MANAGEMENT OF RECURRENT AND METASTATIC CARCINOMA CERVIX

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INTRODUCTION

Cervical cancer

- The most common malignancy amongst Indian women.
- Constitutes 24% of all female malignancies and 70.7% of all gynecological malignancies.
- The leading cause of death by cancer in the developing countries.
- Common presentation is usually advance stage or metastatic disease.

INTRODUCTION.....

- Patients may develop pelvic recurrence, distant metastases, or a combination of both.
- In early stage disease, 10%-20% recurrence rate following primary surgery or radiotherapy.
- 70% recurrence rate in patients with nodal metastases and/or more locally advanced tumors.

PELVIC FAILURE & DISTANT METASTATIC RATES

Stage of Disease	Total Pelvic Failure rate	10-year actuarial Distant Metastatic Rate
IB	10%	16%
IIA	17%	31%
IIB	23%	26%
III	42%	39%
IVA	74%	75%

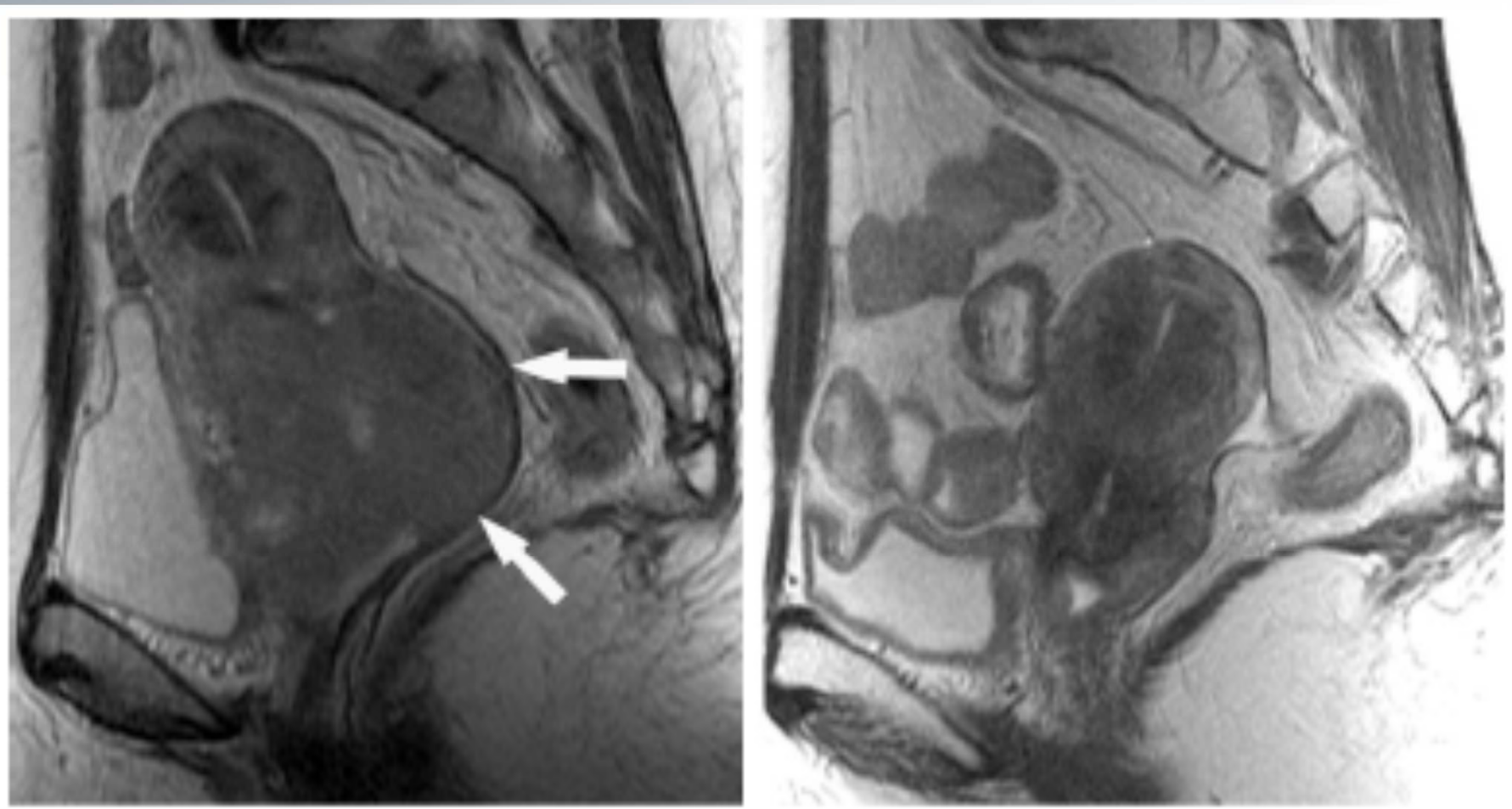
Perez et al

MOST FREQUENTLY OBSERVED METASTATIC SITES

- **Lung** (21%),
- **Bone metastases** (16%) predominantly involving
  - Lumbar spine
  - Thoracic spine
- **Para-aortic nodes** (11%),
- **Abdominal cavity** (8%),
- **Supraclavicular nodes** (7%).

Perez et al

COMPLETE RESPONSE AFTER RT



Before RT **4 months Post-RT**

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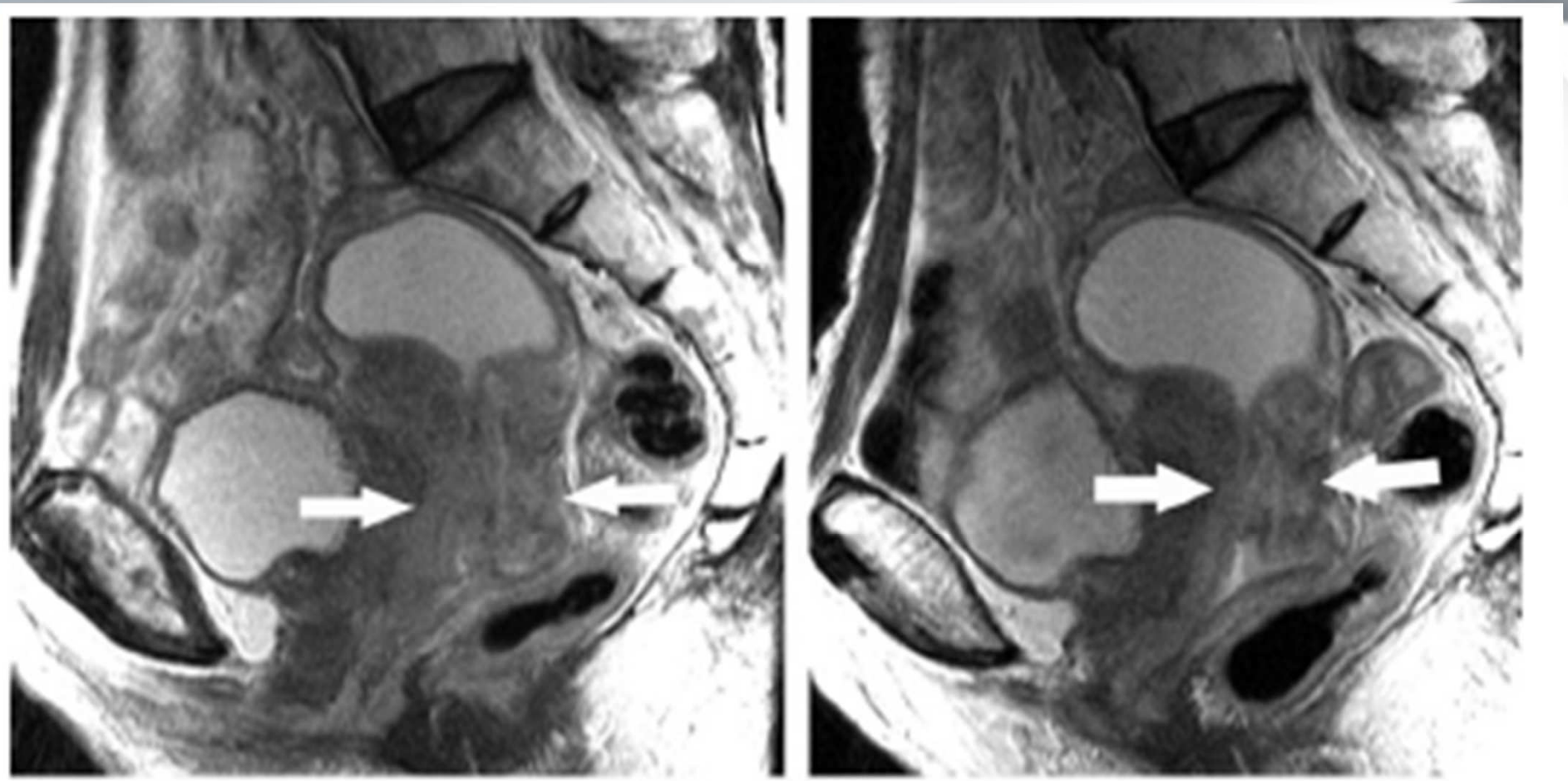
PERSISTENT DISEASE AFTER RT



Before RT **4 months Post-RT**

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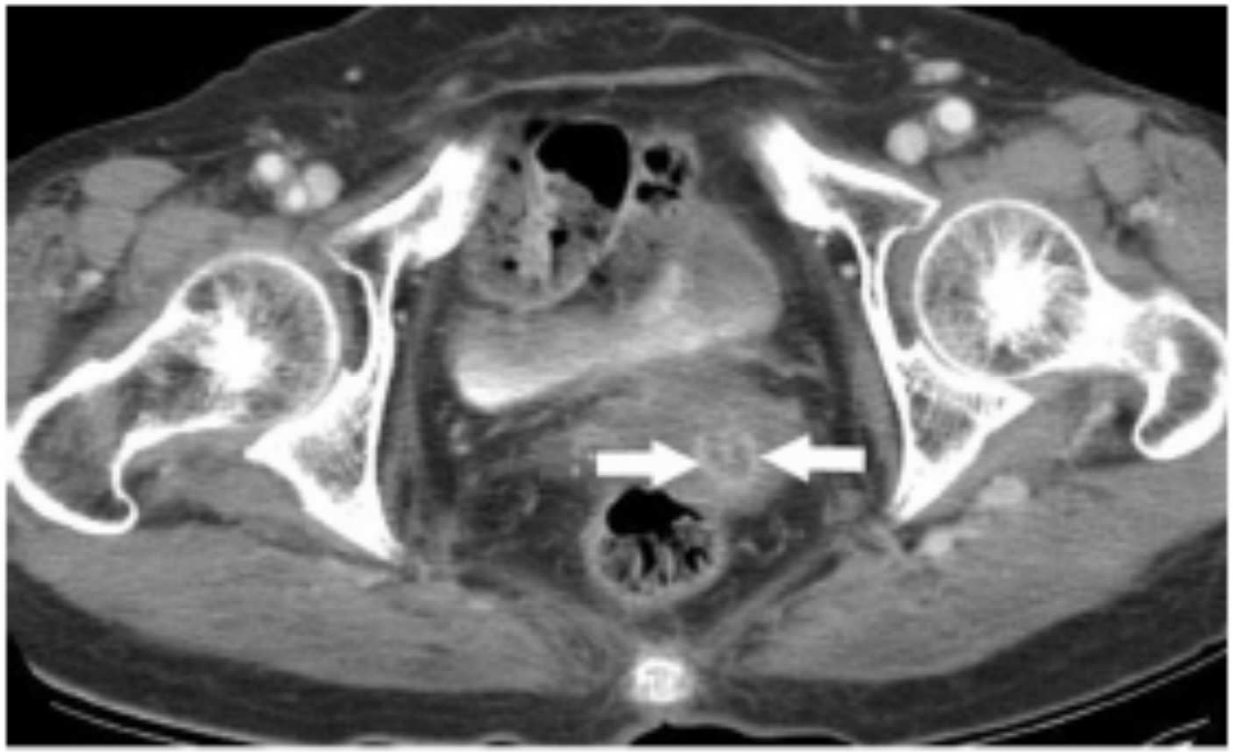
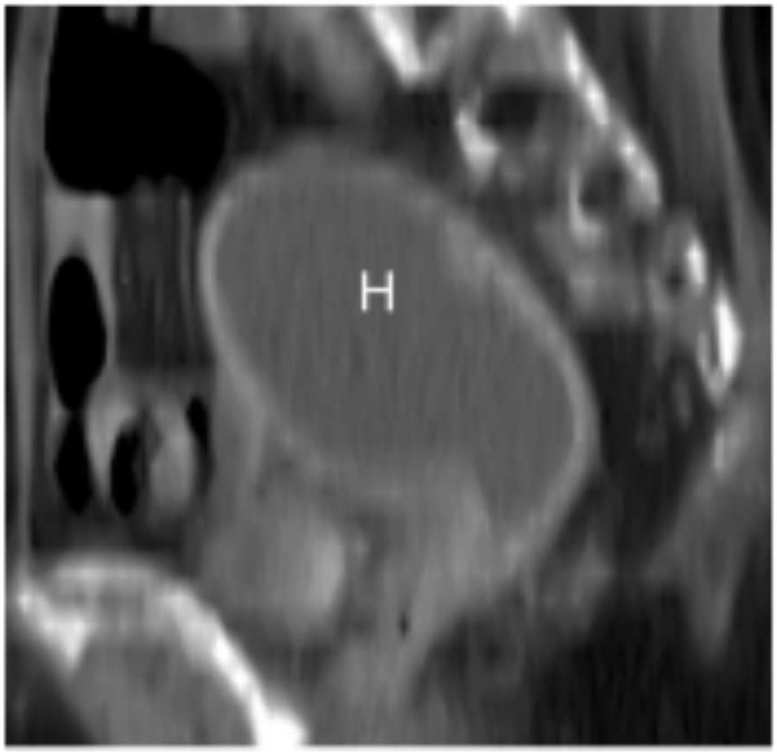
CENTRAL PELVIC RECURRENCE AFTER RT





Central Pelvic Recurrence 10 years after RT in a 78 years old Female

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CENTRAL PELVIC RECURRENCE AFTER SURGERY

Central Pelvic Recurrence after Surgery in a 46 years old Female

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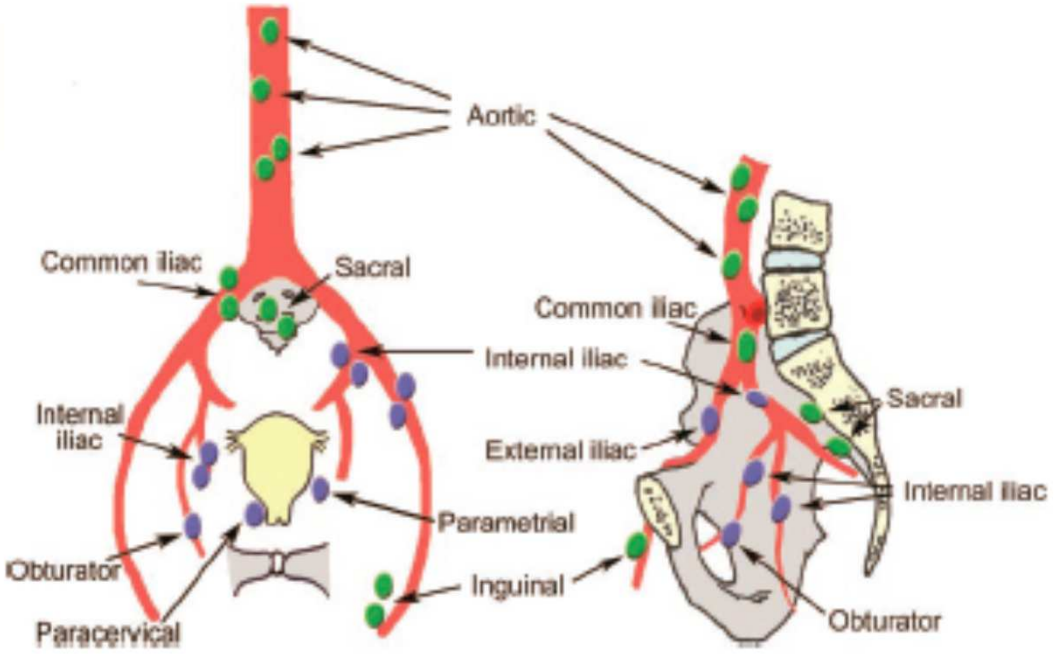
NODAL METASTASIS AFTER SURGERY/RT



Lymphatic pathways of spread

Obturator LN metastasis after Surgery

Para-aortic LN metastasis after RT

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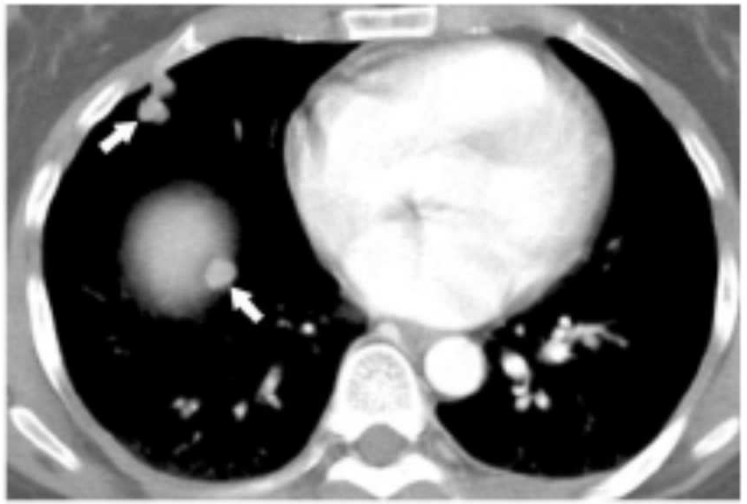
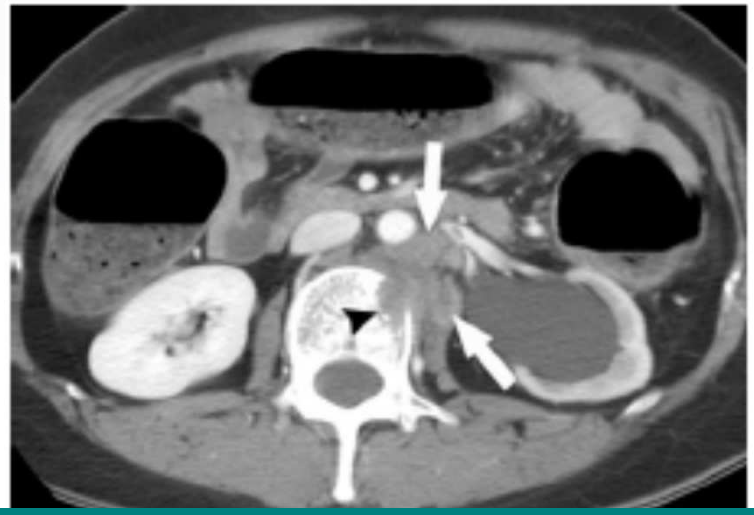
DISTANT METASTASIS AFTER RT



Liver metastasis **Lung metastasis**



Para-aortic metastasis destroying Lumbar vertebrae

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TREATMENT OPTIONS

Depend on:

- **Previous treatment received**
  - Radical Radiotherapy
  - Chemoradiation
  - Radical Surgery
- **Site of failure**
  - Local
  - Loco-regional
  - Local & Distant
- **General condition (KPS) of patient**
- **Most distressing symptom**

VARIOUS TREATMENT OPTIONS

For Recurrent Disease:

- Therapeutic Chemotherapy
- Pelvic Exenteration +/- Pre-operative chemotherapy
- Palliative Chemoradiation/Radiation
- Re-radiation

For Metastatic Disease

- Therapeutic Chemotherapy
- Palliative Radiation

ROLE OF THERAPEUTIC CHEMOTHERAPY

What is Therapeutic Chemotherapy?

- When a treatment modality is used upfront with a premise to eradicate a particular type of cancer, this constitutes the therapeutic treatment modality for that disease.
- In carcinoma cervix, radiation is a proven therapeutic modality of treatment.
- Currently, locally advanced disease is treated with concurrent cisplatin-based chemoradiation.
- But, in recurrent/residual or metastatic disease not amenable to surgery/radiation, Chemotherapy is the therapeutic modality of treatment

DRUGS USED IN THERAPEUTIC CHEMOTHERAPY

Drugs	Response Rates (%)
Alkylating Agents	
Cyclophosphamide	15%
Ifosfamide	22 %
Heavy Metal Complexes	
Cisplatin	23 %
Carboplatin	15 %
Anti-metabolites	
5-Fluorouracil	20 %
Methotrexate	18 %
Hydroxyurea	15 %

DRUGS USED IN THERAPEUTIC CHEMOTHERAPY...

Drugs	Response Rates (%)
Plant Alkaloids	
Vincristine	18 %
Antibiotics	
Doxorubicin	17 %
Newer Substances	
Irinotecan/Topotecan	17-19 %
Paclitaxel	20 %
Gemcitabine	8 %
Drug Combinations	
Ifosfamide/cisplatin	32-54 %
Paclitaxel/cisplatin	46 %
Cisplatin/gemcitabine	41 %

TRIALS OF THERAPEUTIC CHEMOTHERAPY

Author	No. of patients	Drugs used	Results	Conclusion
Sorbe et al; 1982	27	**Adriamycin, cyclophosphamide and vincristine,** +/- **5-fluorouracil**	**CR:** 3.7%; **PR:** 3.7%, **SD:** 48.1%	Poor RR, the regimens not recommended
Alberts et al; SWOG 1987	119	**Cisplatin +/- mitomycin-C, bleomycin and vincristine**	Poor RR & Survival when combination used	emphasis on development of more active agents
Brewer et al; 2006	32	28-day cycle of **Cis D1** & **Gemcitabine D1 & 8**	**PR:** 21.9%; **Med TTP:** 3.5 mths **Obj RR:** 22%	Modest activity of combination

TRIALS OF THERAPEUTIC CHEMOTHERAPY...

Author	No. of patients (n)	Drugs used	Results	Conclusion
Long III; et al 2006	183	**MVAC** vs **Cisplatin (C)** vs **Topotecan + Cisplatin (TC)**	4 deaths in 63 pts. treated with MVAC	RR, PFS & OS same with MVAC/TC vs C, only higher toxicity
Matulonis et al; 2006	28	28-day cycle of **Cis D1** & **Gem D1, 8, 15**	**RR:** 15%, **D:** 41%; **PD:**44% **MTD:** NR	28d regime tolerable toxicity; 21d cycle practical, higher dose intensity & RR

TRIALS OF THERAPEUTIC CHEMOTHERAPY...

Author	No. of patients	Drugs used	Results	Conclusion
Rose et al; 1999	47	**Cisplatin** and **Paclitaxel**	**Overall RR:** 46.3%; Response more in pts with ds. in non-irrad. sites	Recommendedt o be further evaluated in a phase III trial
Morris et al	73	**Cisplatin and Vinorelbine**	**Overall RR:** 30%	Mod activity, additional study in Ph. III setting justified
Dimopaulos et al; 2002	60	**Ifosfamide, Paclitaxel & Cisplatin** with G-CSF	**CR:** 19%; **PR:** 27%; **Objective RR:** 46% **Med PFS & OS:** 8.3 & 18.6 months	well tolerated & moderately active

QOL OUTCOME WITH CHEMOTHERAPY

- Assessment of Quality of Life (QOL) important in evaluating the full impact of cancer therapies on the overall well-being of patients.

- Especially important in advanced disease when one treatment offers a modest survival benefit over another at the expense of increased toxicity.

QOL OUTCOME WITH CHEMOTHERAPY…

McQuellon et al

Gynecol Oncol 2006;101:296-304

- To assess impact of **Cisplatin (C)** vs **Cisplatin + Paclitaxel (CP)** on overall QOL & Pain in recurrent/persistent or metastatic cervical cancer patients
- **264 patients**; August. 97 to March, 99
- CP arm significantly higher **RR & PFS**, no effect on OS
- Increased myelosuppresion in CP arm
- QOL drop-out higher for C (53%) vs CP (38%) ($p<0.05$)
- **No significant difference** in overall QOL scores between 2 arms

REASONS FOR POOR RESPONSE TO THERAPEUTIC CHEMOTHERAPY

- Chemotherapy used more frequently upfront in Chemoradiation Protocols
- Prior Radiotherapy/Surgery leads to poor vascularity
- Poor tolerability to Chemotherapy due to
  - Compromised Renal Functions
  - Compromised Bone Marrow reserves
  - Poor General Condition (Low KPS)
  - Affordability

ROLE OF EXENTERATIVE SURGERY

- Patients who receive primary RT or CRT & have pelvic disease can be offered an ultra radical procedure such as **Pelvic Exenteration**
- Procedure currently limited to patients with small and central tumors
- May offer 5-year survival for up to 50% of patients
- Although some efforts to extend the exenterative procedures to patients with higher disease burdens by use of intraoperative radiation, laterally extended pelvic exenteration, or pre-exenterative chemotherapy none of these options are widely used.

PRE-EXENTERATIVE CHEMOTHERAPY

Lopez-Graniel et al

BMC Cancer 2005,5:118-27

- 17 patients with recurrent or persistent disease & no evidence of systemic disease, not considered to be candidates for pelvic exenteration because of the extent of pelvic tumor, received 3-courses of platinum-based chemotherapy.
- 9 patients responded to chemotherapy (evaluated by bimanual examination) and underwent Pelvic Exenteration.
- **Pathological CR:** 4
- 8 patients did not respond and were not subjected to surgery.
- 1 patient died due to exenteration complications.
- **Median follow up:** 11 months,
- **Median survival:** Whole group: 11 months; 3 months in the non-operated and 32 months in those subjected to exenteration.
- **Concluded that** Pre-exenterative chemotherapy is an alternative for patients who are not candidates for exenteration because of the extent of the pelvic disease. But its place in the management of recurrent disease needs to be investigated in randomized studies

ROLE OF RE-RADIATION

Factors to be kept in mind before selecting for Re-radiation:

- Site of Recurrence: Central Pelvic
- Previous Modality of Radiation used:
  - External RT
  - Brachytherapy
- Previous Dose & Fractionation
- Time duration between initial treatment & Recurrence
- Availability of 3DCRT/IMRT facilities

GUIDELINES FOR TREATMENT - 1

Local recurrence following Prior Radiotherapy	Level of Evidence
Selected patients with resectable central recurrence should be considered for Pelvic Exenteration	III

GUIDELINES FOR TREATMENT - 2

Local recurrence of Cervical Cancer following Surgery	Level of Evidence
Radiation therapy is indicated in patients with locally recurrent cervical cancer following radical surgery	III
Concurrent chemotherapy with either 5-Fluorouracil and/or Cisplatin with radiation should be considered and may improve outcome	III

GUIDELINES FOR TREATMENT – 2...

Local recurrence of Cervical Cancer following Surgery	Level of Evidence
Pelvic exenteration may be an alternative (particularly if a fistula is present) to Radical Radiotherapy and Concurrent Chemotherapy in selected patients without pelvic side wall involvement.	III

GUIDELINES FOR TREATMENT - 3

Systemic Chemotherapy in Metastatic Cervical Cancer	Level of Evidence
Cisplatin is the single most active agent to treat cervical cancer	II
The response rate (31%) with 100 mg/m^2 Cisplatin is higher than that with 50 mg/m^2 (21%), but is not associated with any improvement in Progression-free or Overall survival.	II

GUIDELINES FOR TREATMENT – 3...

Systemic Chemotherapy in Metastatic Cervical Cancer	Level of Evidence
Cisplatin-based combination therapy is associated with higher response rate & longer PFS than single-agent Cisplatin therapy, but there is no difference in OS	II
Response rates to chemotherapy are consistently higher in patients with good performance status and Extrapelvic disease and low in Previously Irradiated sites	III
The Impact of Chemotherapy on Palliation and Survival is unclear	III

OUTCOME OF PATIENTS WITH RECURRENT CERVICAL CANCER

Recurrence	Treatment	Outcome
Central	Pelvic Exenteration	**5-year survival:** 30%-60%
Local recurrence following Surgery	Chemotherapy & Radiotherapy	**5-year survival:** 6%-77%
Distant Metastases	Cisplatin-based Chemotherapy	**Response:** 17-50%; **Median survival:** 4-9 months

CONCLUSION

- In patients with recurrent/residual or metastatic carcinoma cervix, there is an option of using Therapeutic Chemotherapy/ Surgery/ Re-radiation depending upon previous treatment modality used.

- Patient selection requires sound clinical judgement with likely outcome to be kept in mind.

- Assessment of QOL remains a basic parameter before selecting such patients for any salvage treatment protocols.

Thank You