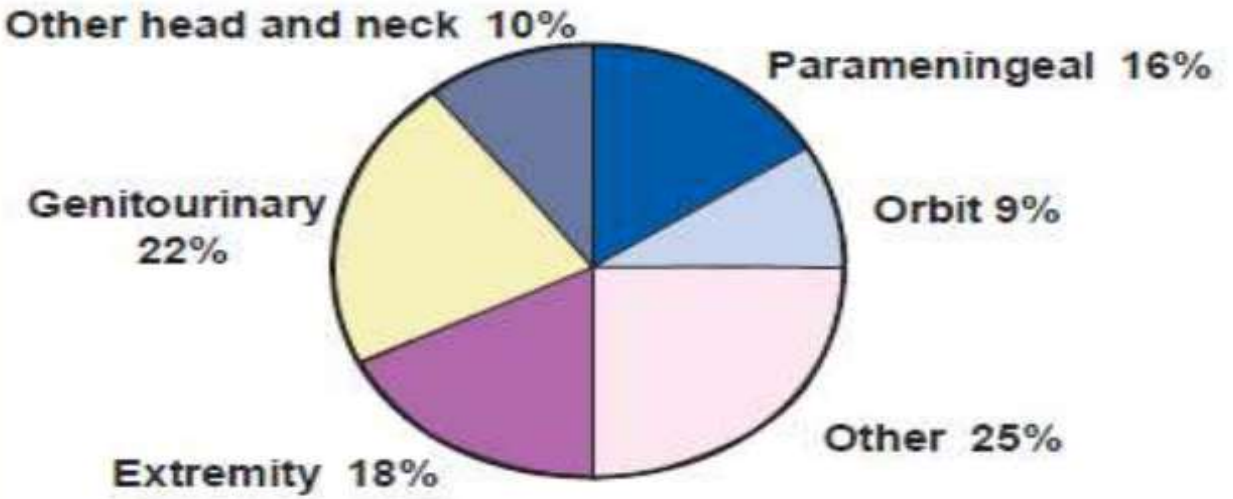
- Trunk/ abdomen

– Nerve root compression, palpable mass, jaundice or pain

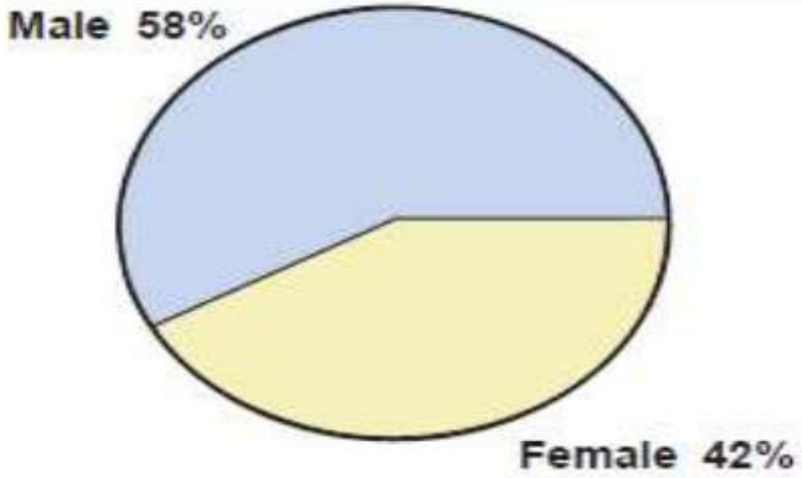
Clinical features of rhabdomyosarcoma



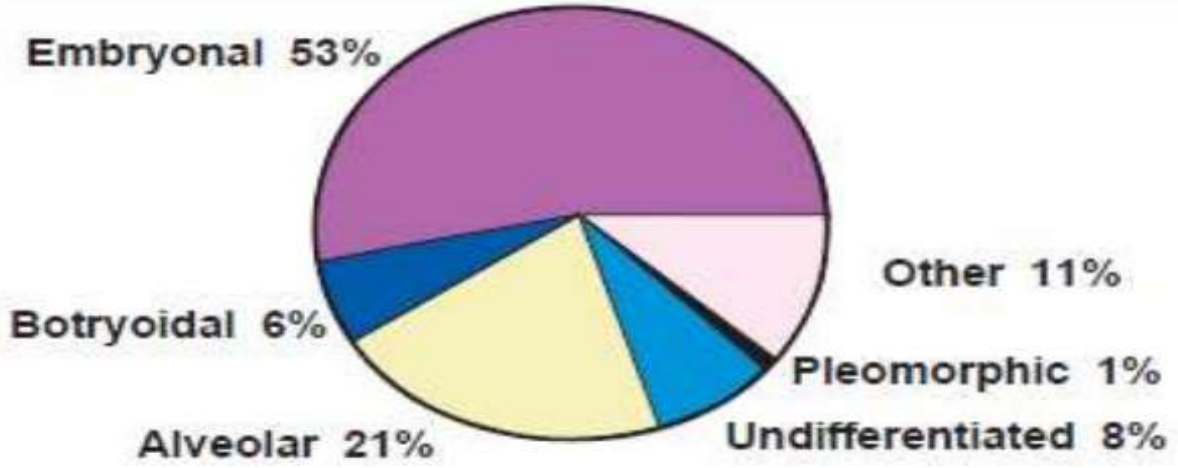
Age at presentation



Site of primary



Gender



Histology

Clinical / Staging evaluation

History & Clinical exam
– Complete blood count & bio-chemistries
– Bone or PET scan
– CT chest in all OR CT abdo + pelvis for abdominal, pelvic, & lower extremity tumors / PET (limited sensitivity for nodal involvement)
– CT / MRI of primary tumor (MRI preferred for children due to better soft tissue / plane delineation & low radiation exposure
- Biopsy: open, adequate
- CSF study
- Sentinal node biopsy (extremity)
- Counselling / Prognostication (History vs future!!)

Intergroup Rhabdomyosarcoma Clinical Grouping System

Group	Extent of Disease
Group I	**Localized disease, excised**
Group Ia	Confined to site of origin
Group Ib	Infiltrative, beyond site of origin; negative lymph nodes
Group II	**Total gross resection with regional disease spread**
Group IIa	Localized tumor with microscopic residual disease
Group IIb	▪ Regional disease with positive lymph nodes, excised ▪ No microscopic residual disease
Group IIc	▪ Regional disease with positive lymph nodes ▪ Grossly resected with microscopic residual disease
Group III	**Gross residual disease**
Group IIIa	Localized or regional disease, Biopsy
Group IIIb	Localized or regional disease, Resection (debulking of more than 50% of tumor)
Group IV	**Distant metastasis**

Classification	Description
Tumor	
T1	Confined to site of origin
T1a	Tumor size < 5 cm
T1b	Tumor size ≥ 5 cm
T2	Extension to / infiltration of surrounding tissue
T2a	Tumor size < 5 cm
T2b	Tumor size ≥ 5 cm
Regional Lymph Nodes	
N0	Lymph nodes not clinically involved
N1	Lymph nodes clinically involved
NX	Clinical lymph node status unknown
Metastasis	
M0	No distant metastasis
M1	Distant metastasis present

Demonstrate that prognosis depends on size & invasiveness of Tm than surgical approach / extent

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	A	Negative	I	Any	N0	Both Favourable
Standard Risk	B	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	D	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Favorable site: orbit, non-para H&N, non-prostate/bladder

Favorable size: <5 cm; Favorable age: <10 yrs

TREATMENT

Historical background

Intergroup Rhabdomyosarcoma Study Group (IRSG) conducted dedicated studies from 1972

- Prognostic groups and staging
- Optimized RT doses to 50.4 Gy (gross) & 41.4 Gy (microscopic)
- Omitted RT in Gp 1 favorable pts
- Excluded the use of hyperfractionation
- Relative lack of benefit from chemo agents apart from VAC
- Significant improvement in LC and OS during 25 years

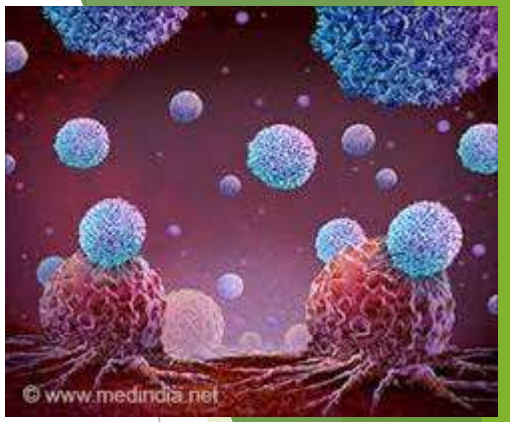
Children Oncology Group (COG): Formed in 2000, converging different gps including IRSG for further modifications

- International soft tissue sarcoma consortium is another collaborative gp

Surgery

- Upfront surgery is important for therapeutic & diagnostic purpose and R0 resection (Gp 1 status) can avoid RT
- Extensive surgeries are unwarranted in current era of reasonable surgeries & recent trend is towards limited resections f/b adjuvant Rx
- RMS is infiltrative & complete excision is achieved in only 20% cases
- 5 mm margin is considered adequate & re-excision of +ve margins in extremity & trunk primaries gives improved survival
- 2nd-look procedures convert partial into complete response & can help tailor dose or eliminate RT in selected cases. It is also helpful in assessing Rx response objectively.
- Sentinal node assessment is recommended over full nodal dissection

Chemotherapy



- Required in all cases
- Currently based on COG protocol
- VAC regimen forms the backbone
- Modified using VA or VI or Ifosfamide (certain protocols) to reduce Cyp exposure (2.2 gm/m2 to 1.2 gm/m2 to avoid infertility/ myelodysplasias / 2nd malignancy)
- Doxorubicin as IVADo is considered for very high-risk, node or fusion-positive cases (RMS 2005)
- Typically conc with RT (omitting Act-D)
- Initial intensive chemo is used for pharmacological debulking
- Maintenance chemo has now become std of care for high risk cases in future EpSSG studies

Radiotherapy

- Radiosensitive disease
- Proximity to organs-at-risk is often the challenge
- Indicated in all except completely resected (Gp I) fusion negative embryonal tumors (low risk)
- Int risk & fusion +ve cases need RT irrespective of resection
- EpSSG RMS 2005 has shown improved treatment results where 85% of localized high & very high- risk cases receive RT as primary local Rx
- No elective radiation to uninvolved nodal region (some consider it in fusion +ve Tm)
- Interstitial brachy to be used in selected cases

The treatment volumes

GTV

– All areas of gross disease (GTV 1 / GTV 50.4) [descriptive nomenclature with standard color coding)

– Areas of initial involvement with good response to chemo (GTV 2 / GTV 36). *Preserve initial records.*

CTV

- 10 mm expansion to respective GTVs & involved node chains for microscopic ds. Note: Mind anatomical spread / barriers, geometric expansions and pediatric dimensions

PTV

- 5 mm expansion to CTVs or as per dept infrastructure /protocol

RT Doses

36 Gy

- R0 unfavorable
- R1 favorable

41.4 Gy

R1 disease / minimal ds. Pathologically proven but grossly negative nodes

45 Gy

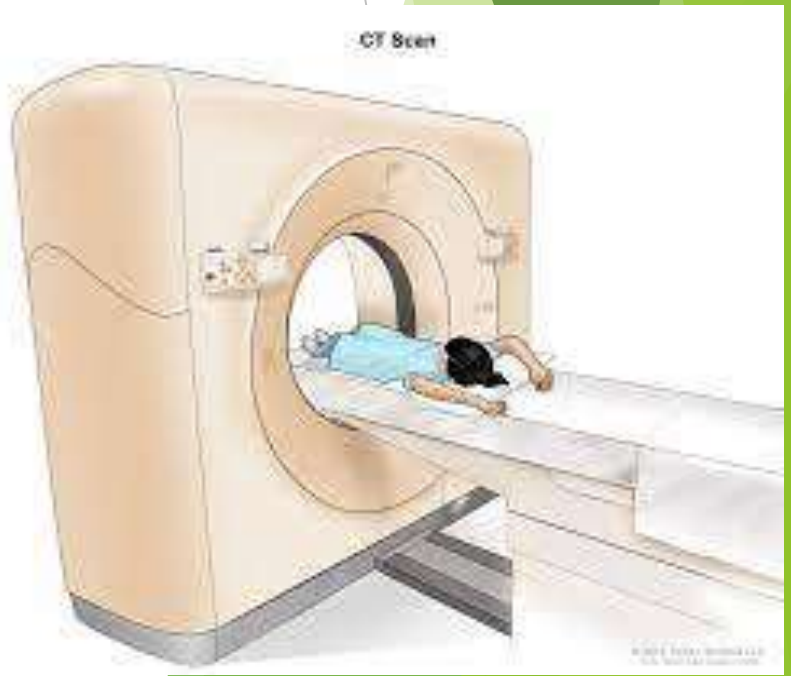
Gp III orbital ds after CR with chemo (supporte
no longer encouraged by COG)

50.4 Gy

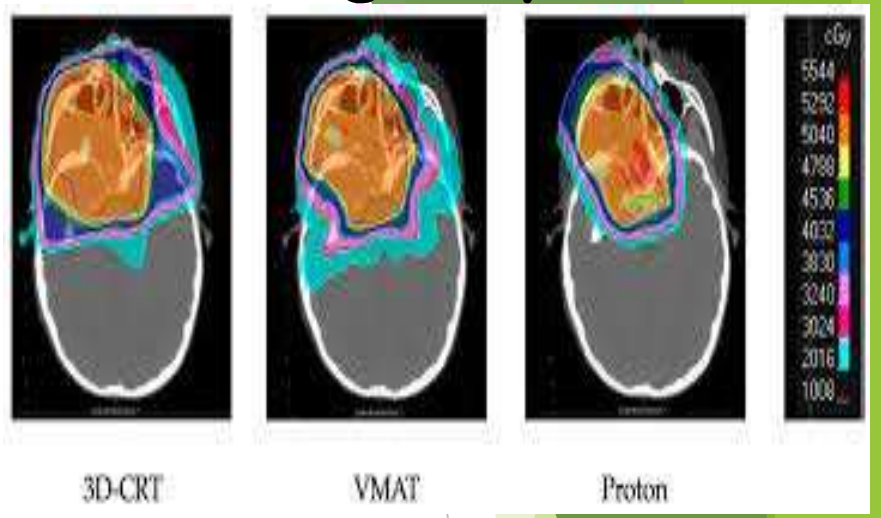
Gross residual (non-orbital disease)
Gross nodal ds

59.4 Gy

Dose escalations for gross Tm >5 cm (D9803)



- Efforts required to limit RT toxicities (severe/disabling sequale reported in 63% cases in 2015 study)
- The strategies include
    - IMRT, IMPT (Proton)
    - Brachytherapy
    - IGRT & adaptive planning
    - Cone-down boost



- 3DCRT / IMRT has shown superior coverage & tissue sparing with similar LC and OS
- Timing of RT is debatable.
- Typically after 12 wk (12-18 wk) after response evaluation after 3rd cycle with concurrent V (low-risk) or VC (Int risk)
- Considered earlier in symptomatic/ intracranial ds while beyond Wk 13 in well responding pts to further downstage ds for Sx or brachy

Head & Neck

Para-meningeal

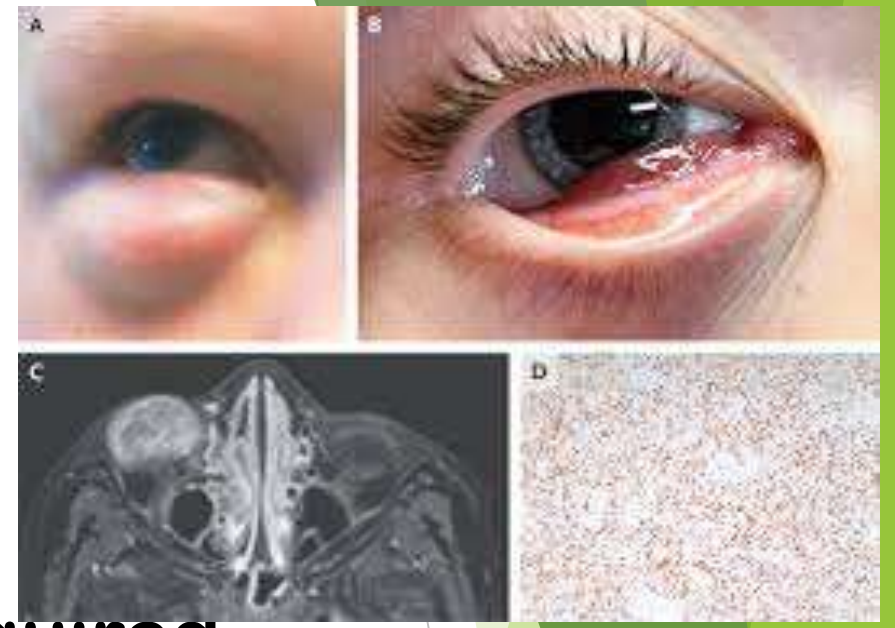
- NPx, nasal cavity, PNS, Middle ear, ITF, Pterygopalatine fossa.
- Propensity for base skull / intracranial / meningeal extn (40%).
- Commonest histology: Embryonal
- Incidence of LN involvement (IRS III): <25%
- Possibility of complete surgical excision (IRS III): <25%
- No surgery except for post RT residual Tm
- CSI and WBRT are not required unless CSF Positive / radiological meningeal involvement
- Early RT (within 2 week of diagnosis) gives better results (LF 18% vs 33%)

Head & Neck

Non-parameningeal

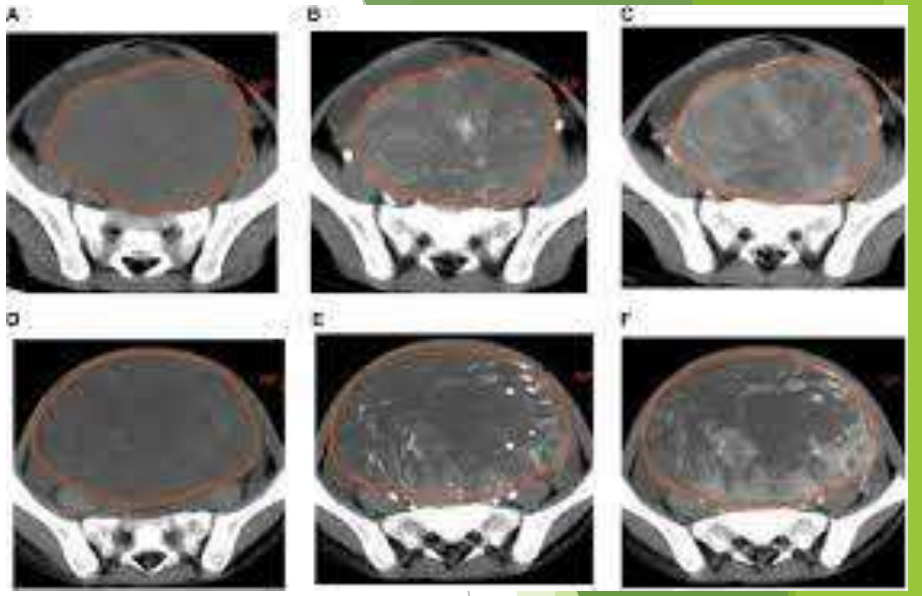
- Parotid, Oral cavity, Oropharynx, scalp, BM & Larynx.
- Better outcome
- Size <5 cm & age <11 yrs carry better prognosis
- Commonest histology: Embryonal (Buccal mucosa: Alveolar)
- More amenable to surgery
- Incidence of LN involvement (IRS III): <20%
- Elective nodal irradiation not recommended

Orbit



- Common subtype: Embryonal RMS
- Favorable site (3 yr PFS 90-100% IRS IV)
- Rarely metastasize
- Rx policy: Biopsy f/b by Chemo+ RT
- 2 chemo agents (VA) instead of three required
- SIOP studies tried delaying RT with poor LC
- Radiotherapy volume: gross Tm with 2 cm margin with shielding of lachrymal gland & duct, cornea, pituitary, chiasm
- Significant role of IMRT / IMPT
- Survival: Excellent (90-95% at 5 yrs (with CT + RT)

Pelvic RMS



- Urinary Bladder, prostate, Gynae
- Common histology: Embryonal

- Treatment Strategy (IRS III): Chemo f/b RT f/b surgery for residual disease with intent of bladder preservation
- Organ preservation achieved in >60% cases with 90% survival
- Vulvar / vaginal tm need biopsy f/b chemo & response assessment for local Rx (limited resection / RT) (SIOP protocols)
- LN involvement: 20% (Hypogastric & Ext. iliac)

Paratesticular

- Along spermatic cord; from intrascrotal area through the inguinal canal.
- Radical inguinal orchidectomy with high ligation of spermatic cord
- Biopsy avoidable
- Scrotal violation / involvement need scrotal resection / hemiscrotectomy and /or scrotal RT (with orchidopexy).
- LN involvement: 30% (paraaortic / renal hilar) with reduced survival (5-yr OS 69% vs 96%)
- For staging I/L RPLND for all boys > 10 yr of age and sampling only if radiological positive nodes in younger boys (<10 yrs)
- RPLN irradiation for positive LNs (41.4 Gy)
- Survival >80% at 5 yrs

Extremity

- Commonest subtype: Alveolar RMS
- LN involvement: 27-30%
- Rx policy: W/E + LN sampling f/b Chemo + RT
- No RT if R0 & N0 & </=5 cm tumor (primary surgery).
- RT used for all alveolar histology
- Entire LN region irradiated if sampling +ve
- Neo-adjuvant chemo-RT may be considered

Retroperitoneal:

- Common subtype: Alveolar RMS
- Rx policy: W/E + Chemo + RT
- Poor prognosis: 5 year survival - 40%

FOLLOW-UP

- Every 3 monthly for the 1st yr
- Every 4 to 6 monthly for the 2nd & 3rd yr
- 6 months to yearly thereafter
- Relevant History
- Physical exam (75% relapse are local)
- Lab evaluation: Thyroid, hormonal evaluation
- Radiological evaluation: 6 mo for 2 yrs & yearly for next 3 yrs.

  Watch for late sequalae like

  Dental & growth anomalies

  Audio-visual sequelae

  Psychological, hormonal & fertility disorders

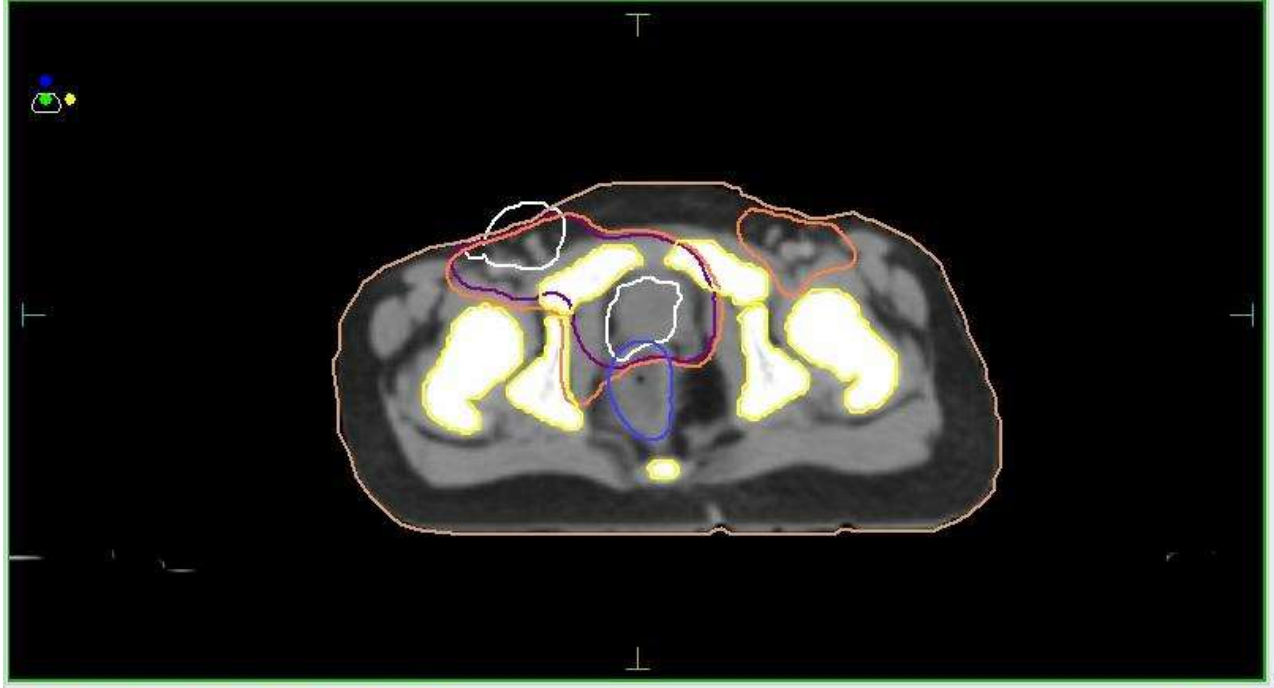
  Second malignancy etc

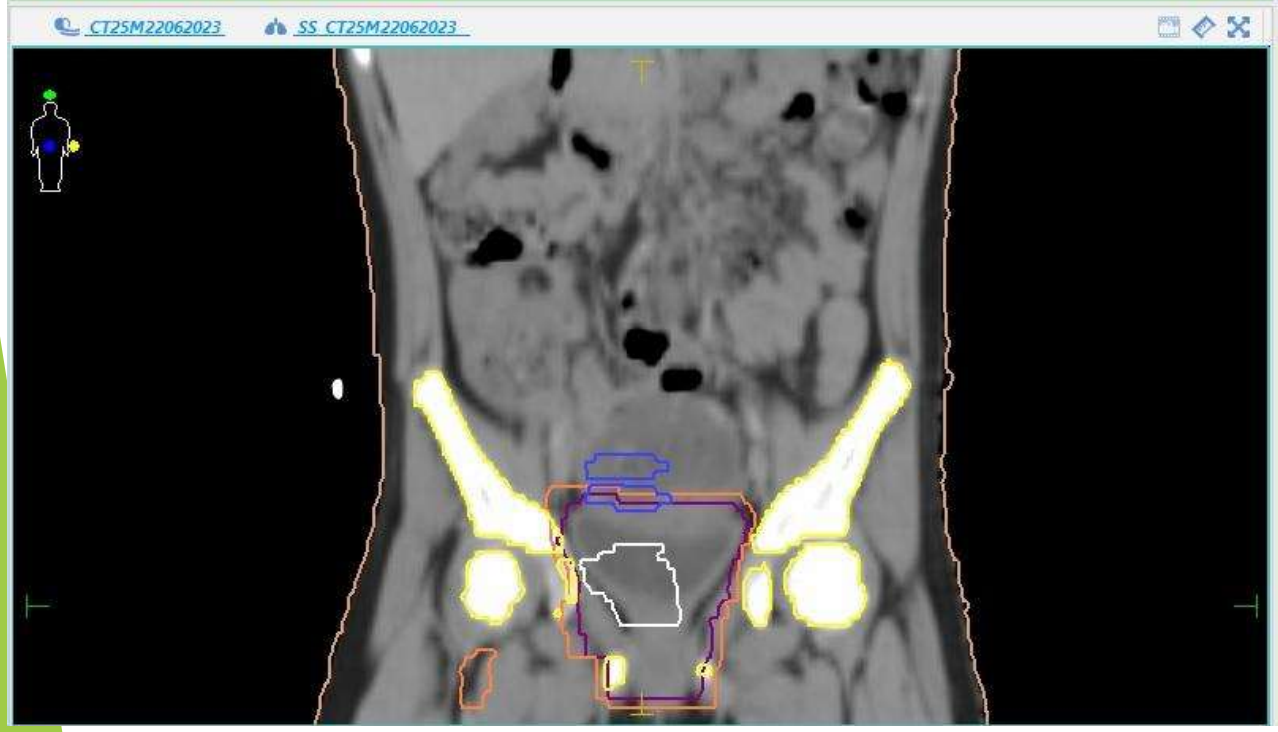
Live case

- 5 yr Female child
- P/W protruding mass from vulva
- Excision Bx: Embryonal RMS (Embryonal variant)
- Rt inguinal LN FNAC: Positive
- MRI Pelvis: 2.6 x 3 cm involving neck & lumen of bladder with gross wall thickening. Multiple B/L inguinal nodes
- PET: No metastatic lesion

Stage: III, IRSG Gp III, high risk

- Planned for radical CT+ RT & started on COG HR RMS protocol
- Check cystoscopy and PET showed good response with minimal gross residual at bladder & inguinal nodal site
- IGRT planned at week 12

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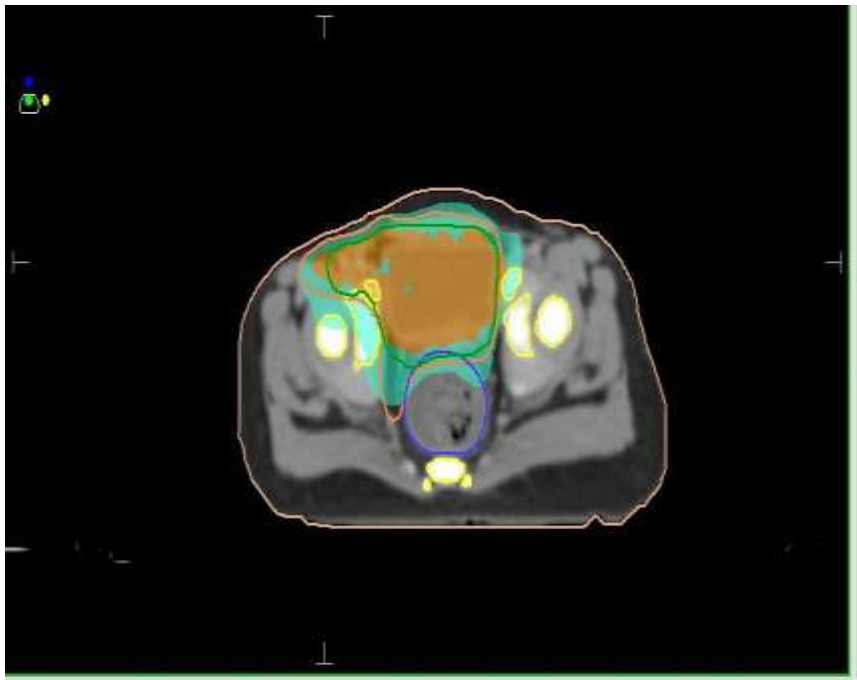

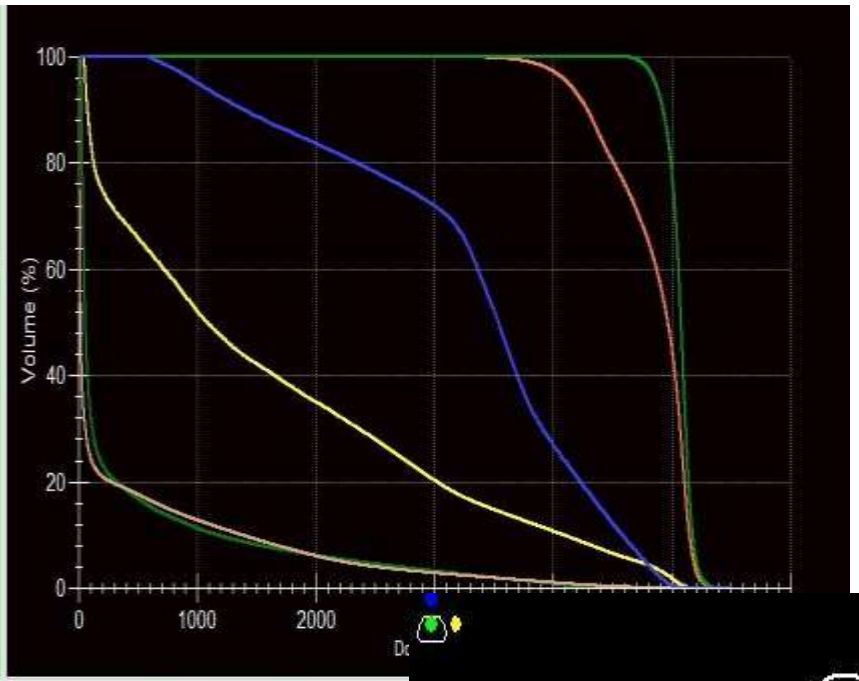
100
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60
40
20
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Volume (%)
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1000
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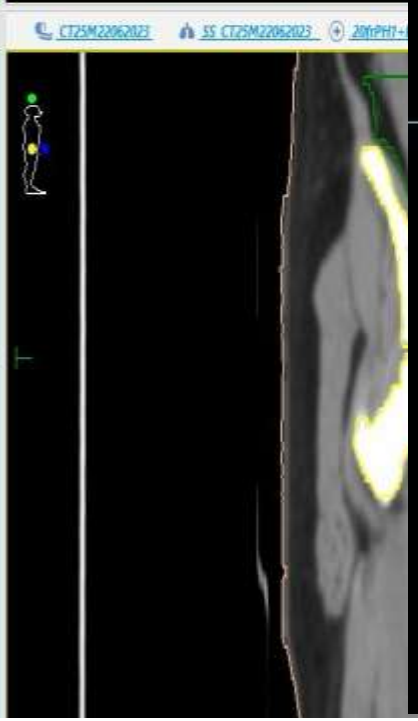
20IVPH1+PH2-PH3
Max Dose: 5498.2 cGy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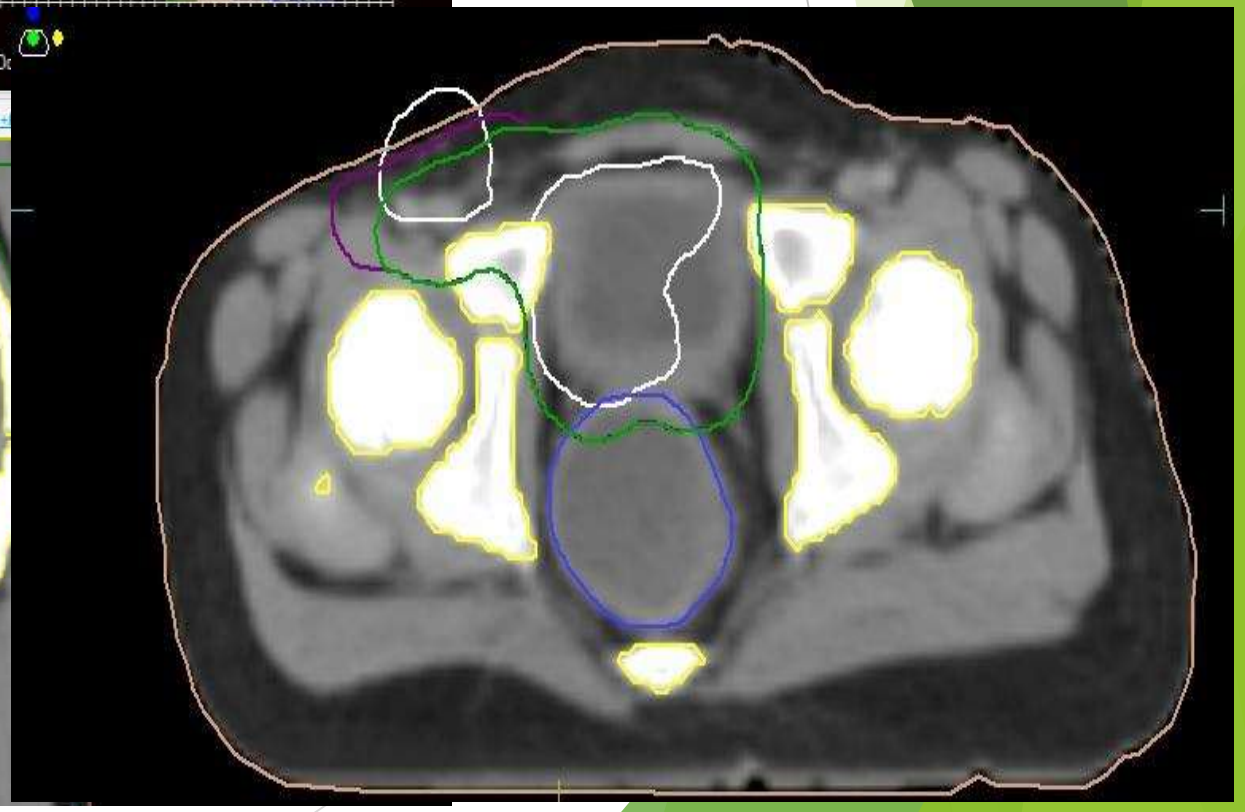

Take Home Message

- RMS is a complex disease requiring robust protocol based multi-disciplinary Mx
- Well organized collaborative approach has been the key to success in this disease
- Chemo-radiation is backbone of treatment

- Though well-defined risk-stratification & Rx protocols are available, more refinements including molecular classification are required
- Preventing treatment toxicities should be the next goal
- Discussion regarding future issues and expectation is imp

Thank You