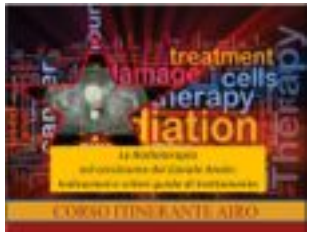


Radiotherapy techniques (3D-CRT - IMRT - IGRT)

Clinical results

Gabriella Macchia

U.O. Radioterapia
Fondazione Giovanni Paolo II- Università Cattolica- Campobasso

Evoluzione

3D-CRT-Chemoradiation

NCCN: AP-PA no longer standard of care

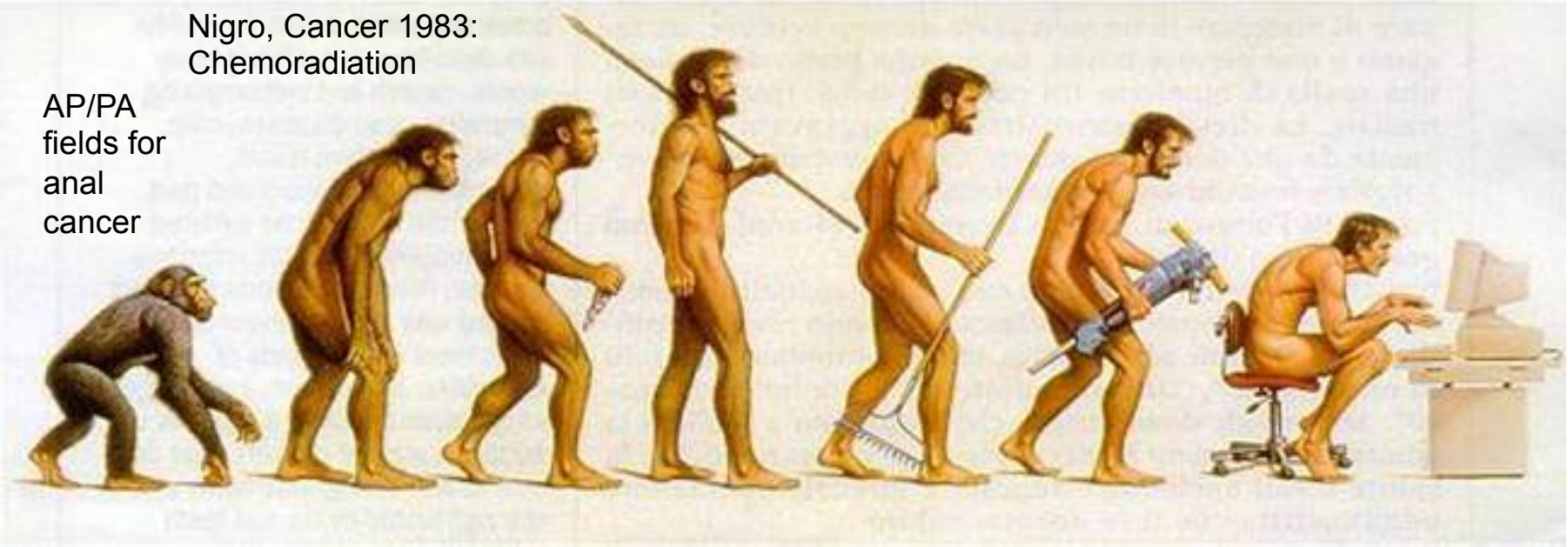
IMRT

IGRT

VMAT

Nigro, Cancer 1983: Chemoradiation

AP/PA fields for anal cancer



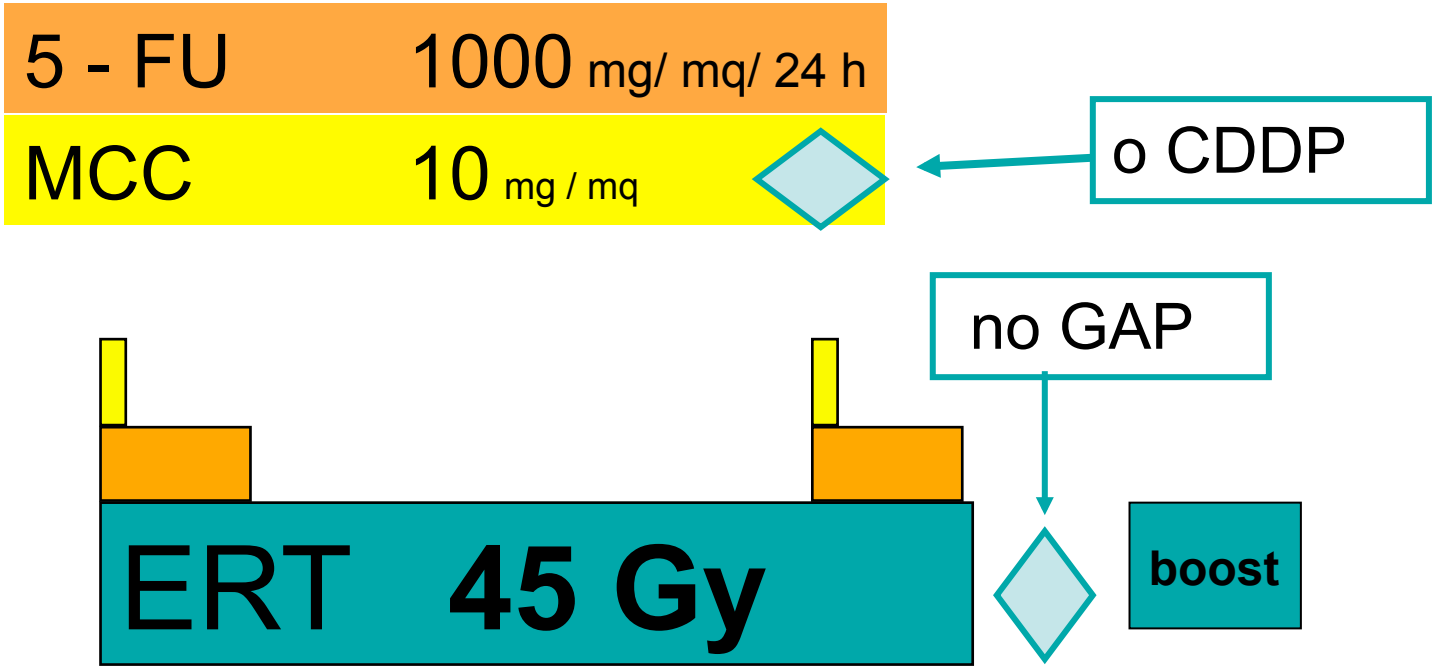
What is the scenario in terms of clinical outcomes?

The established evidences

FU.

MI.

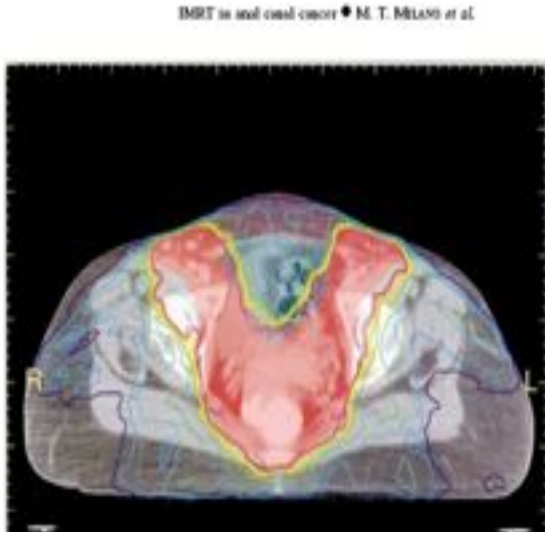
R

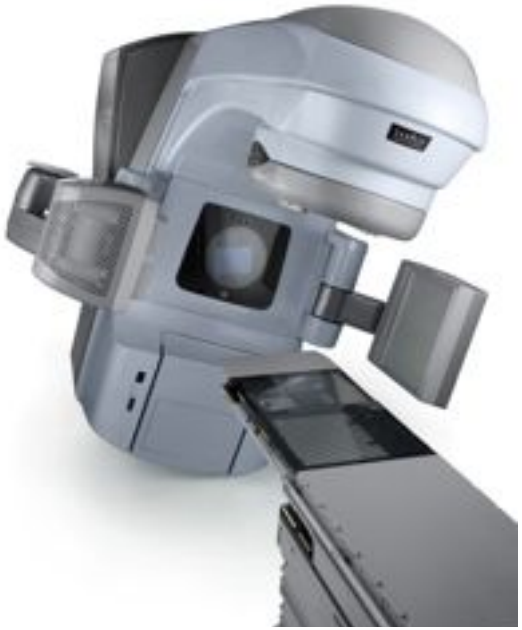


Courtesy G Mantello

FUMIR

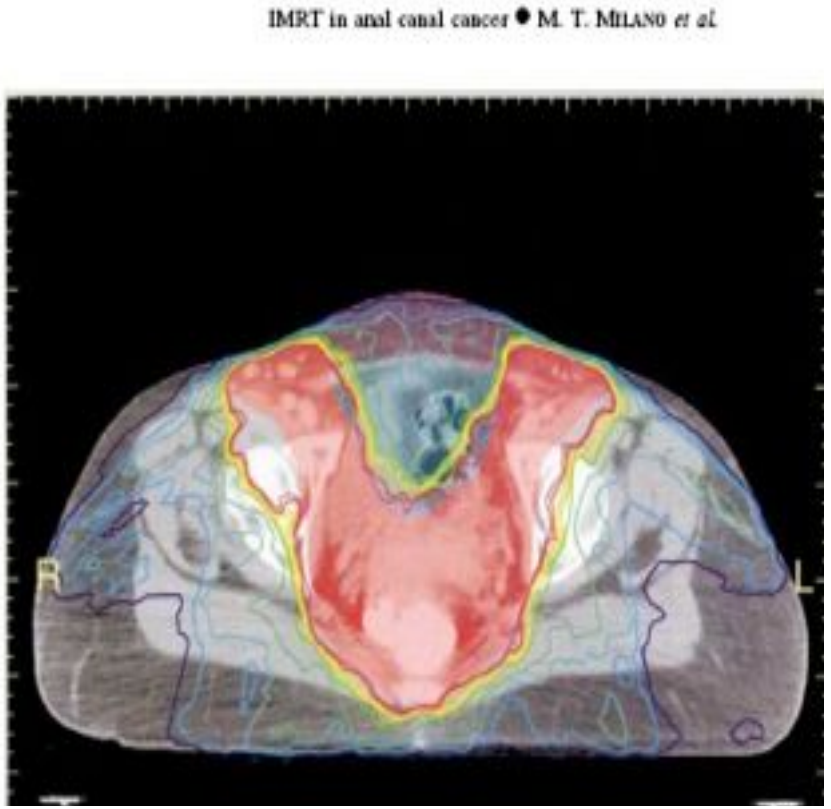

Luigi Pirandello
I vecchi
e i giovani
romanzo
OSCAR
MONDADORI





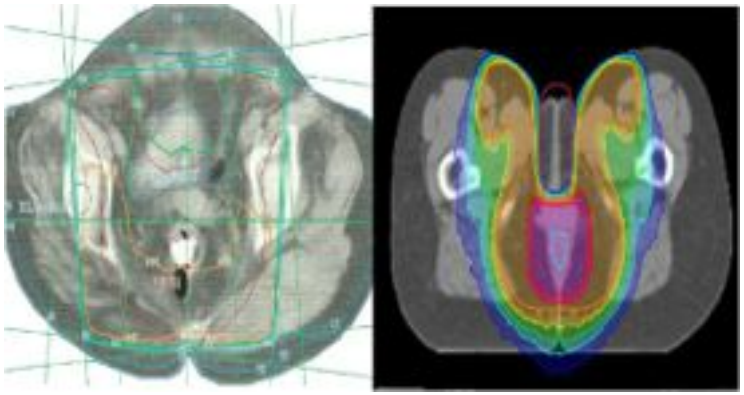
IMRT Literature

- Milano MT, IJROBP 2005
- Salama JK, JCO 2007
- Pepek JM, IJROBP 2010
- Bazan JG, Cancer 2011 (Stanford group)
- Kachnic LA, IJROBP 2012
- Kachnic LA, IJROBP 2013
- Chuong MD, Gastrointest Cancer Res 2013 (Boston group)
- Dasgupta T. R&O 2013



Radiotherapy techniques (3D-CRT - IMRT - IGRT) : Clinical results

- toxicity (3DCRT-IMRT comparison)
- outcomes (3DCRT-IMRT comparison)
- cost-effectiveness (3DCRT-IMRT comparison)
- IGRT clinical benefit



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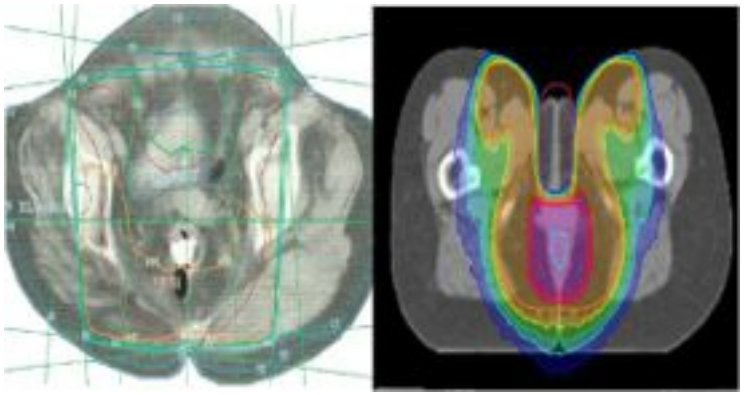

Toxicity (3DCRT-IMRT comparison)

		RT technique	Acute G3+ GI toxicity (%)	Acute G3+ skin toxicity (%)
Chuong study	2013	IMRT	9.6	11.5
		3DCRT	29.7	64.9
Bazan[11]	2011	IMRT	7	21
		3DCRT	29	41
Chuong[12]	2012	IMRT	5	5
Salama[7]	2007	IMRT	15.1	37.7
Pepek[8]	2010	IMRT	10	0
Kachnic[10]	2011	IMRT	7	10

RTOG 98-11 (Ajani, Jama 2008): **Tox ≥ 3: GI 34%**
Tox ≥ 3: cute 48%

3D

RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal

Table 5 Comparisons of acute treatment-related adverse events*

Adverse events	0529 (n=52)	98-11 (Arm 1†) (n=325)	*P* value (1-sided proportions test§)
Grade 2+			
GI/GU‡	40 (77%)	249 (77%)	.50
Derm	39 (75%)	271 (83%)	.10
GI	38 (73%)	237 (73%)	.50
GU	8 (15%)	66 (20%)	.18
Heme	38 (73%)	275 (85%)	.032
Overall	49 (94%)	318 (98%)	.12
Grade 3+			
GI/GU	11 (21%)	120 (37%)	.0052
Derm	12 (23%)	159 (49%)	<.0001
GI	11 (21%)	117 (36%)	.0082
GU	1 (2%)	11 (3%)	.32
Heme	30 (58%)	201 (62%)	.29
Overall	43 (83%)	283 (87%)	.23

The only prospective phase II trial in literature

no standard arm!

Significant sparing

Kachnic L.A. IJROBP 2013

RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal

Lisa A. Kachnic, MD,* Kathryn Winter, MS,† Robert J. Myerson, MD,‡ Michael D. Goodyear, MD,§ John Willins, PhD,* Jacqueline Esthappan, PhD,‡ Michael G. Haddock, MD,‖ Marvin Rotman, MD,¶ Parag J. Parikh, MD,‡ Howard Safran, MD,# and Christopher G. Willett, MD**

*Department of Radiation Oncology, Boston University Medical Center, Boston, Massachusetts; †Radiation Therapy Oncology Group Statistical Center, Philadelphia, Pennsylvania; ‡Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri; §Department of Medicine, Dalhousie University, Halifax, Canada; ‖Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ¶Department of Radiation Oncology, State

Dose-painted IMRT with 5FU and MMC for anal canal cancer is

- Feasible
- The primary endpoint (reducing grade 2 combined gastrointestinal and genitourinary acute adverse events **by 15%** compared with the RTOG 9811 5 fluorouracil/mitomycin- C arm using standard radiation techniques) was not met
- IGRT not mandatory!!!!!

Kachnic L.A. IJROBP 2013

Radiotherapy techniques (3D-CRT - IMRT - IGRT) : Clinical results

- toxicity (3DCRT-IMRT comparison)
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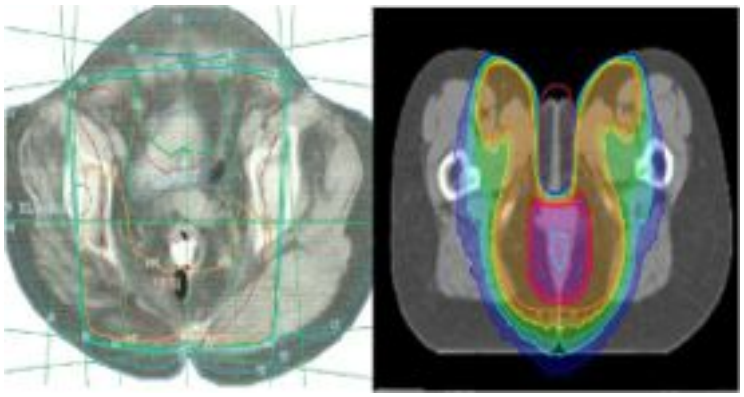
- cost-effectiveness (3DCRT-IMRT comparison)
- IGRT clinical benefit



Outcome 3DCRT

	5FU+MMC EBRT	5FU+CDDP EBRT
DFS (5years)	60%	54%
OS (5years)	75%	70%
LC and DMR	25%	15%
COLOSTOMY	10%	19%

RTOG 98-11, Ajani, Jama 2008

80% 5y LRC

90% 5y CFS **RTOG 98-11 MMC arm**

78.2% 5y OS

Gunderson LL, JCO 2012

Outcome IMRT

	RT technique	Outcomes (y)	Median f/u (mo)	LRC (%)	CFS (%)	OS (%)
Chuong study 2013	IMRT	3	20	90.8	91.3	91.1
	3DCRT		61.9	91.9	93.7	86.1
Bazan[11] 2011	IMRT	3	32	92	91	87.8
	3DCRT		26	56.7	NR	51.8
Chuong[12] 2012	IMRT	3	13.6	93.9	93.2	100
Salama[7] 2007	IMRT	1.5	14.5	83.9	83.8	93.4
Pepek[8] 2010	IMRT	2	19	85	91	100
Kachnic[10] 2011	IMRT	2 **RTOG0529**	24	95	94	94

3DCRT = 3D conformal radiation therapy; IMRT = intensity-modulated radiation therapy; MMC = mitomycin-C; NR = no

IMRT 85%-95% LRC

IMRT 84%-94% CFS

IMRT 87%-100% OS

3DCRT-IMRT comparison

Only few retrospective studies

- Bazan JG, *Cancer 2011*
- Chuong MD, *Gastrointest Cancer Res 2013*
- Dewas CV *Radiation Oncol 2012*
- Dasgupta T. *R&O 2013*
- Koerber SA *Radiation Oncol 2014*

Intensity-Modulated Radiation Therapy Versus Conventional Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal

Bazan JG, Cancer 2011

Clinical retrospective comparison:

17 pts 3DCRT vs 29 pts IMRT

1. OTT reduced
2. breaks limited in number and length
3. IMRT> OS, LCR, CFS about 90% vs 55% 3D

Potential explanations
- > n° Stage III in Bazan
- Lower median dose
- More N+ pts

ORIGINAL RESEARCH

Intensity-Modulated Radiation Therapy vs. 3D Conformal Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal

Michael D. Chuong,[1] Jessica M. Freilich,[1] Sarah E. Hoffe,[1] William Fulp,[2] Jill M. Weber,[3] Khaldoun Almhanna,[3] William Dinwoodie,[3] Nikhil Rao,[1] Kenneth L. Meredith,[3] Ravi Shridhar[1]

Clinical retrospective comparison:

37 pts 3DCRT vs 52 pts IMRT

1. Reduced toxicity
2. **NOT** confirmed survival benefit albeit with twice as many patients

Chuong MD, Gastroint Cancer Research 2013

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Anal cancer

Intensity-modulated radiotherapy vs. conventional radiotherapy in the treatment of anal squamous cell carcinoma: A propensity score analysis

Tina Dasgupta [a,b], Diana Rothenstein [b], Joanne F. Chou [c], Zhigang Zhang [c], Jean L. Wright [b,d], Leonard B. Saltz [e], Larissa K. Temple [f], Philip B. Paty [f], Martin R. Weiser [f], Jose G. Guillem [f], Garrett M. Nash [f], Karyn A. Goodman [b,*]

MSKCC experience

223 ASCC (45 IMRT e 178 3DCRT)

no significant difference in outcomes

Effect of IMRT vs. CRT on OS, LRFS, DMFS and CFS.[a,b]

Outcome by propensity score	HR for CRT	HR for IMRT	95% CI	*P*
OS	1.00	1.14	0.32–4.0	0.83
Time to recurrence	1.00	0.85	0.31–2.3	0.75
Time to distant metastasis	1.00	1.23	0.41–3.7	0.71
Time to colostomy	1.00	0.58	0.07–4.7	0.61

Radiotherapy and Oncology 107 (2013) 189–194

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Efficacy and toxicity of chemoradiation in patients with anal cancer - a retrospective analysis

Stefan Alexander Koerber[1,2]*, Alla Slynko[3], Matthias F Haefner[1,2], David Krug[1,2], Clara Schoneweg[1,2], Kerstin Kessel[1], Annette Kopp-Schneider[3], Klaus Herfarth[1,2], Juergen Debus[1,2] and Florian Sterzing[1,2]

Heidelberg experience

105 pts: 68 IMRT e 37 3DCRT

The use of IMRT can **reduce acute severe side effects** of the **skin** and **gastrointestinal** tract but did **not** demonstrate **improved** results regarding **OS, PFS, LC and CFS**

Radiation Oncology 2014, **9**:113

Table 3 Different SIB-IMRT schedules in treatment of anal cancer

Study/year	Patients	Mean FU (months)	SIB-IMRT dose levels (prescription total dose/single dose)	Number of series	Range of SIB-single dose	DFS	LRC	CFS	OS	Acute ≥ grade 3 toxicity
Menkarios 2007	5	*	Concept: 2 dose levels (SIB): 49.5/1.5Gy 59.4/1.8Gy or 2 series (45/1.8 and 59.4/1.8Gy)	1-2	1.5-1.8Gy	*	*	*	*	*
Salama 2007	53	14.5	PTV: 32-60.9Gy (median: 51.5Gy) ENI: 30.6-45Gy (median: 45Gy) Concept: 3 dose levels: 41.25/1.65Gy,45/1.8, 50/2.0 (+/-boost)	1-2	1.65-2.0Gy		84%/1.5y	84%/1.5y	93%/1.5y	GI: 15% skin: 38% hematologic: 59%
Vieillot 2010	10	*	Concept: 2 dose levels: 49.5/1.5Gy 59.4/1.8Gy	1	1.5-1.8Gy	*	*	*	*	*
Call 2011	34	22	PTV: 48.6-57.6Gy (median: 50.4Gy) ENI: 38-45Gy No standard concept	1	1.28-2.25Gy	80%/3y			87%/3y	Not reported
Barzan 2011	29	32	Concept: 3 dose levels: 40/1.6Gy 45/1.8Gy +boost 5.4Gy (T1/2), 9-14.4Gy (T3/4)	2	1.6-1.8Gy		92/3y	91/3y	88%/3y	GI: 7% skin: 21% hematologic: 21%
Kachnic 2012	43	24	Concept: T-stage based SIB (2 dose levels) T2N0: 42/1.5Gy ENI, 50.4/1.8Gy to PTV T3-4N0-3: 45/1.5Gy ENI, 50.4/1.68Gy to lymph nodes<3cm 54/1.8Gy to PTV and lymph nodes>3cm	1	1.5-1.8Gy		95%/2y	94%/2y	92%/2y	GI: 7% skin: 10% hematologic: 51%
Deenen 2012	18	28	49.5/1.5Gy ENI 59.4/1.8 for PTV Boost 5.4/1.8Gy for macroscopic residual tumor after 5 weeks	1-2	1.5-1.8Gy		83%/2y			GI: 0%, skin: 50% hematologic: 0%
Mitchell 2013	65	19	PTV: 50-58.8Gy (median: 54Gy)	1	1.62-2.0Gy	86%/2y			96%/2y	GI: 9%

Janssen S. Radiation Oncology 2014, 9:199 (8 September 2014)

Radiotherapy techniques (3D-CRT - IMRT - IGRT) : Clinical results

- toxicity (3DCRT-IMRT comparison)
- outcomes (3DCRT-IMRT comparison)
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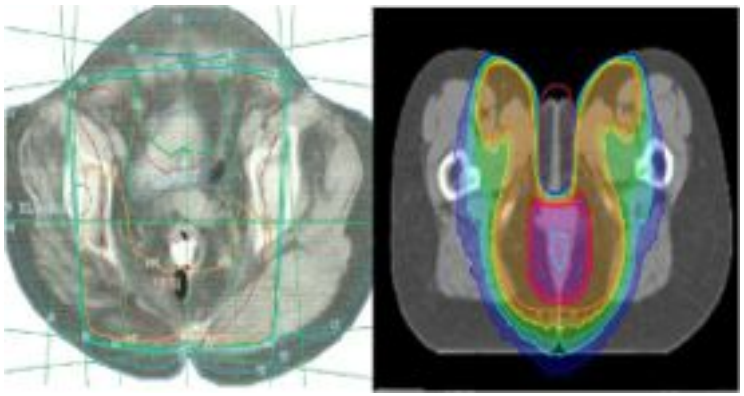

International Journal of Radiation Oncology biology • physics

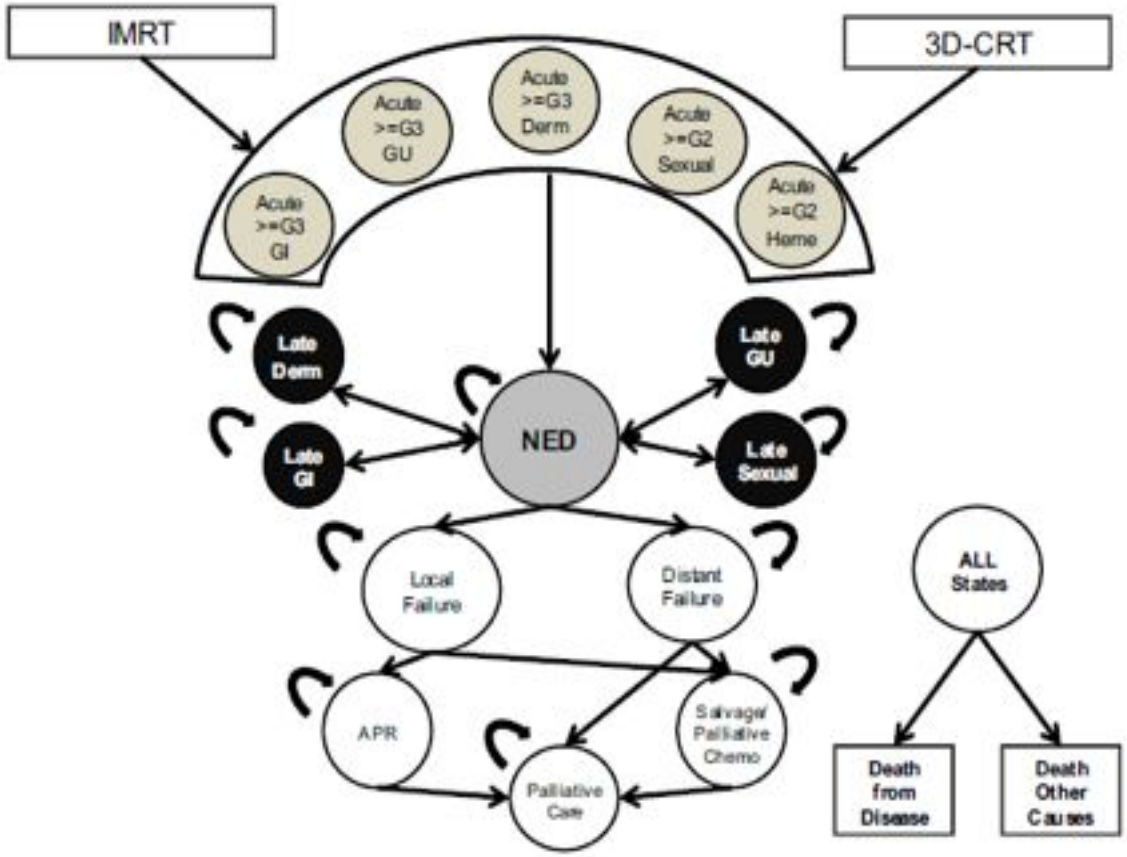

Fig. 1. Markov model. 3D-CRT = 3-dimensional conformal radiation therapy; APR = abdominoperitoneal resection; Derm = dermatologic; GI = gastrointestinal; GU = genitourinary; Heme = hematologic; IMRT = intensity modulated radiation therapy; NED = no evidence of disease.

Hodges JC, IJROBP April, 2014

« Back

International Journal of Radiation Oncology * Biology * Physics

Article in Press

Cost-Effectiveness Analysis of Intensity Modulated Radiation Therapy Versus 3-Dimensional Conformal Radiation Therapy for Anal Cancer

Given currently available information, IMRT is a cost-ineffective strategy for treating anal cancer, despite the reduced acute treatment-related toxicities and reduced costs associated with managing these toxicities.

However, the results were highly sensitive to key treatment- and disease specific variables, implying that any modest improvements in LC or patient-reported utility due to an improved toxicity profile would lead to cost-effectiveness of IMRT over 3D-CRT.

Hodges JC, IJROBP April, 2014

IMRT key issues

Important reduction in acute toxicity and treatment interruptions impacting positively on the potential late toxicity

Excellent cure rates and sphincter preservation

NOT seems to offer survival b

NO cost-effectiveness

Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Requires expertise (In a recent multicenter study, even after centers had been approved and accredited, **81%** of IMRT plans **required field modification** of elective nodes **after central review**)

Not recommended:
Obese with nonreproducible external skin contours
Major component of tumor outside the anal canal

Tips and tricks

NATIONAL GUIDANCE FOR IMRT IN ANAL CANCER

R Muirhead[1], RA Adams[2], DC Gilbert[3], M Harrison[4], R Glynne-Jones[4], D Sebag-Montefiore[5], MA Hawkins[1]

[1]The Gray Institute for Radiation Oncology & Biology, Oxford, UK; [2]School of Medicine, Cardiff University, Cardiff, UK; [3]Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, UK; [4]Mount Vernon Hospital, Northwood

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Guidelines

Anal cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up ☆

Robert Glynne-Jones[a], Per J. Nilsson[b], Carlo Aschele[c], Vicky Goh[d], Didier Peiffert[e], Andrés Cervantes[f], Dirk Arnold[g,*]

www.analimrtguidance.co.uk

Tips and tricks

6.0 Therapeutic Schema

Dose prescription T1 N0 or T2 N0 (and T3N0 at clinicians discretion)

- Elective – 40 Gy in 28# (1.43 Gy per #) in 5.5 weeks
- Gross anal disease –50.4 Gy in 28# (1.8 Gy per #) in 5.5 weeks

Dose prescription T4N0 or Tany N+ (and T3N0 at clinicians discretion)

- Elective (PTV_Elec) = 40 Gy in 28# (1.43 Gy per #) in 5.5 weeks
- Gross nodal disease (PTV_Nodes) = 50.4Gy in 28# (1.8Gy per #) in 5.5 weeks.
- Gross anal disease (PTV_Anal) = 53.2 Gy in 28# (1.9Gy per #) in 5.5 weeks

Concurrent Chemotherapy

Concurrent chemotherapy should be prescribed in all patients that are considered fit for standard treatment.

Acceptable regimens are:

- Mitomycin 12mg/m2 Day 1 with 5FU 1000mg/m2 days 1-4 and day 29-32
- Mitomycin 12mg/m2 day 1 with Capecitabine 825mg/m2 BD on days of XRT.

Dose reductions in fluoropyrimidines should be considered if patients are elderly or the renal function is impaired.

www.analimrtguidance.co.uk

Tips and tricks

7.0 Pre-Treatment

Patient Simulation and Immobilisation:

- Standard position: supine with immobilisation for popliteal fossa and feet.
- Prior to pre-treatment scan, the clinician will assess the diagnostic imaging and ascertain if in supine position the tumour is adequately bolused by the surrounding buttocks, this will depend on site and position of disease. If the buttocks do not provide sufficient bolus the patient may require to be positioned prone or lying supine on a solid sheet of bolus material.
- The distal point of macroscopic disease or anal verge will be wired prior to imaging, whichever is more inferior.
- All patients must be scanned with a comfortably full bladder (>250mls).
- IV contrast to aid delineation of pelvic vessels
- Once patient is scanned, tattoo and document as per local protocol

8.0 Delineation

- If possible the diagnostic or planning MRI and PET/CT can be fused with planning CT: The treating consultant shall review and approve the registration.
- The GTV should be determined by the treating clinician using the clinical data, MRI and PET/CT.
- The borders of the GTV should not be defined using the PET/CT.

www.analimrtguidance.co.uk

Tips and tricks

10.0 Treatment Modality

Inverse plan using simultaneous intergrated boost technique delivered with cop
An advanced convolution superposition' algorithm should be used for calculatic

For IMRT:
Suggested Beam positions if supine: 0°; 310°; 275°; 210°; 150°; 85°; 50°
Suggested Beam positions if prone: 180°; 130°; 95°; 30°; 330°; 265°; 230°

11.0 Planning Parameters

Prescription Point - 100% to the median dose in PTV (ICRU 83)

Target coverage and OAR requirements are documented on Anal IMRT planr r each patient by clinician and planner.

12.0 Treatment Delivery

CBCT should be performed Days 1-5 and weekly thereafter as a minimum.

Organ	OAR / Target	Dose Constraint
PTV	V99%	>90%
	V95%	>95%
	V50%	Between 99% - 101%
	V5%	<105%
	V2%	<107%
Small Bowel	D200cc	30Gy
	D150cc	35Gy
	D20cc	45Gy
	Dmax	54Gy
Femoral Heads	D50%	30Gy
	D35%	40Gy
	D5%	50Gy
Genitalia	D50%	<20Gy
	D35%	<30Gy
	D5%	<40Gy
Bladder	D50%	<35Gy
	D35%	<40Gy
	D5%	<50Gy

www.analimrtguidance.co.uk

Radiotherapy techniques (3D-CRT - IMRT - IGRT) : Clinical results

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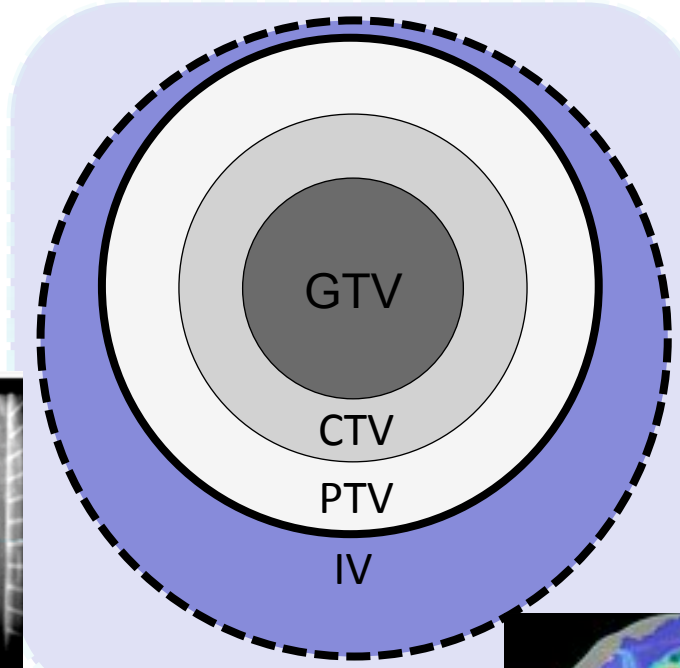
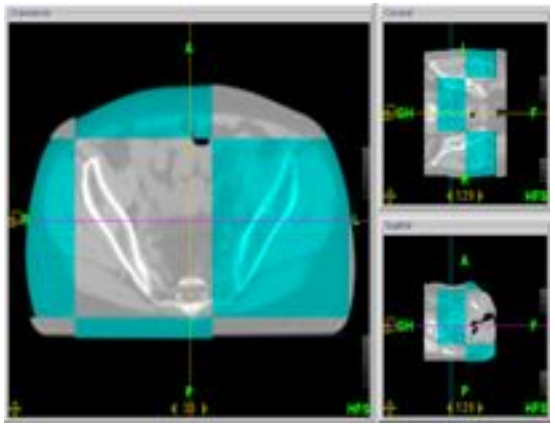
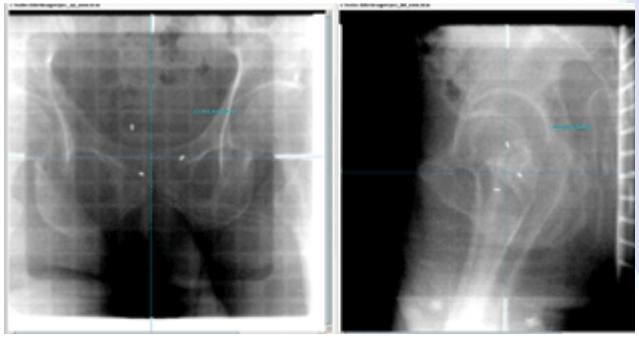
- IGRT clinical benefit

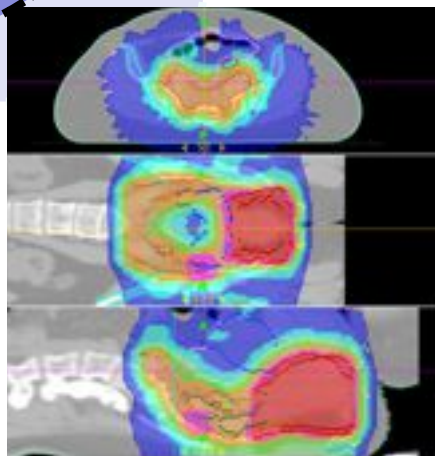
No IMRT without IGRT

IMRT + **IGRT =** Conformity + **Precision**









Physics Contribution

Setup Variations in Radiotherapy of Anal Cancer: Advantages of Target Volume Reduction Using Image-Guided Radiation Treatment

Yi-Jen Chen, M.D., Ph.D.,* Steve Suh, Ph.D.,* Rebecca A. Nelson, Ph.D.,† An Liu, Ph.D.,* Richard D. Pezner, M.D.,* and Jeffrey Y.C. Wong, M.D.*

*Divisions of *Radiation Oncology and †Information Sciences, City of Hope Medical Center, Duarte, CA*

Received Mar 29, 2011, and in revised form Oct 26, 2011. Accepted for publication Oct 28, 2011

12 pts
PTV=CTV+5mm
Daily IGRT

Volume 84 • Number 1 • 2012

Table 2 Mean systemic setup error (μ), SD of μ (Σ), and average random setup error (σ) for all 12 cases (365 data sets)

	Overall displacement			
Direction	μ	∑	σ	$2\sum + 0.7\,\sigma$
AP (mm)	1.1	1.1	3.8	4.9
Lateral (mm)	2.1	3.6	5.5	11.1
SI (mm)	−2.3	3.2	2.9	8.5
Roll (°)	−0.3	0.3	0.5	N/A

Chen YJ, IJROBP 2012

Physics Contribution

Setup Variations in Radiotherapy of Anal Cancer: Advantages of Target Volume Reduction Using Image-Guided Radiation Treatment

Yi-Jen Chen, M.D., Ph.D.,* Steve Suh, Ph.D.,* Rebecca A. Nelson, Ph.D.,†
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Received Mar 29, 2011, and in revised form Oct 26, 2011. Accepted for publication Oct 28, 2011

Without daily IGRT, margins of 4.9, 11.1, and 8.5 mm in the AP, lateral, and SI directions would have been needed to ensure that the planning target volume (PTV) received 95% of the prescribed dose.

Conversely, daily IGRT required no extra margins on PTV and resulted in a significant reduction of V15 and V45 of intestine and V10 of pelvic bone marrow.

Conclusions

In summary, daily MVCT scans before each radiation treatment can effectively detect setup variations and thereby reduce PTV margins in the treatment of patients with anal cancer. The use of concurrent chemotherapy and IGRT provide satisfactory clinical outcomes and favorable toxicities, except for acute hematologic toxicity.

Chen YJ, IJROBP 2012

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Feasibility of Image-guided Radiotherapy Based on Tomotherapy for the Treatment of Locally Advanced Anal Carcinoma

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Abstract. *Background: The standard of care for locally advanced anal cancer has been concurrent chemoradiation. However, conventional treatment with 3-dimensional radiotherapy is associated with significant toxicity. The feasibility of new radiotherapy techniques such as image-guided radiotherapy (IGRT) in combination with chemotherapy for the treatment of this malignancy was assessed. Patients and Methods: A retrospective review of five patients with locally advanced anal carcinoma treated with Tomotherapy-based IGRT was conducted. All the patients received concurrent chemotherapy. Results: Gastrointestinal toxicity remained the limiting factor as four patients experienced grade 3-4 enteritis requiring a break during treatment. No patient experienced grade 3-4 hematological toxicity. Despite the large tumor size, three patients achieved local control at a median follow-up of 19 months. Conclusion: Tomotherapy-based IGRT may be a promising treatment for locally advanced anal cancer and needs to be investigated in further prospective trials.*

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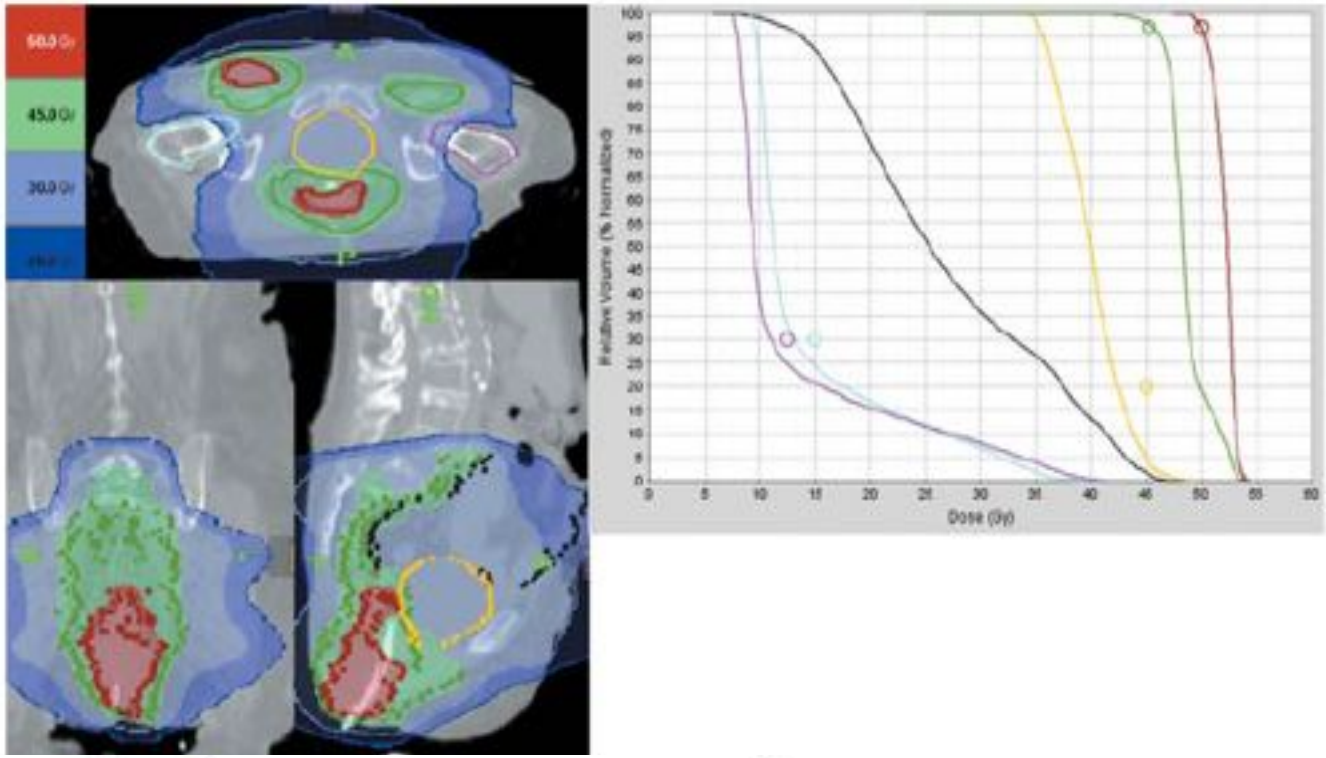

Conclusion

Tomotherapy-based IGRT is feasible for the treatment of locally advanced anal cancer and should be investigated in future prospective trials to assess treatment efficacy and toxicity.

IGRT (IG-IMRT) key issues

- ! Adequate target coverage + OAR sparing
- ? Containment of the GI and GU toxicity
- ? Improved compliance with treatment combinations
- ? Containment haematological toxicity

further studies….

Thanks