Radiation Therapy for Anal Canal Malignancies – EBRT and Brachytherapy

Dr S. Alex. A Prasad MD

Chennai Cancer Care Hospital

Billroth Hospitals

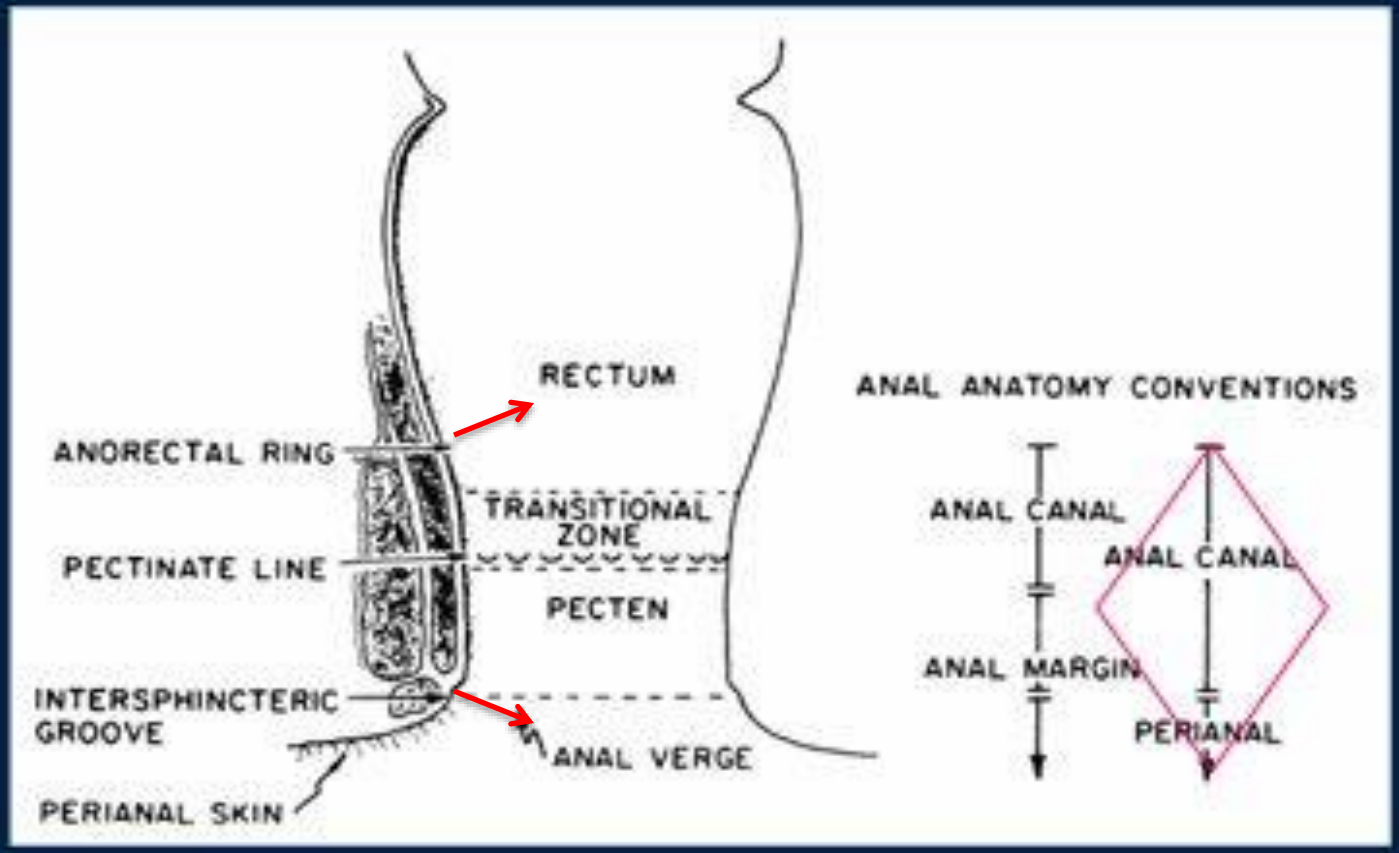
Westminster Healthcare

Chennai

Anal Cancer Facts

- 1-2% of all large bowel cancers, 4% of anorectal cancers
- Estimated 4,660 new cases in 2006
  - (1,910 - male; 2,750 - female)
- 75-80% are squamous cell cancers
- 15% are adenocarcinomas
- Keratinizing and low-grade squamous morphology associated with anal margin cancers
- 70% are stage I or II on presentation
- 20% have nodes on presentation; 30-63% will have nodes on surgery
- Cancers involving the anal canal below the dentate line have a higher risk of inguinal nodes

First Decision: Is This an Anal Margin or an Anal Canal Cancer?



Staging of Anal Canal Cancers

Tx	Cannot assess primary
T0	No evidence
Tis	Carcinoma in situ
T1	<2 cm
T2	2-5 cm
T3	>5 cm
T4	Adjacent organ invasion

Nx	Cannot assess
N0	No nodes
N1	Perirectal nodes
N2	Unilateral internal iliac and/or inguinal
N3	Perirectal & inguinal; Bilateral internal iliac and/or inguinal

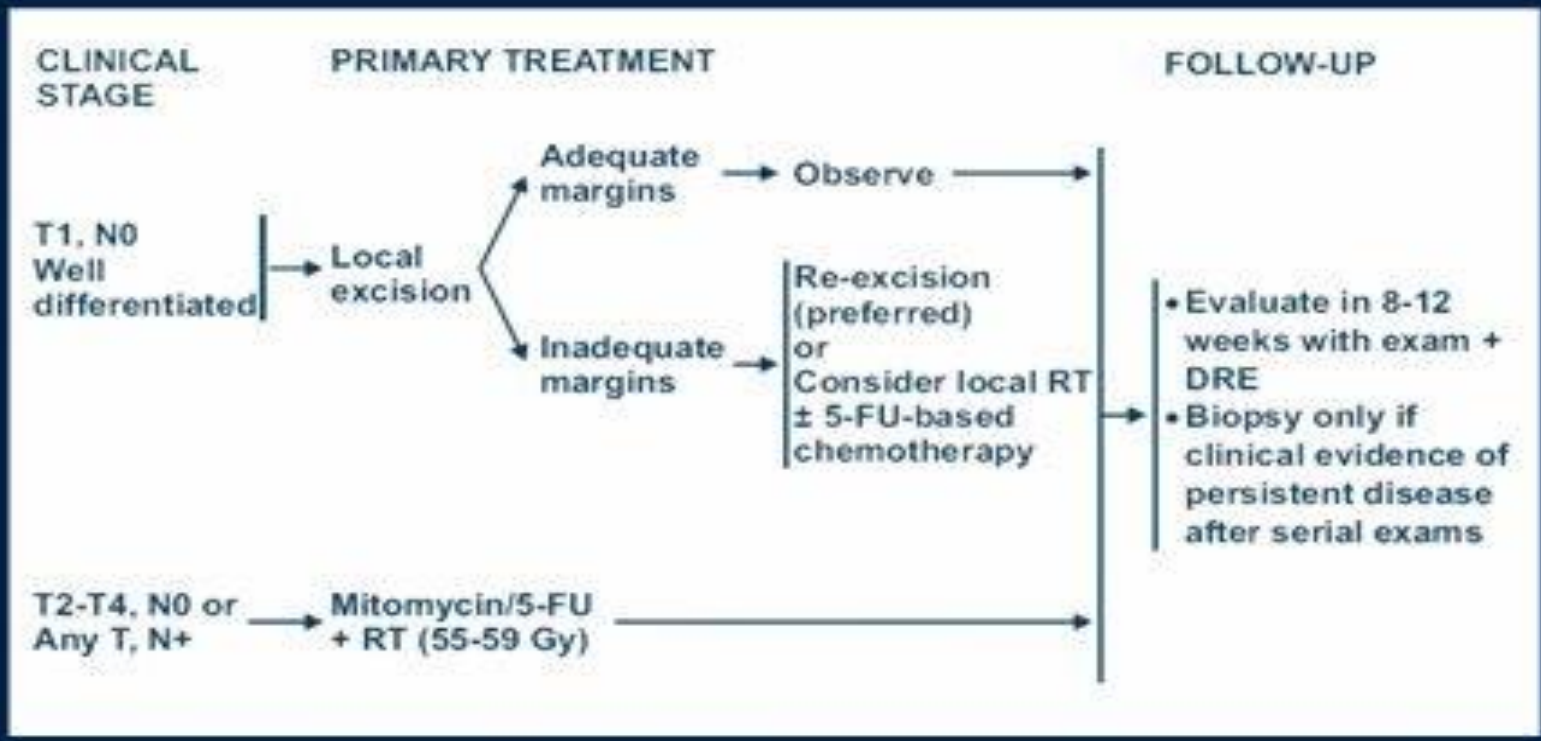
M0	No distant mets
M1	Distant mets

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	T1-4	N2	M0
	T1-4	N3	M0

National Comprehensive Cancer Network®

Anal Margin Cancer

Clinical Practice Guidelines in Oncology – v.1.2007



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Anal Canal Cancer

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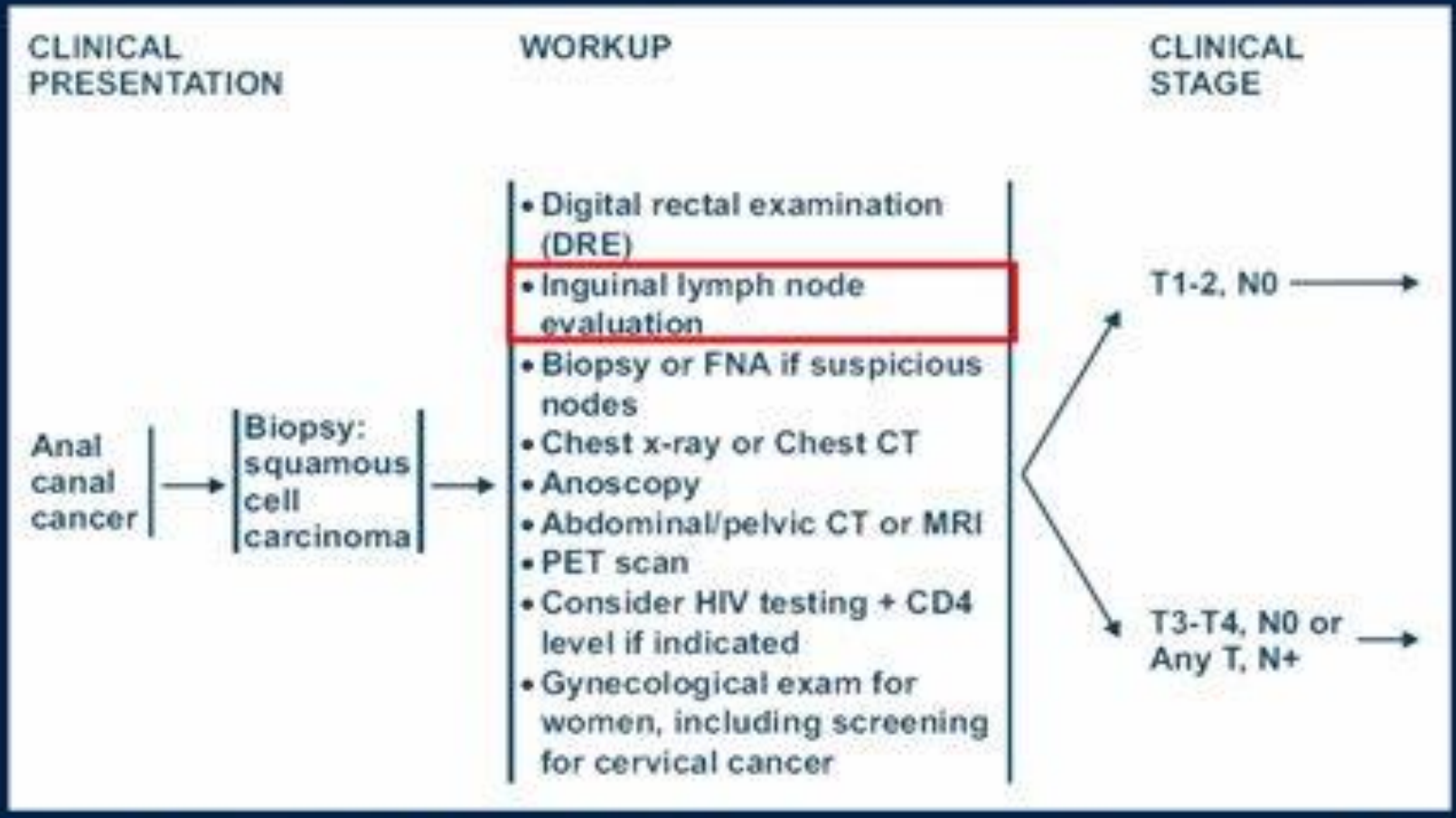

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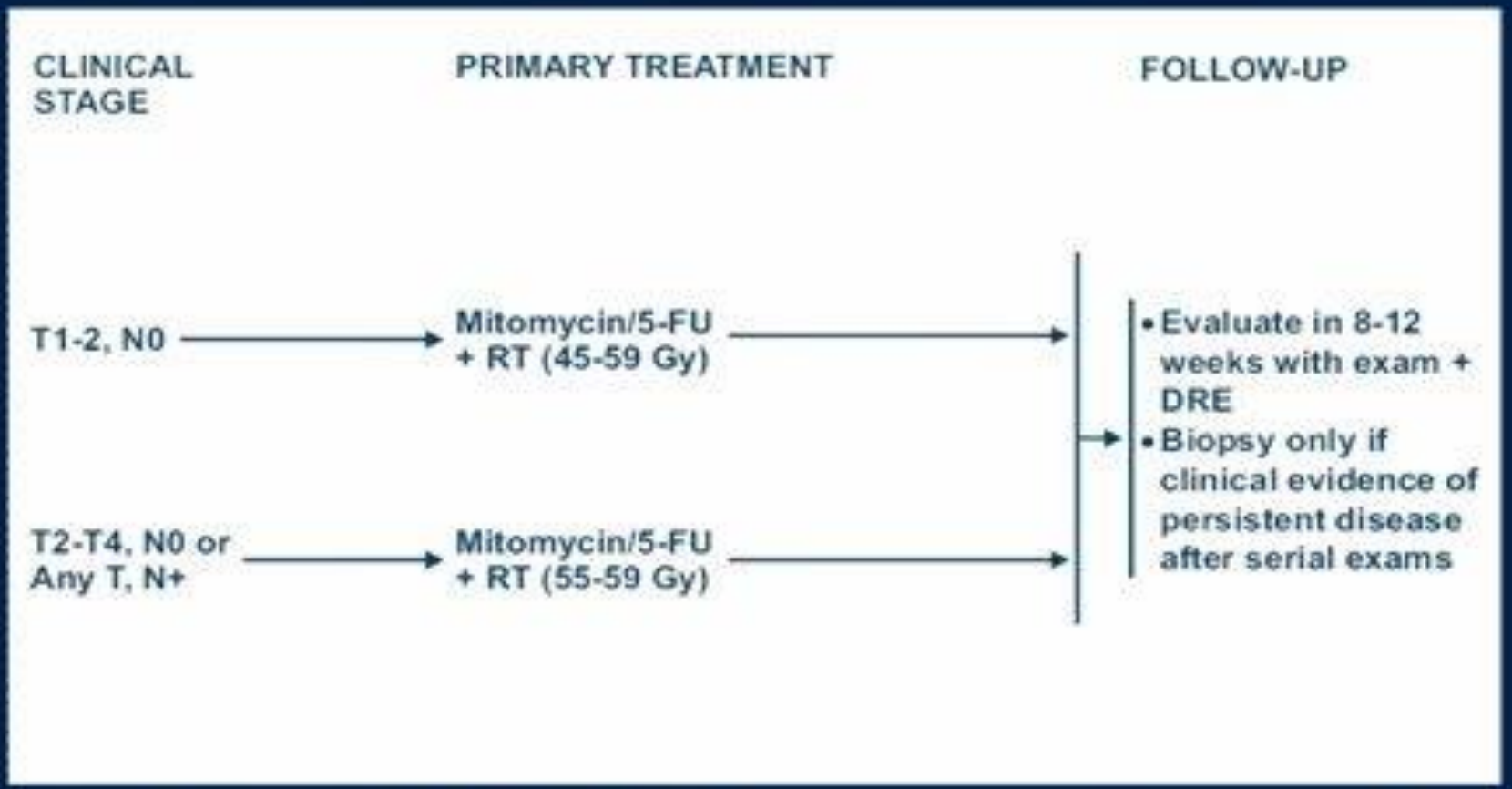
Anal Canal Cancer

Clinical Practice Guidelines in Oncology – v.1.2007



NCCN Guidelines

- What's new in the guidelines?
  - PET scans
- What's missing?
  - Rectal ultrasound

Utility of Other Tests

- PET scans
  - Nagle – 14 patients
    - Sensitivity = 50%, specificity = 72%, predictive value positive (PVP) = 50%, predictive value negative = 80%
  - Trautman – 24 patients
    - 24% had disease not seen on CT scans
  - Cotter – 41 patients
    - 20% had groin nodes negative on CT scan
    - 23% had groin nodes negative on physical examination
    - 91% had primary tumor identified vs. 59% on CT scan
- Ultrasound
  - Giovanni – 146 patients
    - Advantage was in determining complete response

Local Excision Alone for Anal Canal Cancer

	Cases	5-yr survival	Locoregional recurrence
Hardcastle & Bussey	38	63%	34%
Greehall et al	42	62%	48%
Bornan et al	17	88%	18%

Surgical Treatment

- Abdominoperineal resection
  - Local failures range from 27-47%
  - 5-year survivals range from 50-70%

Radiation Therapy Alone for Anal Cancer

- External beam
- External beam + brachytherapy
- Brachytherapy

Radiation Therapy Alone for Anal Cancer

- External beam alone
  - Mayo clinic
    - 18 patients with T1and 2 cancers
    - 100% local control with doses of 67 Gy
    - 94% 5-yr survival
    - Little toxicity
  - PMH
    - 50 Gy/20 fractions
    - 81% control for T1/2
    - 65% control for T3/4
  - *RT alone may be sufficient for small low-grade lesions*

Radiation Therapy Alone for Anal Cancer

- Brachytherapy and external beam
  - Papillon
    - 45-50 Gy & Ir-192
    - Anal preservation = 61%
    - 5-yr survival = 65%
    - 20% tissue necrosis
  - Sandhu
    - External beam & Ir-192
    - CR - 90% T1 & 78% T2
    - Local failure 22%
    - No significant toxicity

Historical Context

- The disease was managed surgically until 1970s
  - With APR, requiring removal of sigmoid rectum, rectum, anal canal leaving stoma and requiring permanent colostomy
- Early studies of neoadjuvant chemoradiation followed by surgery revealed high rates of pCR and led to primary chemoradiation
- Optimal parameters for chemoradiation are now under investigation.

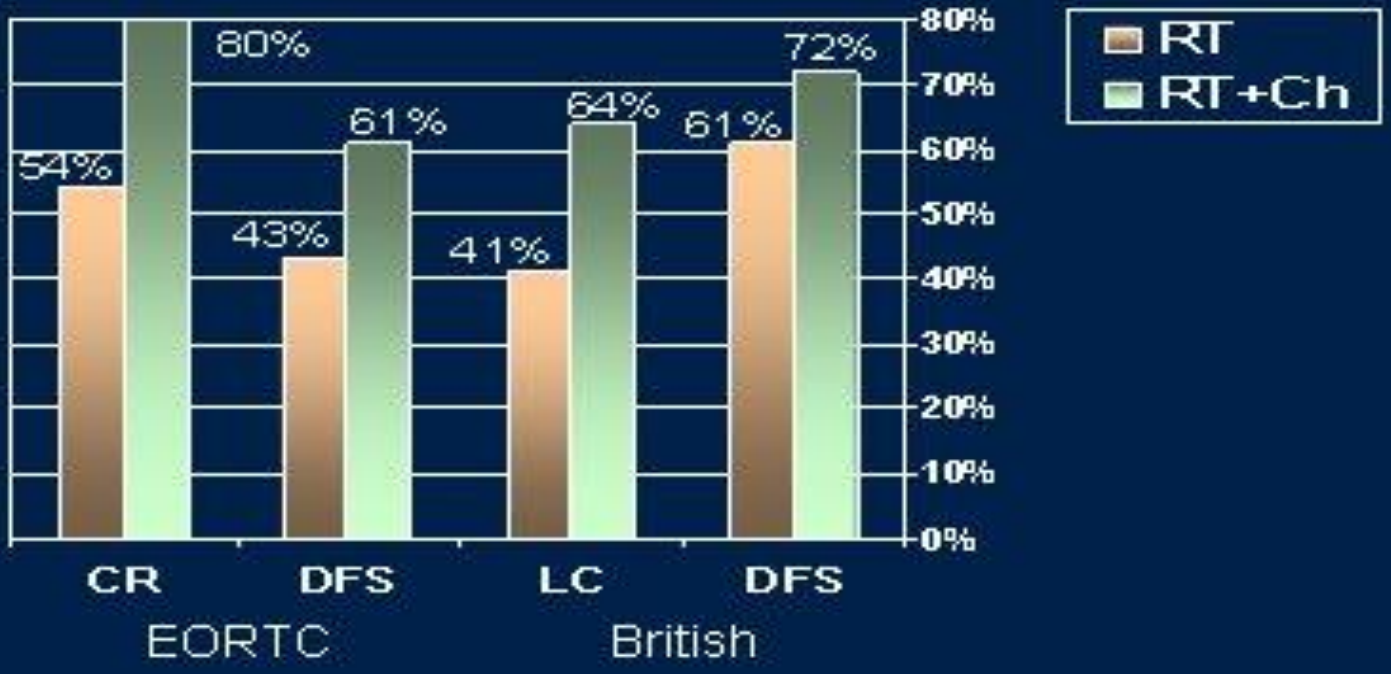
History of Combination Radiochemotherapy (Nigro et al)

Combination Therapy – Wayne State

- 1970s - investigators preoperatively administered fluorouracil and mitomycin combined with RT to decrease the surgical failure rate:
  - 5-FU (1000 mg/m^2 per day, days 1-4 & 29-32)
  - Mitomycin (10 to 15 mg/m^2, day 1 only)
  - Intermediate dose RT (30 Gy in 15 fractions via AP/PA fields to the true pelvis, medial inguinal LN, and primary lesion with margin)
- Surprisingly, first 3 patients had no residual tumor when abdominoperineal resection was performed
- Suggested it might be possible to cure anal cancer without permanent colostomy

Nigro ND, et al. *Dis Colon Rectum*. 1974;17:354-356.

Anal Carcinoma: Is Combined Modality Treatment FU and Mitomycin Better Than RT Alone?

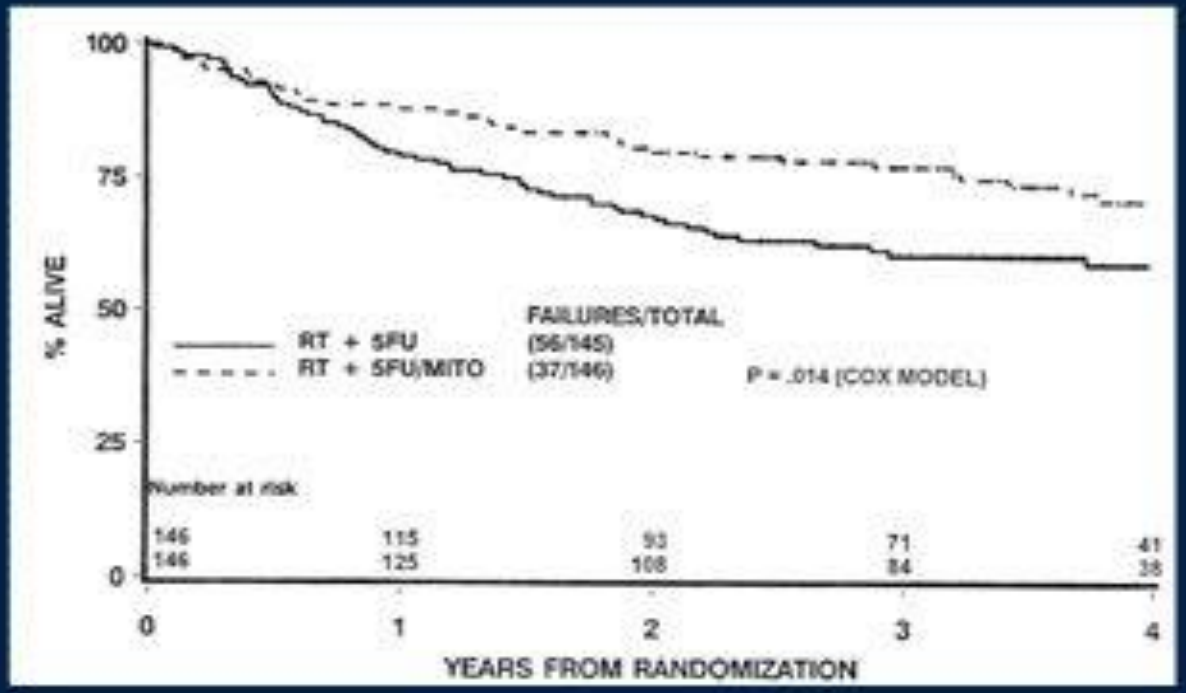


Bartelink H, et al. *J Clin Oncol*. 1997;15:2040-2049.
UKCCCR Anal Cancer Trial Working Party. *Lancet*. 1996;348:1049-1054.

Additional Questions

- Is FU without mitomycin C sufficient?
- Are there alternative chemotherapy combinations?
- What dose of radiation?

Combined Modality Trial for Anal Carcinoma



- 50% of local failures were salvaged
- In MMC arm, 27% LFs in T3-4 cancers 27% and 17% in T1-2
- Local failures of N positive patients was 41%

Is the Mitomycin C Necessary? Results of RTOG 87-04/ECOG 1289

- 30.6 Gy to pelvis + boost to 50.4 Gy
- 5-FU 1000 mg/m^2/d × 4 wk 1 and 5
- Mitomycin C: 10 mg/m^2 × 2
- 9 Gy with 5-FU & cisplatin for salvage after positive biopsy

	FU+MMC	FU
+ biopsy at 6 weeks	7%	15%
5-year colostomy rate	11%	22%
DFS	67%	50%
Toxicity	23%	7%

Flam M, et al. *J Clin Oncol*. 1996;14:2527-2539.

- 5FU + MMC + RT vs 5FU+ Cisplatin + RT

Anal Cancer: RTOG 98-11

- Arm 1: Concurrent 5-FU + mitomycin C & XRT
  - Fu: 1000 mg/m²/d on days 1-4 and 29-32
  - Mito C: 10 mg/m² iv bolus days 1 and 29
- Arm 2: 5-FU + cisplatin × 2 cycles pre-XRT and current with XRT
  - FU: 1000 mg/m²/d on days 1-4, 29-32, 57-60, and 85-88
  - Cisplatin 75 iv over 60 min days 1, 29, 57, 85
  - XRT starts day 57

RTOG 98-11

3-year	Mitomycin	Cisplatin
Disease-free survival	68%	62%
Survival	84%	76%
Locoregional failure	25%	38%
Colostomy rate	10%	17%

Ajani JA, et al. *J Clin Oncol*. 2006;24(18S pt 1). Abstract 4009.

Radiation Dose

- Earlier trials were 30 Gy
  - May be sufficient for microscopic cancer
- MGH retrospective study (< or >54 Gy)
  - 84% vs. 47% 5-year survival
  - 77% vs. 61% local control
- MDAH
  - >55 Gy better response and control
- Night
  - >55 Gy better disease control

Outcomes

	RTOG 0529 (2 years)	RTOG 9811 MMC/5-FU (5 year)	RTOG 9811 Cisplatin (5 year)
Disease-Free Survival	95%	~60%	~55%
Overall Survival	94%	75%	70%
Colostomy-Free Survival	90%	90%	81%
Distant Met-Free Survival	92%	85%	81%

Acute Toxicity with dose-painted IMRT

	Gr 0(%)	Gr 1(%)	Gr 2(%)	Gr 3(%)	Gr 4(%)
Derm	2 (5)	10 (23)	27 (63)	2 (5)	2 (5)
GI	9 (21)	13 (30)	18 (42)	3 (7)	0
Heme	4 (9)	4 (9)	9 (21)	21 (49)	5 (12)
GU	32 (74)	6 (14)	2 (5)	2 (5)	1 (2)

NCI CTCAE v3.0

Improved toxicity versus historical controls of RTOG 98-11 with promising outcomes.

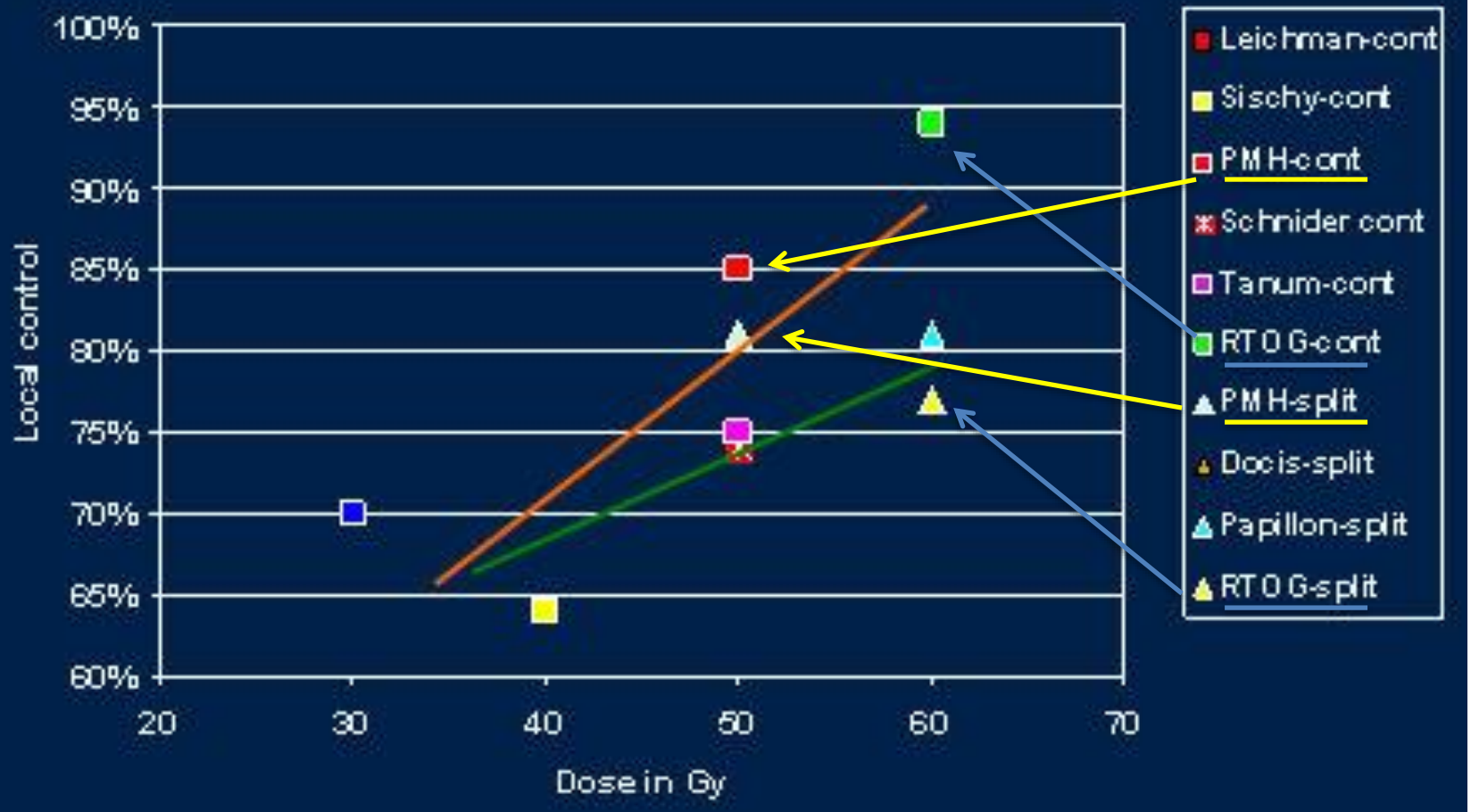
DON'T BIOPSY FOR 12 WEEKS, EVEN IF RESIDUAL DISEASE!!! ONLY FOR PROGRESSIVE DISEASE.

There can be continued regression for up to 12 weeks.

Cummings etal IJROBP 1991.

An additional 9Gy with 5FU/MMC can be delivered to residual disease for salvage prior to APR (RTOG 87-04)

Local Control vs. Dose and Splits in Treatment



Adenocarcinoma of Anal Canal

	Epidermoid	Adenocarcinoma
Local recurrence	18%	54%
Distant mets	10%	66%

Adenocarcinoma of Anal Canal

- MDAH series: RT + 5-FU with mitomycin C or cisplatin

	Epidermoid	Adenocarcinoma
# patients	92	16
Median age	57 years	58 years
Female	77%	38%
N positive	30%	31%
T3/4 Local Control	75%	56%

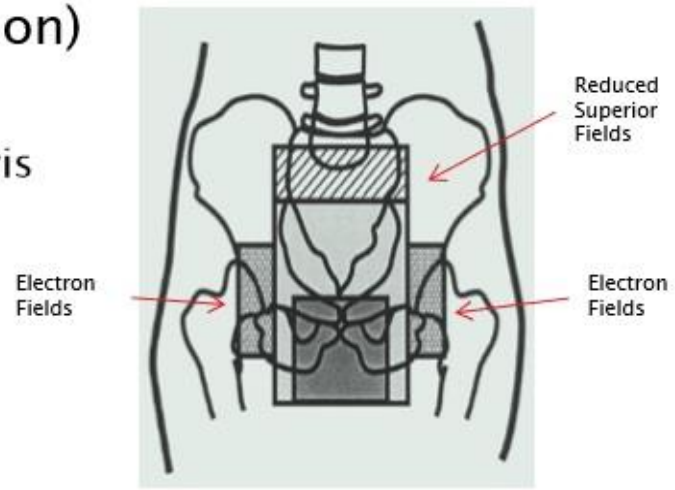
Papagikos M, et al. *Int J Radiat Oncol Biol Phys*. 2003;55:669-678.

Radiation Therapy portals

Treatment (RTOG 98-11)

Conformational Radiation Therapy (3D-CRT)

- 45 Gy in 25 fractions (180cGy/fraction)
- Initial Field (AP-PA) to 3060 cGy
  - Include anus, perineum, inguinal LNs, pelvis
  - Superior border – L5-S1
  - Inferior border – 2.5cm below tumor
  - Lateral – inguinal LNs
- Reduced Field (AP-PA) to 4500 cGy
  - Superior border – SI Joints (at 3060 cGy)
  - Lateral – Reduced fields to come off the inguinal LNs (at 3600 cGy)



CT Simulation

If treating with 3D CRT

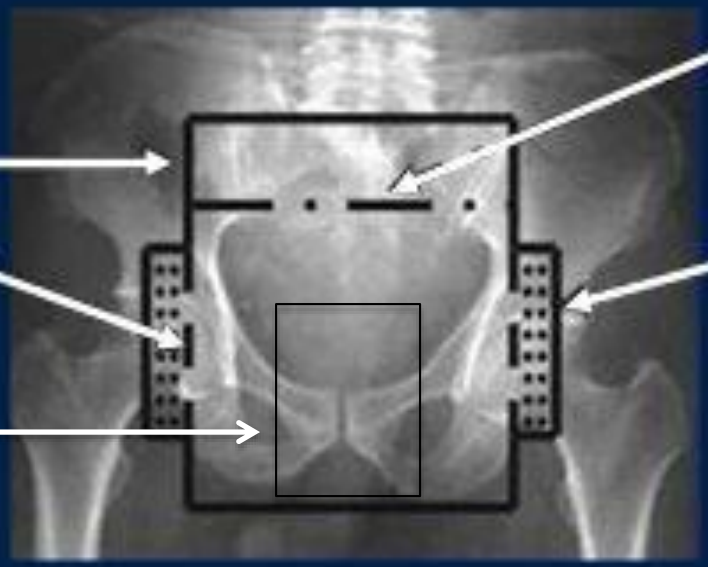
- Head-first supine position (can't boost inguinals with electrons in prone position)
- Immobilize legs in frog-leg position to minimize skin folds.
- Marker at anal verge, marker on palpable or biopsy-proven adenopathy.
- Consider bubble wrap in skin folds for large patient to minimize autobolus effect.

If treating with IMRT

- Can position supine as above or prone in select patients,
- important to choose most reproducible setup
- (IMRT allows the risk of geographic miss if patient moves.)
- Place markers similarly.

Typical Radiation Fields

- Typical RT fields from RTOG 9811 guidelines



Do You Need to Treat Inguinal Nodes? Prophylactic

- Adds to toxicity of treatment
- Trans-Tasman Radiation Oncology Group trial 99-02 closed early due to high rate of nodal relapse

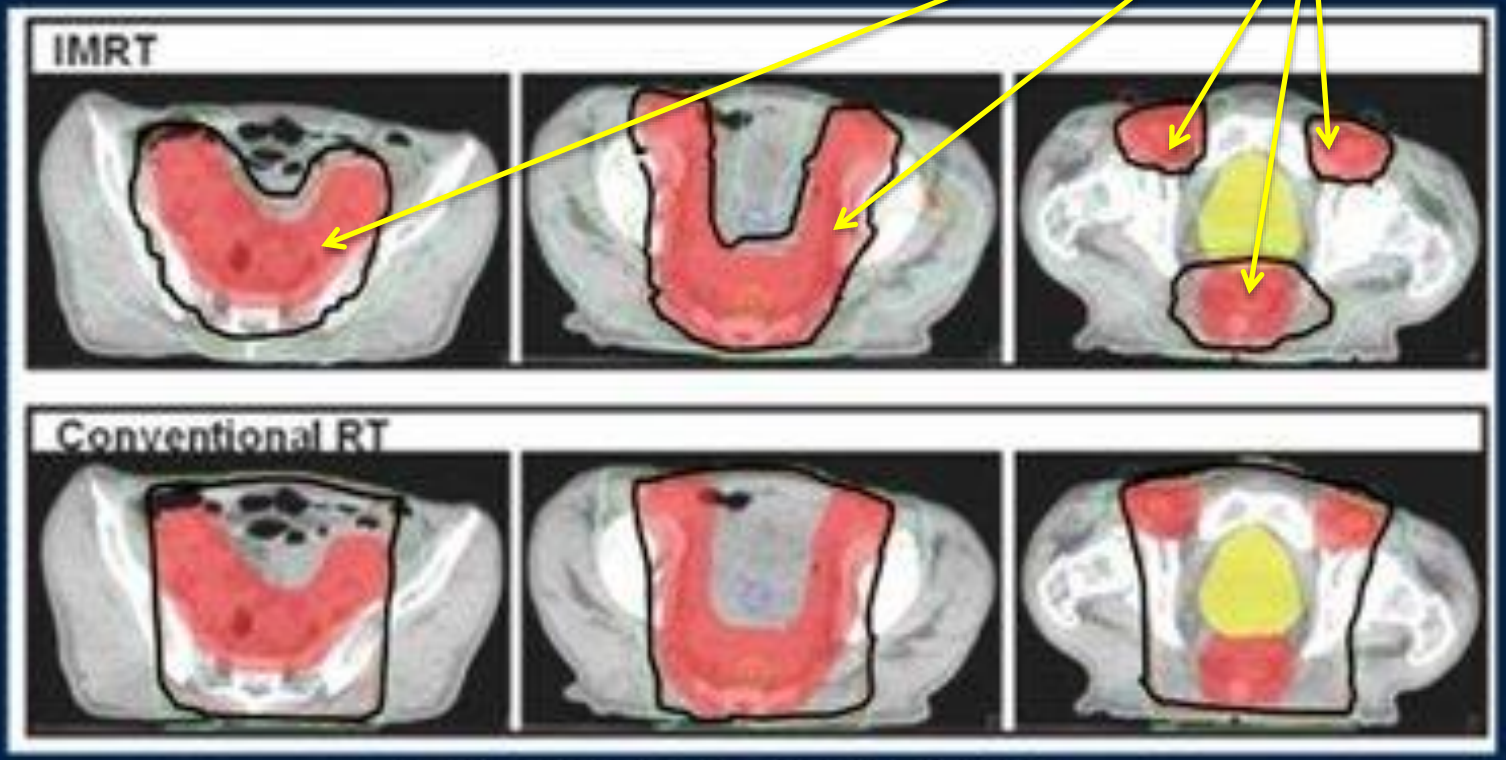
- Toxicities of Radiochemotherapy

Typical Toxicities

- ~ 50% require some treatment break
- 2.7% of patients had grade 5 toxicity in the FU-mitomycin vs. 0.7% with FU alone
- 1/3 of patients develop acute anoproctitis and dermatitis with 30 Gy; 1/2 to 2/3 with 54-60 Gy
- RT with brachytherapy have up to 20% colostomy rates for toxicity alone
- Late side effects: urgency, frequency of defecation chronic perineal dermatitis, dyspareunia, and impotence

Advantages of Newer Technology

Comparison of large pelvic field treated to 30.6 Gy with IMRT vs. conventional RT



The planning target volume is shaded red.

Treatment (RTOG 0529)

Radiation Therapy

- ◦ Tumor receives 5400 cGy in 30 fx
- ◦ Uninvolved LNs receives 4500 cGy in 30 fx
- ◦ Involved LN <3cm receives 5040 cGy in 28 fx
- ◦ Involved LN >3cm receives 5400 cGy in 30 fx

Chemotherapy

- ◦ 5-FU infusions days 1 - 4 and days 29 – 32 (1000mg/m2)
- ◦ Mitomycin C on day 1 and 29 (10mg/m2)

DVH and Dose Distribution

Femoral Heads

Bladder

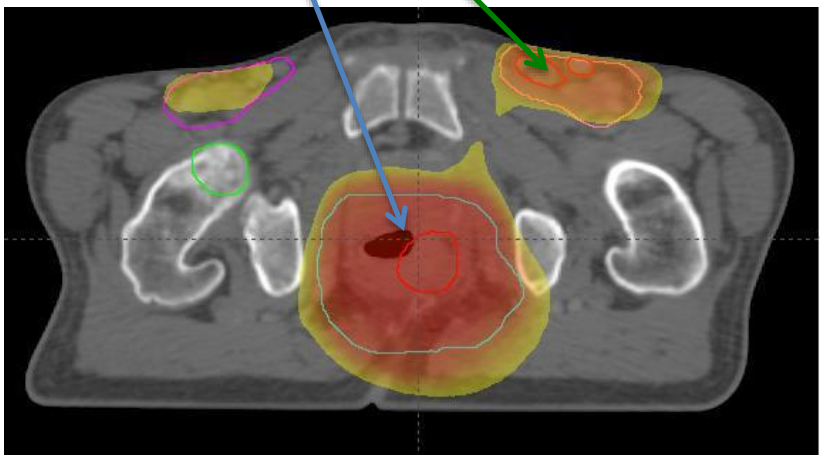
PTV 5400

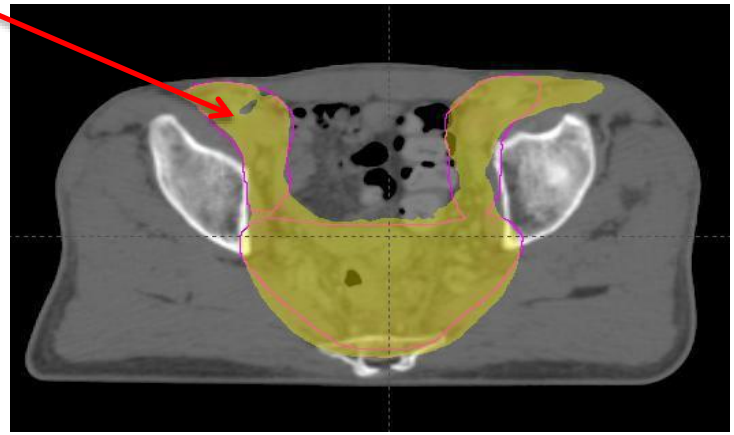
PTV 5040

PTV 4500

Dose Color Wash:

- 4500 cGy
- 5040 cGy
- 5400 cGy





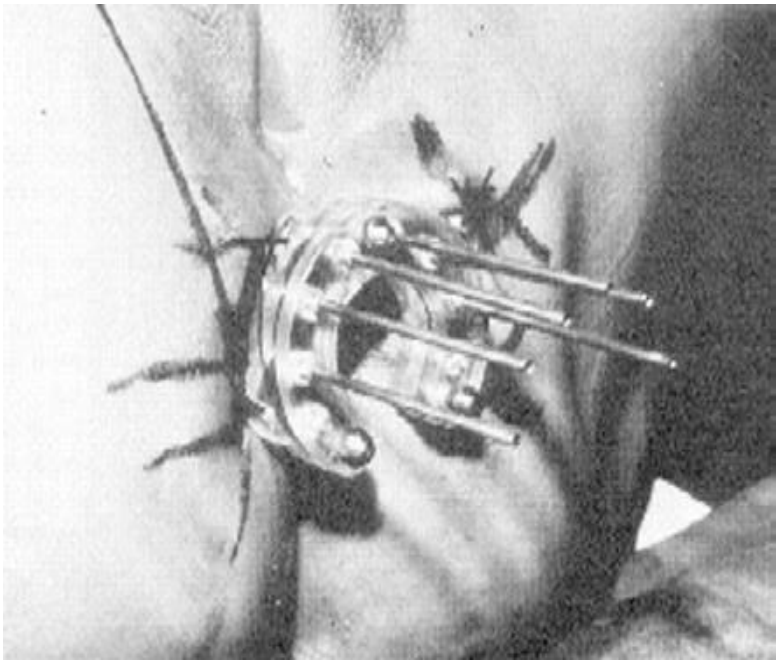
Anal Canal Treatment – Toxicity IMRT vs 3DCRT

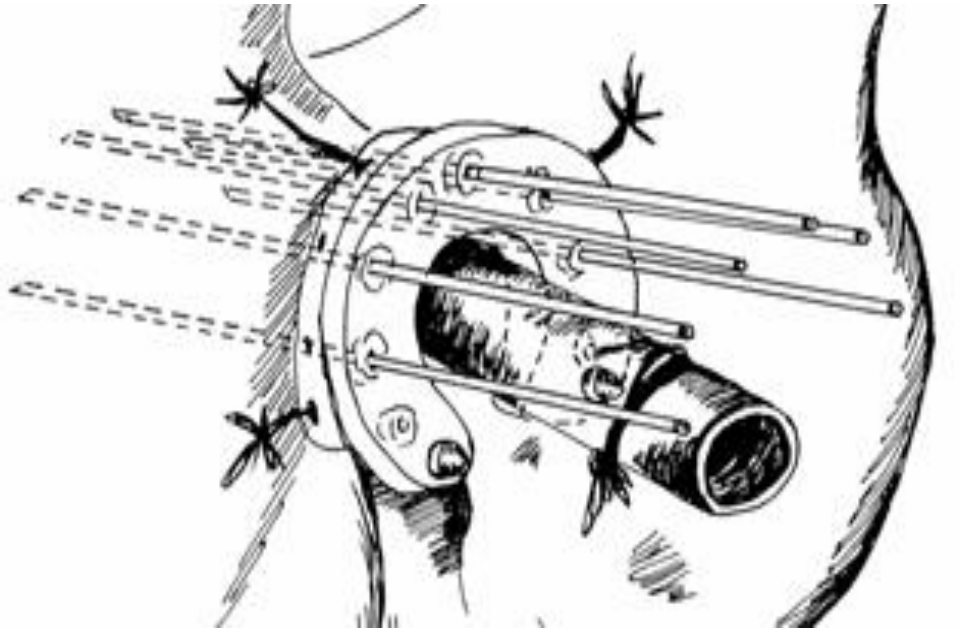
- Analysis of Saarilathi et al compared IMRT vs 3DCRT
- IMRT Group – 13/22 pts Grade 2 GI Toxicity
- 3DCRT Group – 22/39 pts Grade 2 GI Toxicity and 12/39 pts Grade 3 GI Toxicity

In 3DCRT Group

- Grade 3 & 4 radio dermatitis was the predominant acute toxicity
- Grade 3 & 4 late toxicity was anal stenosis in 3.8%, chronic ulceration in 2.5% and anal incontinence in 8.8%

Anal Canal Brachytherapy





Anal Canal Brachytherapy - Technique

- Guide needle technique – Papillon's template, crescent moon shaped, open shape allows palpating finger in anus during needle insertion
- Blind end steel guide needles – 15 cm long, 1.7 to 1.9 mm diameter
- Other templates can also be used – needle entry points marked on perineal skin with anal dilator in place

- Goal – anal canal sphincter preservation, Reduce long term toxicity grade
- Limitations – Lesion involving more than the ½ circumference, larger tumors involving >5cm longitudinally

Anal canal brachytherapy - procedure

- Perineal shaving & Cleansing enemas, GA or Spinal, Lithotomy position, foleys catheter
- Meticulous exam under Anaesthesia, template sewn firmly against perineum, orientation around anus determined by perineal sector to be implanted
- Blind end needles passed thro the holes in template into anal wall – while a finger is in rectum to avoid rectal lumen penetration
- Needles inserted about 5mm beneath anorectal mucosa
- Rectovaginal septum – tough to penetrate

Anal Canal Brachytherapy

- A typical implant contains 5 needles spaced at 1cm, 5 to 7 cm long for a T1-2 tumor
- 6 to 7 needles, 7 to 8 cm long for a small T3 tumor
- All needles are positioned at same depth & needles should not retract on leg extension
- Anal dilator or Obturator – must, to hold the involved mucosa against needles & healthy tissues away - limiting dose to them

Anal canal brachytherapy – Target volume

- Clinical Exam under anaesthesia -Tattoo tumor margins on the distal perineal skin and place metal clips at the proximal end of gross disease
- Target volume – Palpable & Visible tumor before any treatment with a margin of at least 5 mm

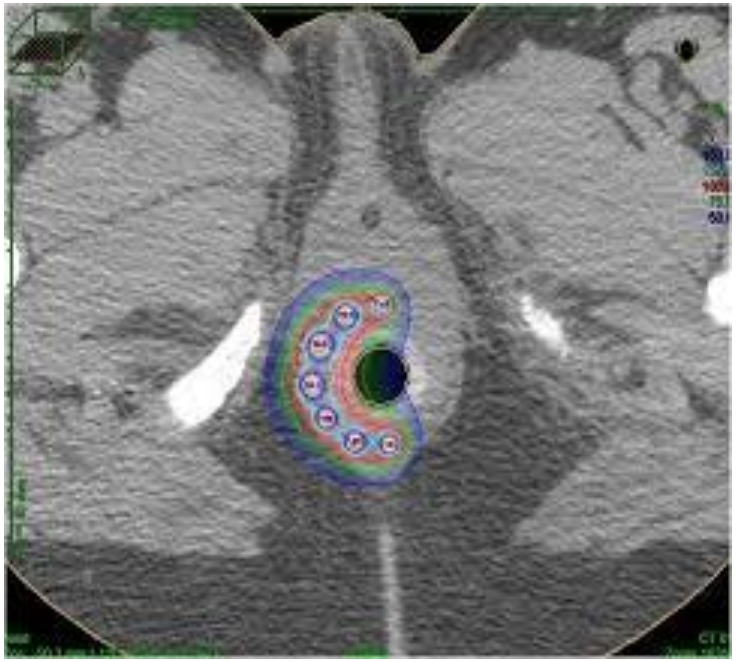
1. Compressive Elastic tape dressing – 10 cm broad horizontal part with central slit to hold template against perineum

2. Two long strips from Right and left iliac crest to opp buttock

3. Followed by 2nd horizontal strip with central slit and final vertical inverted Y SHAPED closing tape

Anal canal brachytherapy dose

Isodose distribution



- > 55 Gy better response rates
- Total dose to anorectal mucosa should not exceed 60 -65 Gy [includes EBRT & Brachytherapy]
- HDR – 4-6Gy / fraction X 2
- LDR /PDR – 15 -20 Gy
- Number of fractions depend on EBRT dose
- Preferred time interval between EBRT & BT – 2 to 3 weeks [Lyon 5-6 weeks]

Anal Canal Brachytherapy – LDR Papillon et al

- 221 patients with epidermoid anal cancer
- 2 months after Radiochemotherapy [5FU & MMC – Interstitial BT boost 15 to 20 Gy in 15 to 28 hours
- Anal preservation rate – 61%, 5 year survival rate – 65%, Anal sphincter function preservation >90%

Anal Canal Brachytherapy – Results Brachytherapy(LDR) Vs EBRT Boost

- CORS-03 Study – EBRT 45Gy & EBRT Boost mean dose 18.3 Gy [range 8 to 25 Gy] vs LDR Boost 17.4Gy [range 10 to 25 Gy]
- Local Recurrence rate at 5 years – 33% for EBRT arm & 12% for BT arm

Nodal involvement – not a contraindication to BT Boost. Subgroup analysis of CORS-03 trial

- 99 pts with LN mets [67 perirectal, 32 iliac and or inguinal]
- 45 Gy EBRT – EBRT Boost 18.8Gy [range 14 to 25 Gy] – BT Boost 17.2 Gy [range 10 to 25 Gy]
- 5 year Cumulative Rate of Local Recurrence (CRLR)11% in BT arm & 32% in EBRT arm
- 5 year Overall Survival rate (OS) 75.5% in BT arm & 73.3% in EBRT arm

Anal Canal Brachytherapy Boost Results
HDR - Brachytherapy

- The Kiel Group – 50 pts treated with TRUS Guided HDR BT Boost
- EBRT Dose – 45Gy, BT Dose 2x4 Gy within 6 weeks of EBRT
- 5 year Overall Survival (OS) was 74%
  Disease Specific Survival (DSS) was 82%
  Complete Response (CR) rate was 92%

Updated analysis from Kiel – 104 pts, mean follow up 10 years.

- LC - Local control rate was 89% (93/104)
- OS – Overall Survival rate was 93% (96/104)

Anal Canal Treatment – Toxicity
Acute & Late Toxicity – EBRT Boost vs BT Boost

- Chronic proctitis >2 Grade – 19% BT boost vs 32% EBRT boost
- Grades 1 & 2 Anal incontinence 18% BT boost vs 28% EBRT boost
- BT boost less toxic than EBRT boost

Conclusions

Definitive combined Radio chemotherapy is current standard for function preservation treatment of anal cancer

- IMRT Treatment techniques to be used instead of 3DCRT

If the tumor is eligible for BT

- Image guidance is recommended in BT target definition and for the Implantation procedure. TRUS Guided BT better
- With HDR BT expertise – Boost is safe, maximally individualized
- Increased Local Control in BT Boost compared to EBRT boost

Other Prognostic factors

- The Overall Treatment Time (OTT) and time gap between EBRT & BT boost are the best prognostic factors for Local Control rate
- OTT - >80 days vs <80 days
- EBRT & BT Boost gap >37.5 days vs <37.5 days. 2 to 3 weeks gap is good – 2 fractions of 4 to 6 Gy each may be preferred

Conclusions

Newer Strategies

- From Targeted therapies to Immunotherapy and Photodynamic therapy are studied
- Vaccination as a preventive strategy might be the ideal means to reduce the anal canal cancer incidence

I

APPRECIATE

YOUR

TIME

Local Excision Alone for Anal Cancer: Incidence Pelvic Nodal Involvement

Primary size	Pts with nodes
<2 cm	5%
Superficial invasion	10%
Sphincter invasion	30%
Beyond sphincter invasion	60%

Frost DB, et al. *Cancer.* 1984;53:1285-1293.

How Often Are Inguinal Nodes Positive?

- Series of 270 patients from Lyon treated with radiotherapy to anal canal alone

	Synchronous nodes	Metachronous nodes
T1-2	6.4%	5%
T3-4	16%	11%

Gerard JP, et al. *Cancer*. 2001;92:77-84.

Size on Imaging May Not Matter in Determining Involvement

- 44% of metastatic nodes in internal iliac and superior hemorrhoidal chains were <0.5 cm

Wade DS, et al. *Surg Gynecol Obstet*. 1989;169:238-242.

Anal Cancer: Single Institution Results of Week Infusion 5-FU, Mitomycin C, and XRT

Author	Dose/dose per fraction (Gy)	Local control	Survival
Leichman (45)	30/2	84%	76%
Sischy (79)	41.4-5/1.7	84% T1-2 62% T3-4	85% T1-2 68% T3-4
Flam (30)	41-50/1.7-2	97%	90%
Cummings (69)	48-60/2-2.5	86%	61%

- With RadioChemotherapy

Expected Results of Anal Cancer

Stage	5-year survival	Local control
T1	80%	90-100%
T2	70%	65-75%
T3-4	45-55%	40-55%
Overall	65-75%	60%

Cummings BJ, Ajani JA, Swallow CJ. Cancer of the anal region. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:1125-1137.

RTOG 0529: A Phase II Evaluation of Dose-Painted IMRT in Combination With 5-FU and Mitomycin C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal

- Patient population:
  - Histologically-proven, invasive primary squamous, basaloid, or cloacogenic carcinoma of the anal canal; T2-4 and N0-N3
- 5-FU + mitomycin C and IMRT
  - 5-FU by 96-hour continuous infusion (M-F) & mitomycin C on days 1 and 29
    - RT dose
      - T2N0: 28 fractions over 5.5 weeks
      - T3N0 or T4N0: 30 fractions over 6 weeks
      - N+: 30 fractions over 6 weeks

Trials

- Neoadjuvant chemoRT-> Surgery (Wayne State experience)
  - Nigro ND. **Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal.** Cancer. 1983 May 15;51(10):1826-9. PMID 6831348
    - 28 pts neoadjuvant RT 30 Gy /15fx (tumor+margin, pelvic +inguinal LN) + chemotherapy (5-FU/Mitomycin), followed by surgery 4-6 weeks later -> 12 APR, 16 cCR, of APR (7 pCR)
    - Take Home Point: chemoRT is great. Look below.
  - Leichman et al. "**Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy.**" Am J Med. 1985 Feb;78(2):211-5. PMID 3918441
    - 45 pts T2+ treated as above, initially APR (5/6 pCR), remaining avoided APR if neg Bx at 4-6 weeks. No relapses in biopsy negative patients.
    - Take Home Point: Patients with pCR on biopsy don't need APR. (84%)

- Surgery vs RT
  - Swedish: Goldman S. **Management of anal epidermoid carcinoma--an evaluation of treatment results in two population-based series.** Int J Colorectal Dis. 1989 Dec;4(4):234-43. PMID 2614221
  - Improvements in colostomy-free survival and comparable survival measures.
    - Take Home Point: RT avoids colostomy while maintaining survival.

Randomized Trials

- Treatment Intensification
  - RTOG 98-11: Gunderson LL. **Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin.** J Clin Oncol. 2012 Dec 10;30(35):4344-51. PMID 23150707
    - 682 pts, Concurrent 5-FU/Mitomycin C vs. Induction/concurrent cisplatin/5-FU
      - (inclusion of induction chemo into cisplatin arm is big criticism of trial, increased package time)
    - Long-term results reveal 5yr DFS, 67.8% v 57.8% ,5yr OS, 78.3% v 70.7%; Both SS.
    - Take Home Point: Concurrent Mitomycin C demonstrates survival benefit over cisplatin. RT/5FU/MMC The Standard
  - UKCCCR ACT II: James R. **A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II).** J Clin Oncol 27:18s, 2009 (suppl; abstr LBA4009). Reported ASCO 2009
    - 4 arm trial, 940 pts, 2x2 design for concurrent CDDP vs MMC and 5FU/50.4Gy RT. 2nd rand for obs vs adj CDDP/5FU x 2 cycles
    - No difference in CFS (CR rates ~95%), secondary endpoints or hematologic toxicity.
    - Take Home Point: Mitomycin C remains standard of care over cisplatin. No adjuvant treatment.
  - Intergroup ACCORD 03: Conroy T, Ducreux M, Lemanski C. **Treatment intensification by induction chemotherapy (ICT) and radiation dose escalation in locally advanced squamous cell anal canal carcinoma (LAAC): definitive analysis of the intergroup ACCORD-03 trial.** J Clin Oncol 2009;27(15s). (Part I of II): 176s (Abstr 4033). Reported at ASCO 2009
    - 4 arm trial, 307 pts, 2x2 design for 2 cycles induction cisplatin and 20Gy RT boost.
    - No differences in CFS (80-86%), primary endpoint, or secondary endpoints.
    - Take Home Point: No benefit of CFS for either induction chemo or higher RT dose.

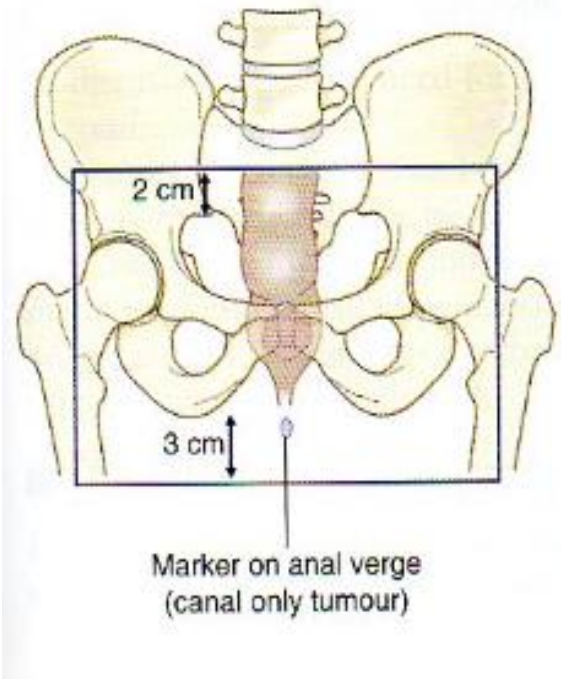
Randomized Trials

- RT with and without Chemotherapy
  - EORTC: Bartelink H. **Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups.** J Clin Oncol. 1997 May;15(5):2040-9. PMID 9164216
    - 110 pts, no T1N0, Arm 1) RT 45/25, if CR/PR ->RT boost 15-20 Gy after 6 weeks or 2) RT 45/25 + CI 5-FU 750 mg/m2 + MMC 15 mg/m2 single bolus
    - LC 50% vs. 68% (SS); CFS 40% vs. 72% (SS); 5-year OS: 56% (NS), no toxicity differences
    - Take Home Point: ChemoRT is superior, standard of care with MMC/5FU
  - UKCCCR ACT I: Northover J. **Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I).** Br J Cancer. 2010 Mar 30;102(7):1123-8. PMID 20354521
    - 585 pts, no T1N0, Rt 45/20-25 vs same RT + CI 5-FU 1000 mg/m2 + Mitomycin 12 mg/m2 bolus
    - If CR-> boost 15 Gy, NR-> APR. Local Failure primary endpoint.
    - 12 yr: LRC 41% vs 66% SS, CFS 20% vs 30%., OS 27% vs 33%. Majority recur in first 2 years.
    - Take Home Point: ChemoRT is superior, standard of care with MMC/5FU

Anal Canal Cancers – Recurrent and Residual disease

- Salvage APR is required in 30% cases due to Primary non – response or recurrence
- Tumors invading local structures may require multi visceral resection
- Flam et al suggested the use of salvage CRT (9Gy along with 5FU and Cisplatin) in cases with residual disease following definitive CRT before a radical surgery – 50% salvage rate in biopsy proven residual tumor 4 to 6 weeks after definitive CRT

Conventional Planning
Volume (Phase I Volume - all Tumors)

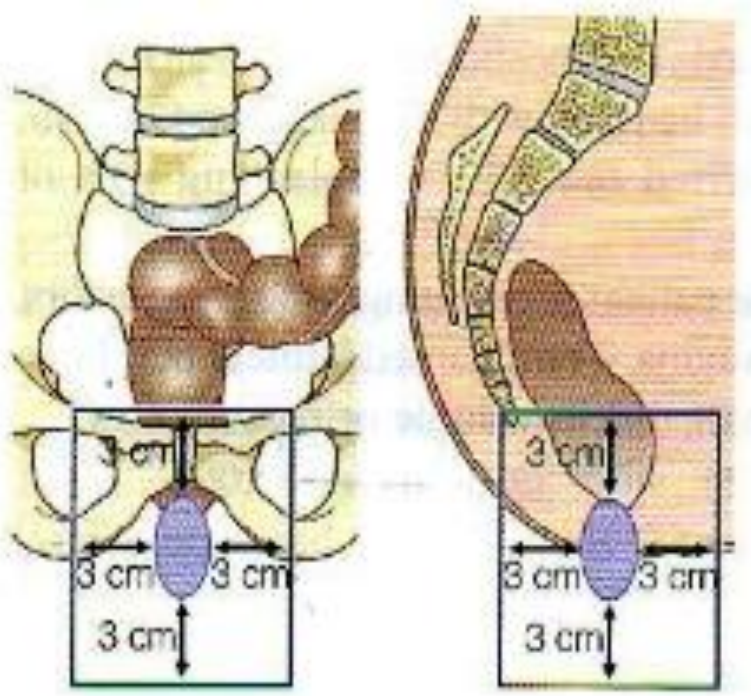


Superior border – 2 cm above inferior aspect of SI joint. Superior border to include a minimum margin of 3cm above upper extent of GTV-T Or GTV-N

Inferior border – 3 cm below anal margin or 3cm below most inferior extent of tumor

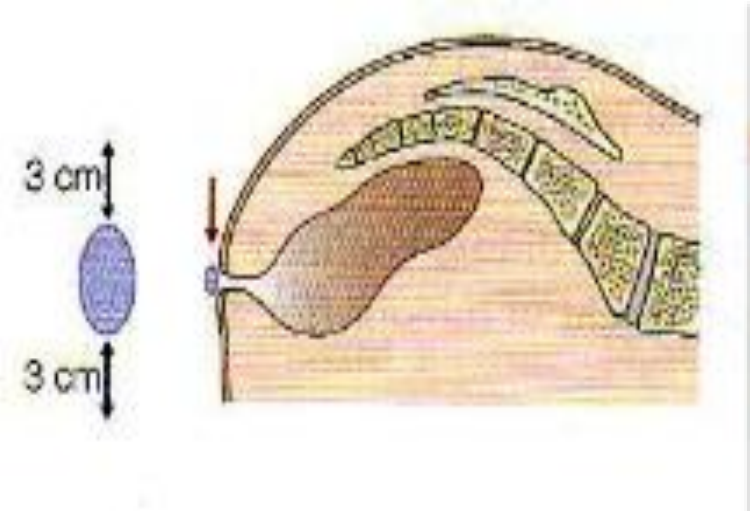
Lateral border – to include both inguinal nodal regions – lateral to femoral haed

Phase 2 - Volume for lymph node negative cases
N0 – Anal Canal tumors



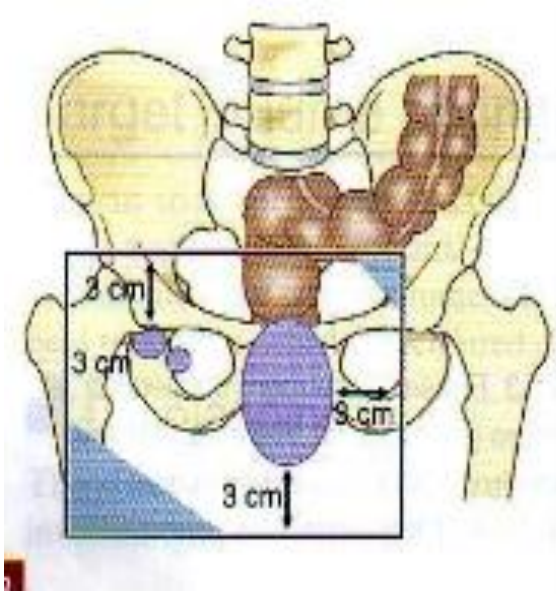
All borders allow 3 cm around the GTV defined at initial planning

Phase 2 -Volume for lymphnode negative cases
N0 Anal canal tumors



Direct field with 3 cms margin Superior, Inferior and lateral to GTV

Phase 2 - Volume for lymph node positive disease (N+)



Treatment of GTV with 3 cm margin and MLC or lead shielding to exclude normal tissue and reduce toxicity