Radiotherapy & Cervical Cancer

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Cervical Cancer treatment

- *Treatment planning should be made on a multidisciplinary basis (generally at a tumor board meeting) and based upon the comprehensive and precise knowledge of prognostic and predictive factors for oncological outcome, morbidity and quality of life. Patients should be carefully counseled on the suggested treatment plan, and potential alternatives, including risks and benefits of all options. Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of gynecologic cancers*

- *Treatment strategy should aim for avoiding the combination of radical surgery and postoperative external radiotherapy, due to the significant increase of morbidity and no evident impact on survival*

ESGO guidelines 2017

Radiotherapy +/- chemo

- Definitive treatment LACC
  - focus of todays presentation

- Post op treatment
  - high risk factors/ incidental finding

- Recurrence post surgery

- Palliation

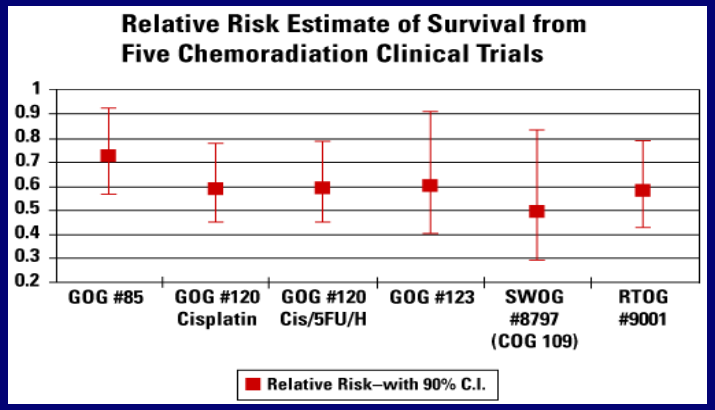
Locally advanced disease

Locally advanced disease

- Heterogenous group FIGO IB2/IIB-IVA
- Variation in treatment (IB/II) based on surgical expertise and availability of RT & Brachy
- Neoadjuvant chemo/surgery v CRT
- Challenges- nodal staging
  - treatment technique
  - morbidity
  - outcome

Feb 1999: NCI clinical announcement on cervical cancer-changed clinical practice worldwide

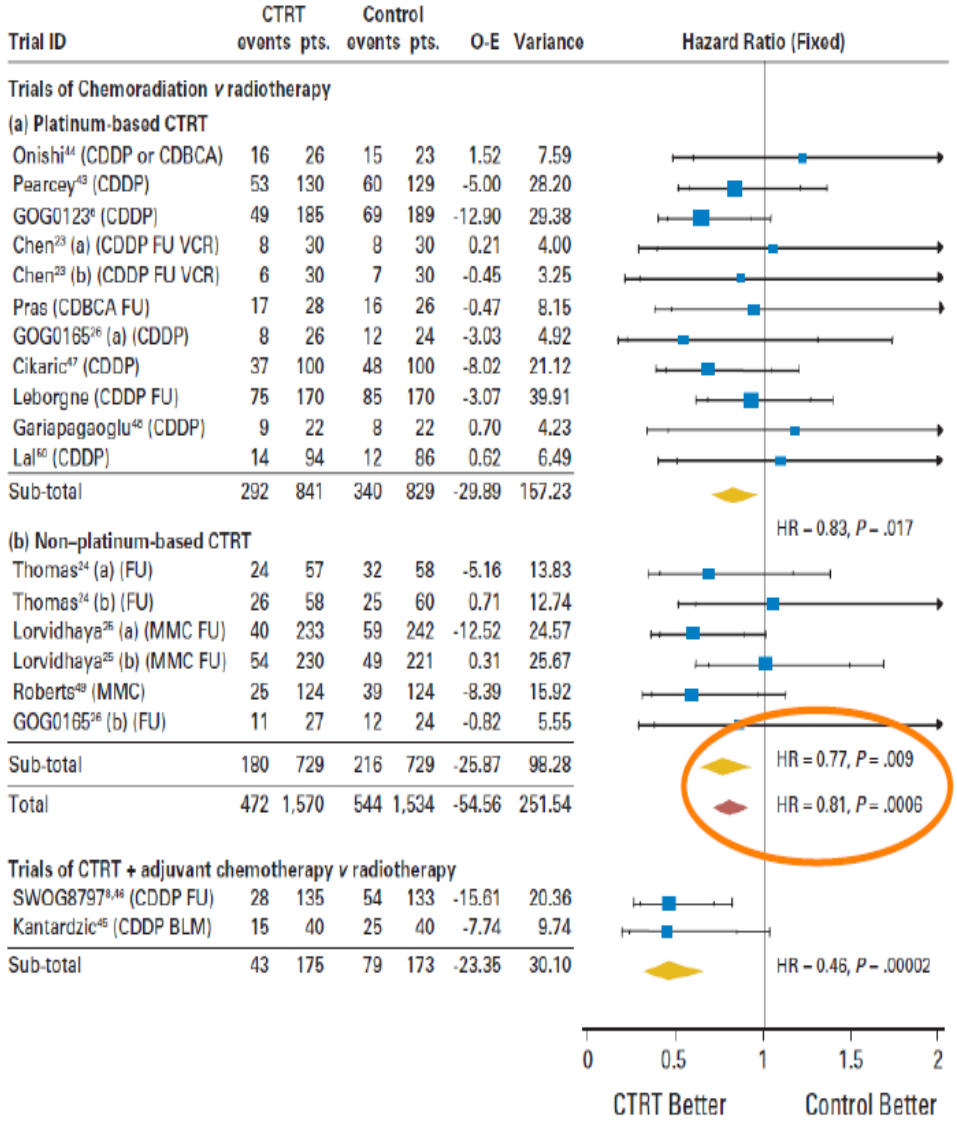
5 Pivotal Trials of Chemoradiation



NCI Clinical Announcement 1999:
www.cancer.gov/newcenter/cervicalcancer

Morris M, et al. N Engl J Med 1999;340:1137–43.
Rose PG, et al. N Engl J Med 1999;340:1144–53.
Keys HM, et al. N Engl J Med 1999;340:1154–61.
Whitney CW, et al. J Clin Oncol 1999;17:1339–43.
Peters WA 3rd, et al. J Clin Oncol 2000;18:1606–13.

Primary RT & Chemotherapy Meta-analysis



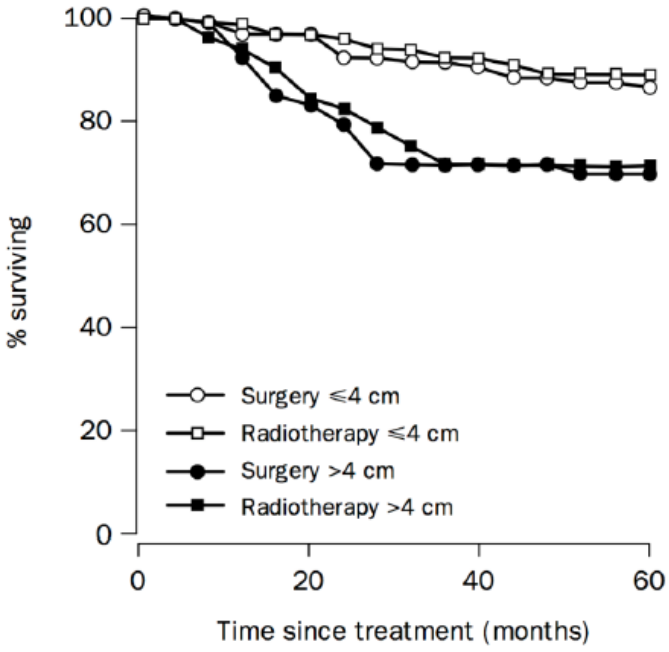
Vale et al JCO 2008

- 18 trials from 11 countries/analysis limited to 13 trials
- Confirmed benefit of CRT- smaller effect
- Overall HR survival 0.81 / HR DFS 0.78
- Suggestion that greatest benefit with earlier stage (7-10% I/II vs 3% III/IV)
- Significant benefits with non-platinum agents
- Suggestion that adjuvant chemo may improve outcome further

Primary surgery v radiotherapy

343 women, stage IB-IIA cervical cancer

	Surgery (n=170)		Radiotherapy (n=167)	
	⩽4 cm	>4 cm	⩽4 cm	>4 cm
Number of patients	115	55	113	54
Mean (SD) age in years	51·8 (11·3)	46·1 (10·1)	55·2 (10·9)	50·0 (9·8)
FIGO stage				
Ib	107 (93%)	47 (85%)	99 (88%)	45 (83%)
IIa	8 (7%)	8 (15%)	14 (12%)	9 (17%)
Positive lymphangiography	12 (10%)	12 (22%)	9 (8%)	13 (24%)
Histological type				
Squamous	94 (82%)	44 (80%)	97 (86%)	45 (83%)
Adenocarcinoma	18 (16%)	8 (15%)	13 (11%)	7 (13%)
Small cells	3 (2%)	3 (5%)	3 (3%)	2 (4%)
Postoperative radiotherapy	54%	84%		
Morbidity G2-3	30%	25%	12%	11%



Landoni et al. Lancet 1997

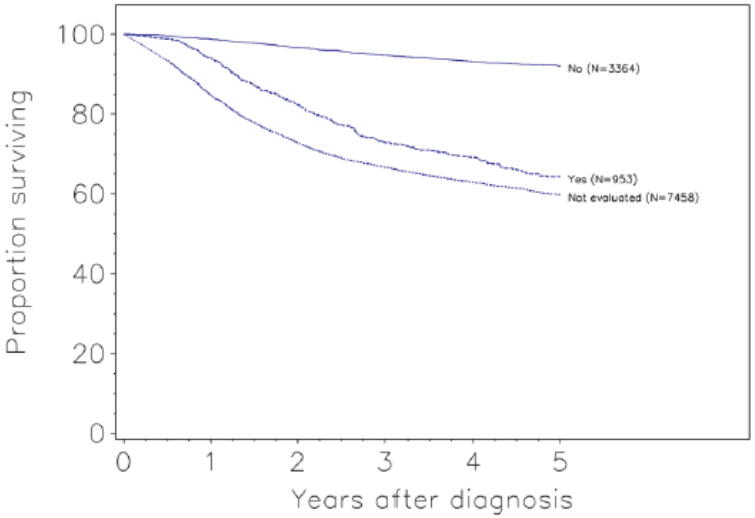
Challenges in management

- Nodal staging—determine RT fields/prognosis
- Local control
- Morbidity & QOL
- Overall outcome

Nodal staging

Risk of nodal involvement

FIGO stage	Patients (*n*)	Lymphnodal involvement			
		Positive		Negative	
		N	%	*N*	%
Total	5173	1161	22.4	4012	77.6
Ia1	356	14	3.9	342	96.1
Ia2	238	23	9.7	215	90.3
Ib1	2687	460	17.1	2227	82.9
Ib2	685	209	30.5	476	69.5
IIa	486	140	28.8	346	71.2
IIb	491	185	37.7	306	62.3
IIIa	29	14	48.3	15	51.7
IIIb	117	71	60.7	46	39.3
IVa	28	16	57.1	12	42.9
IVb	24	22	91.7	2	8.3
Missing	32	7	21.9	25	78.1



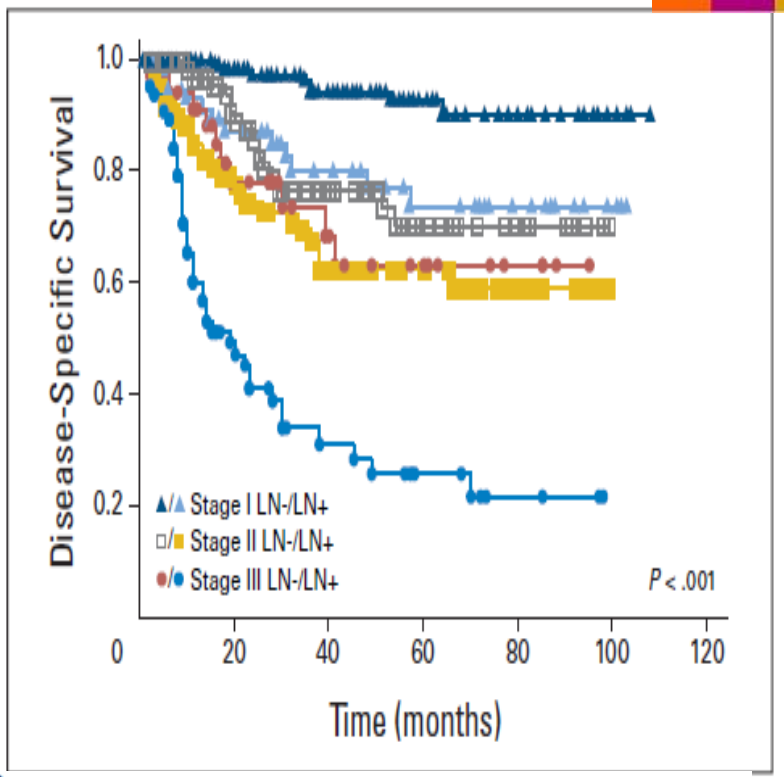
Quinn et al FIGO annual report 2006

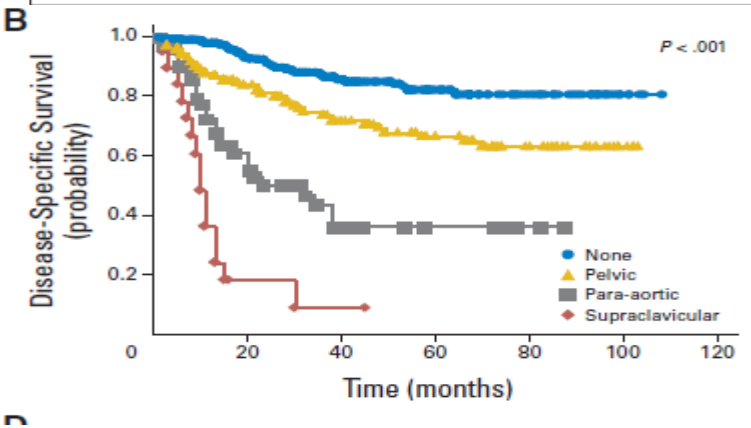
Outcome & Nodal status

Table 2. Comparison of Pelvic and Para-Aortic Lymph Node Metastasis by Stage From Combined Historical Data[3,16-19] and Data From This Study With FDG-PET Lymph Node Staging

	Pelvic Nodal Metastasis (%)		Para-Aortic Metastasis (%)	
FIGO Stage	Historical Data	Current Study	Historical Data	Current Study
I	12-38	9-51	0-5	0-9
IIA	10-45	50	0-12	21
IIB	26-62	54	10-21	17
IIIA	39-59	50	21-33	25
IIIB/IV	39-88	55-85	13-38	27-60

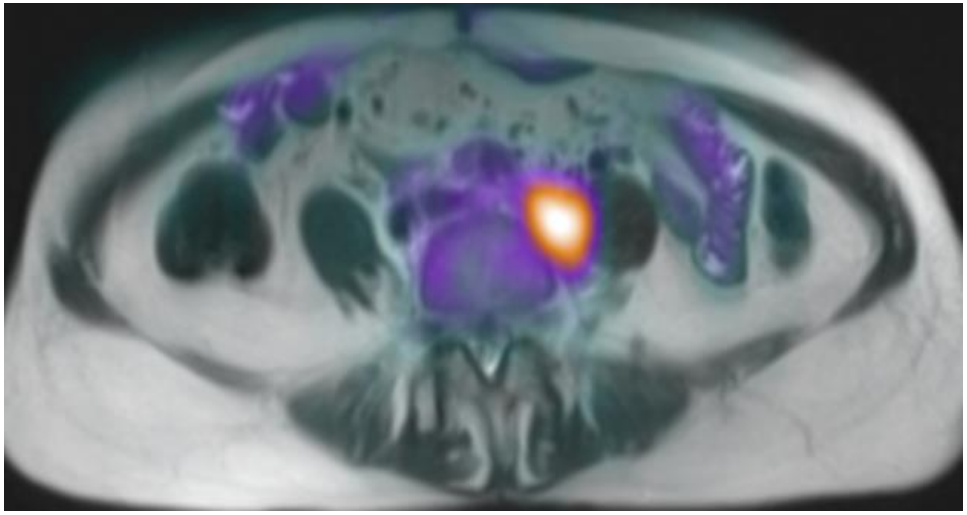
Abbreviations: FDG-PET, positron emission tomography with [^{18}F]fluoro-deoxyglucose; FIGO, International Federation of Gynecology and Obstetrics.

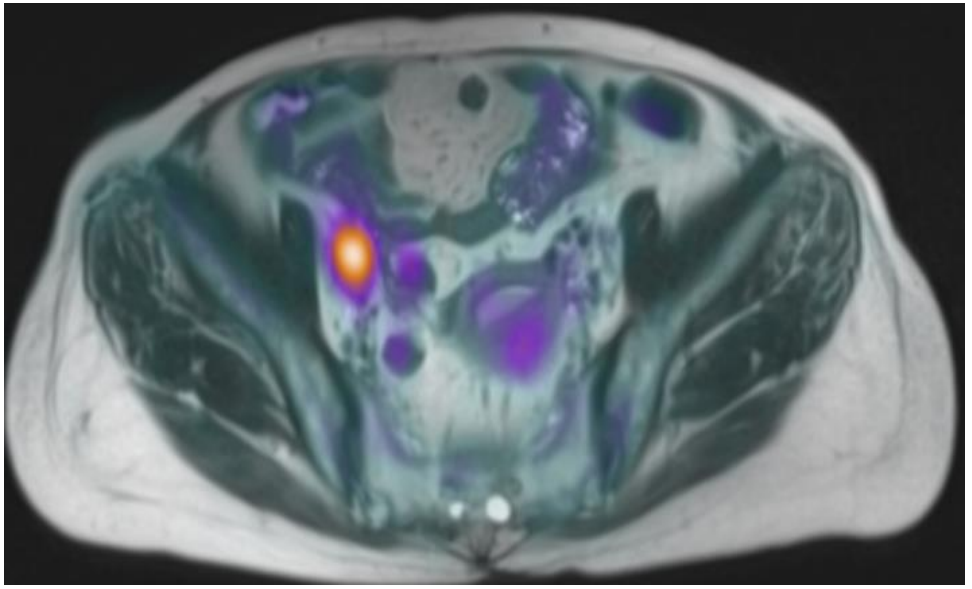




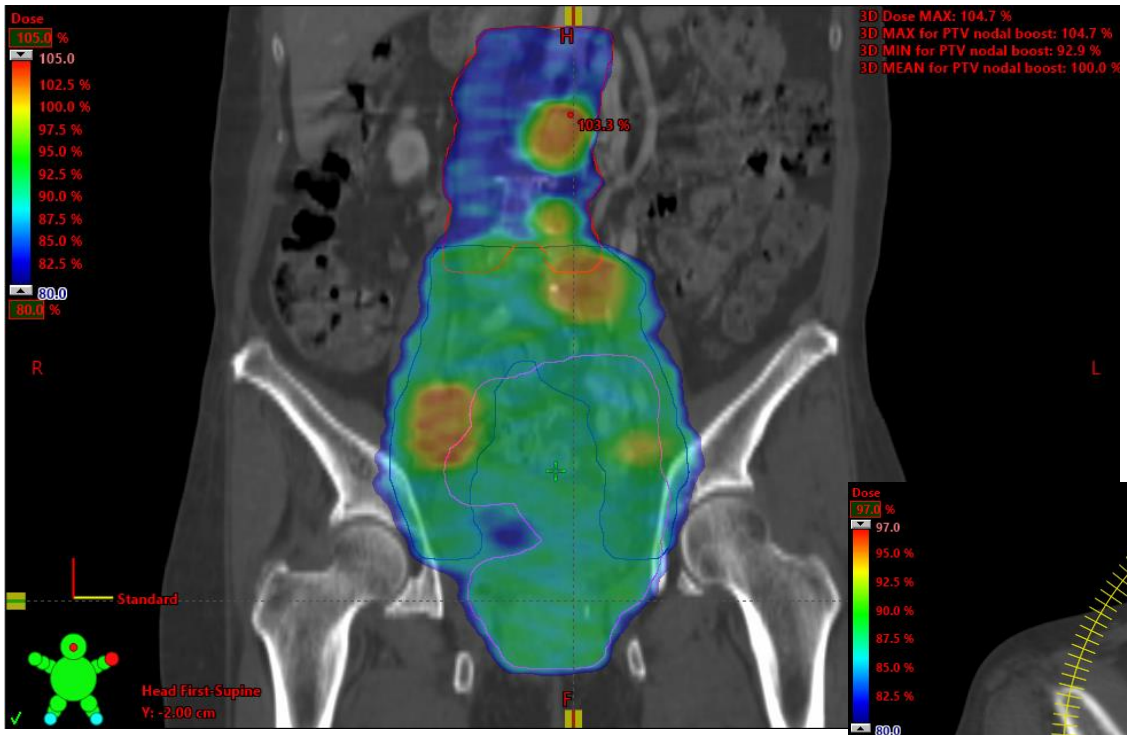
Kidd et al JCO,2010

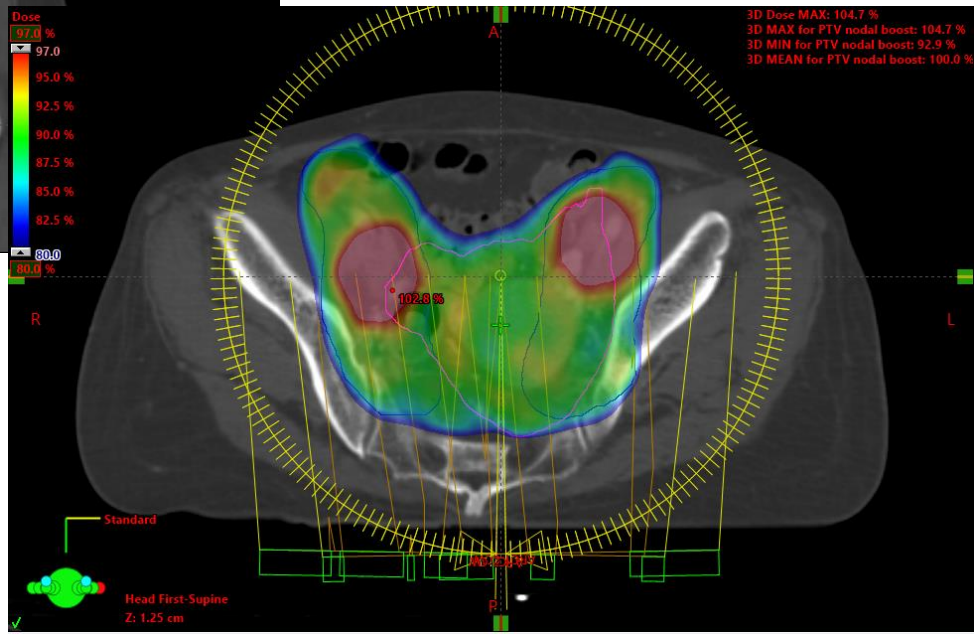
Staging- nodal





Accurate target definition





PA nodal metastasis & outcome in PET negative patients

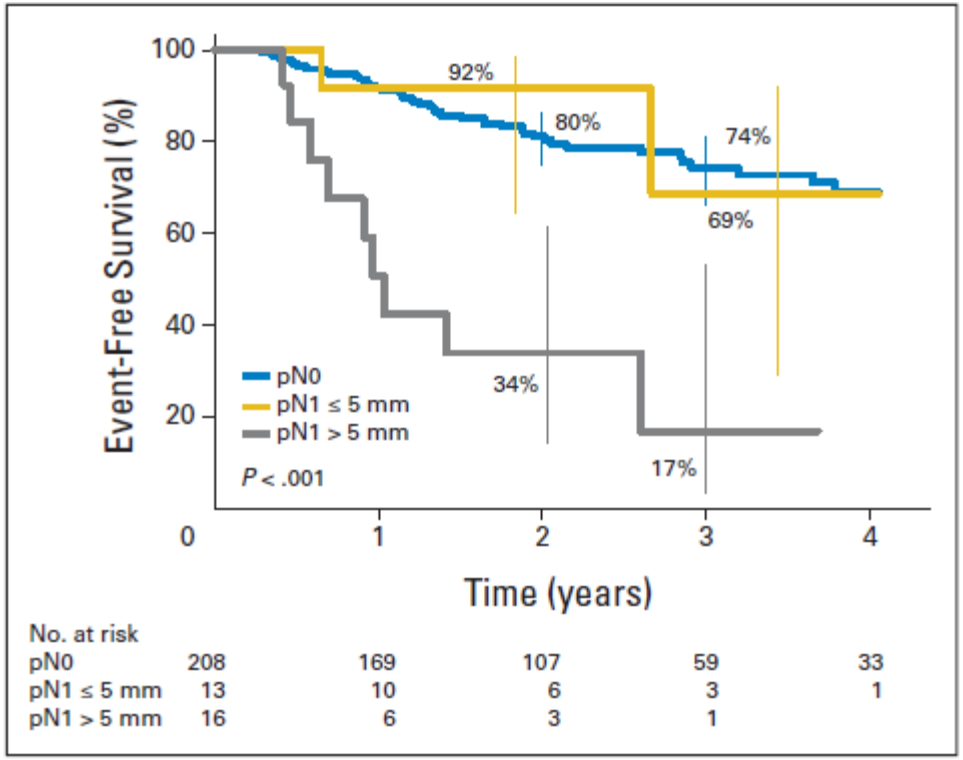


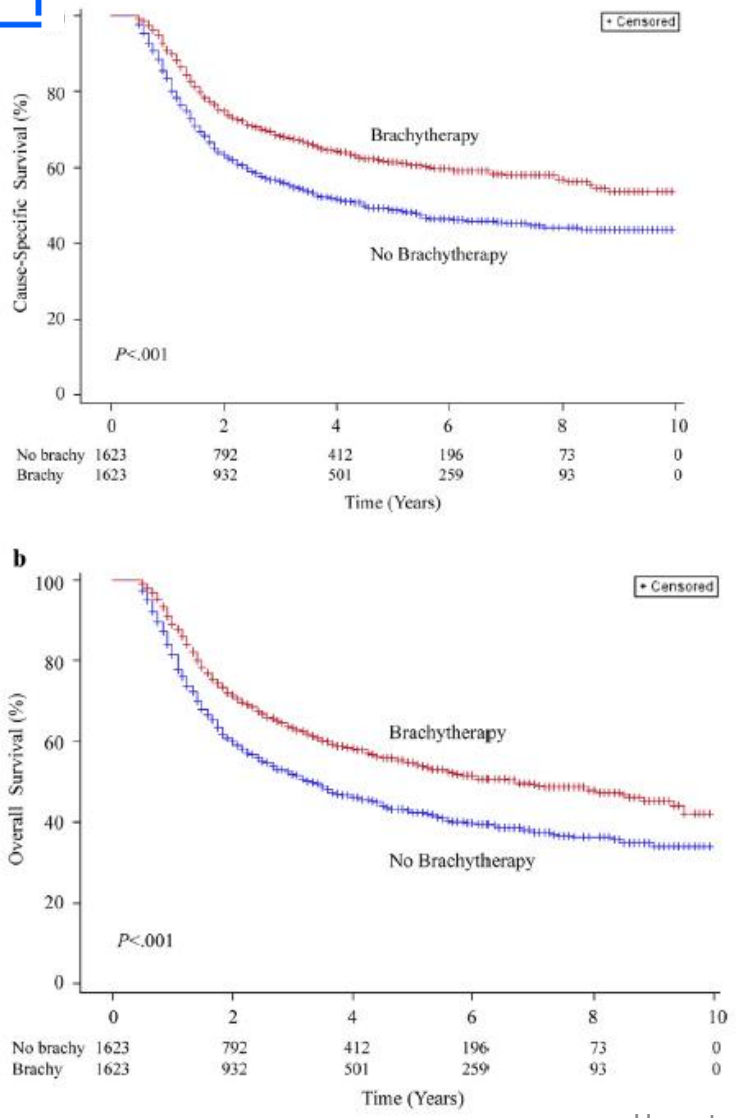
Fig 2. Prognostic impact on event-free survival of the size of metastatic para-aortic nodes.

- Prospective muliticenter study
- 237 pts PA node negative on PET
- Lap surgical staging
- 12% positive PA nodes
- Outcome related to size

Gouy et al J Clin Oncol 2013

Local control

Role of Brachytherapy



Seer analysis of 7359 cases stage IB2-IVA cervical cancer definitive RT (ExBRT+/-Brachy)

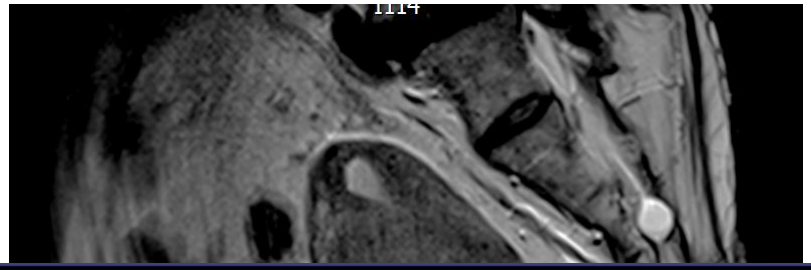
- Matched cohorts 2000-09
- CSS- 64% V 51% (No BT)
- OS –58% V 46% (No BT)
- BT independently associated with CSS/OS

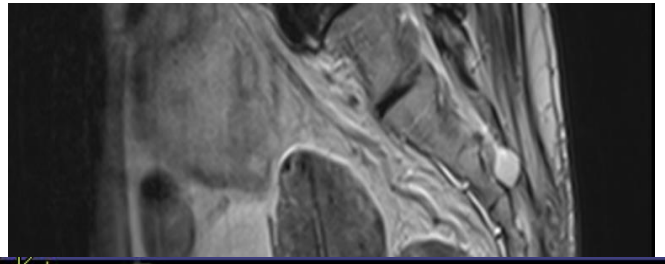
Han et al IJROBP 2013

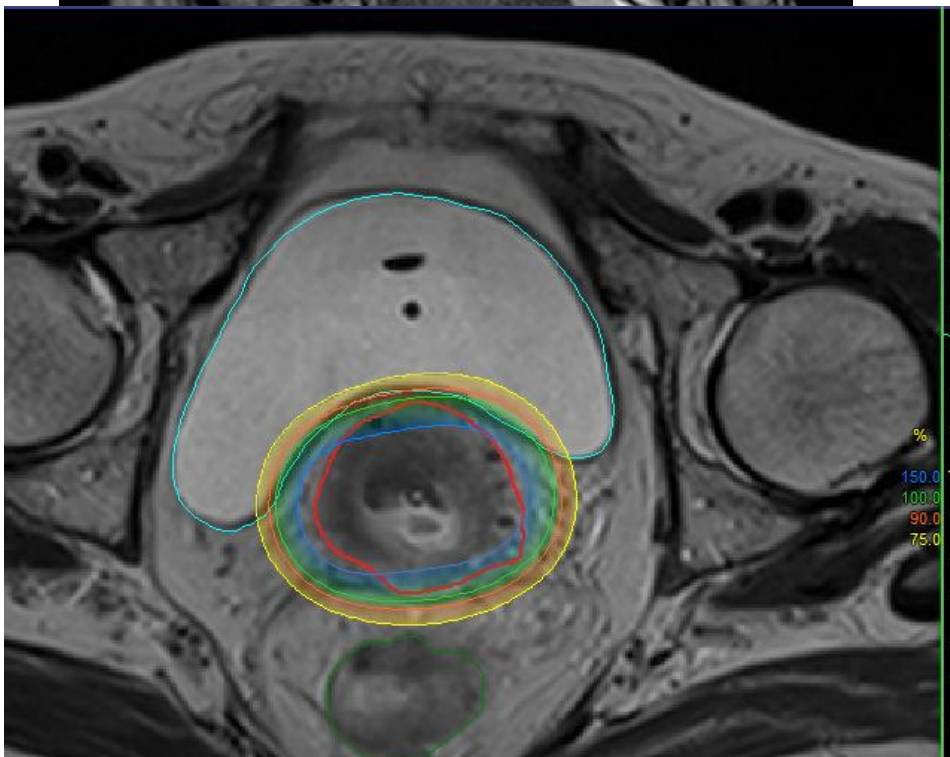
Image guided adaptive brachytherapy

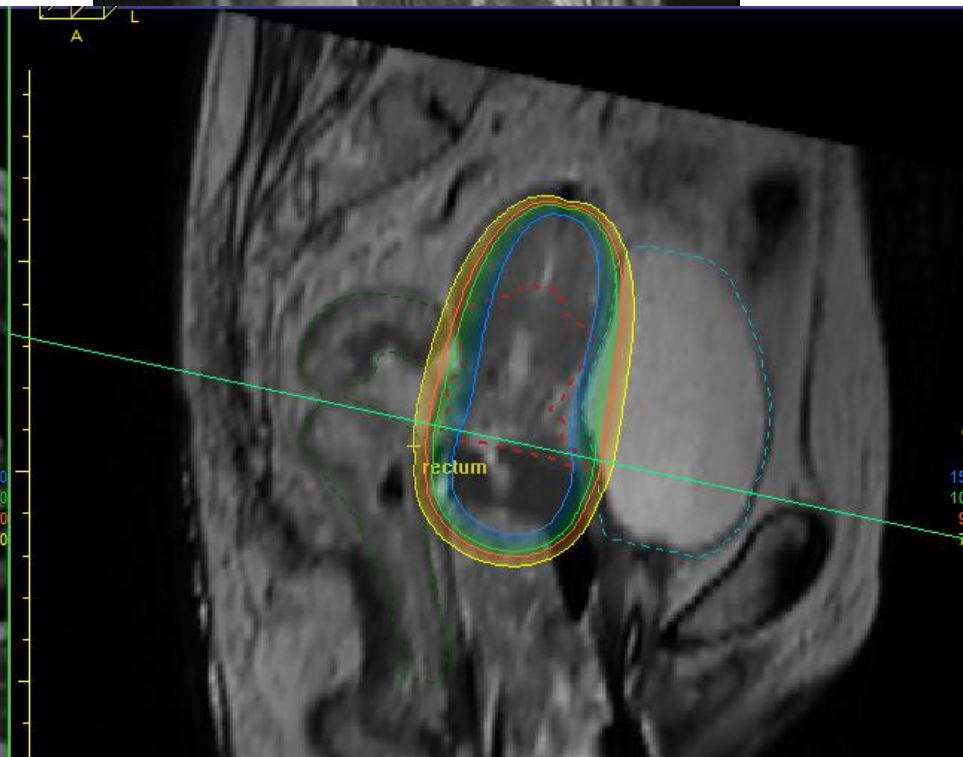
- Technical advances in imaging & RT planning led to increased precision in brachytherapy practice
- More accurate definition of target volume & dose escalation
- Dual aim-improve LC & reduce normal tissue toxicity
- Colleagues in Vienna, Denmark and France led the way in developing IGABT

MRI -local staging & target definition for Brachy









RetroEMBRACE

Table 1
Patient and tumour characteristics.

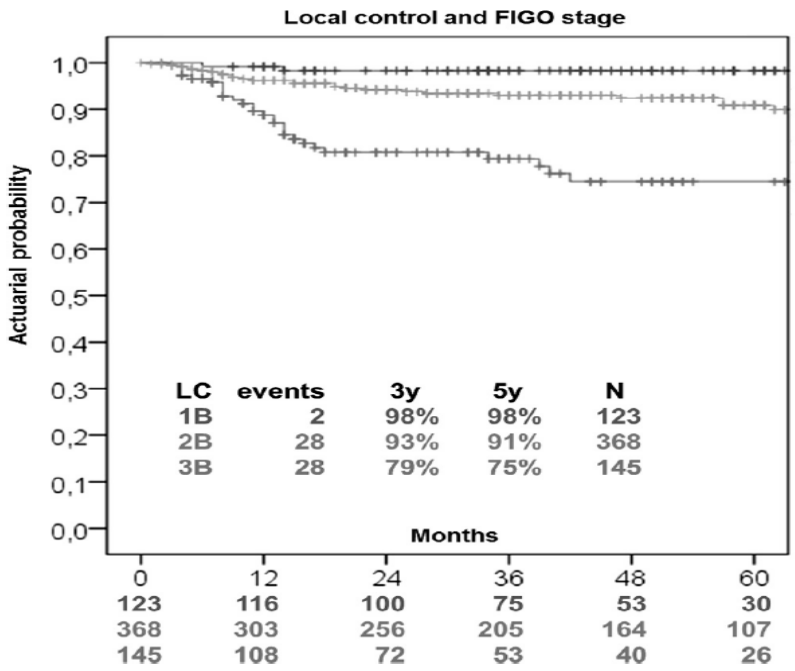
Variable		No of patients *n*/%
Median age (years)	53 (23–91)	731
FIGO stage	1B	123 (16.8%)
	2A	42 (5.6%)
	2B	368 (50.3%)
	3A	23 (3.1%)
	3B	145 (19.8%)
	4A	23 (3.1%)
Histology	Squamous cell Ca	591 (84.7%)
	Adenocarcinoma	9.3%
	Others	6%
Median tumour width at diagnosis	Clinically: 50 mm	MRT: 46 mm
Nodal status	N+	40%
	N−	60%
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)

- Retrospective obs study 731pts
- Cohorts 12 institutions
- 91% treated 3D conformal EXBRT
- All MR guided BT

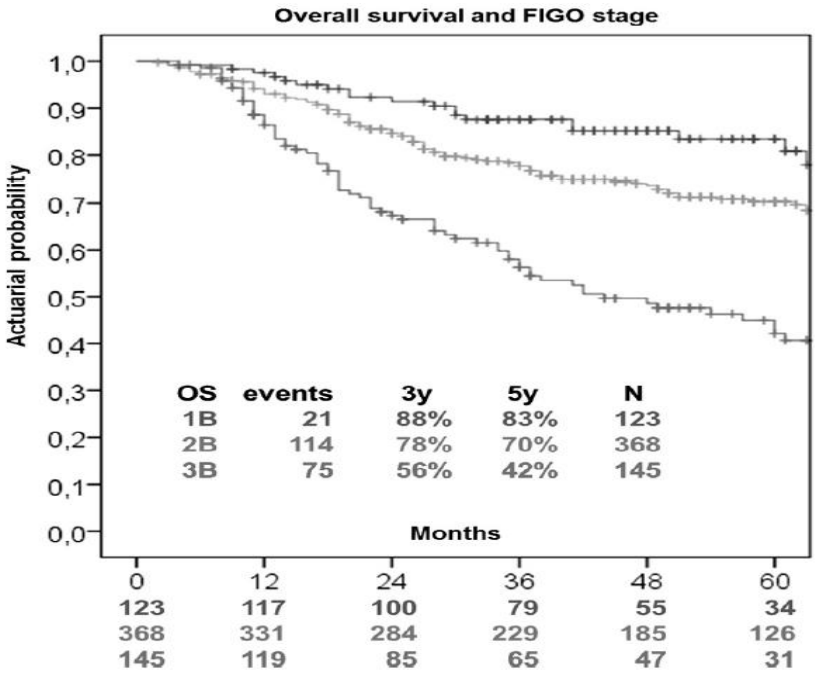
Sturdza et al Radiotherapy & Oncol 2016

RetroEMBRACE

Local control



Overall survival



G3-5 morbidity at 5 years
5%,7%,5% for bladder/GI tract/vagina

Sturdza et al Radiotherapy & Oncol 2016

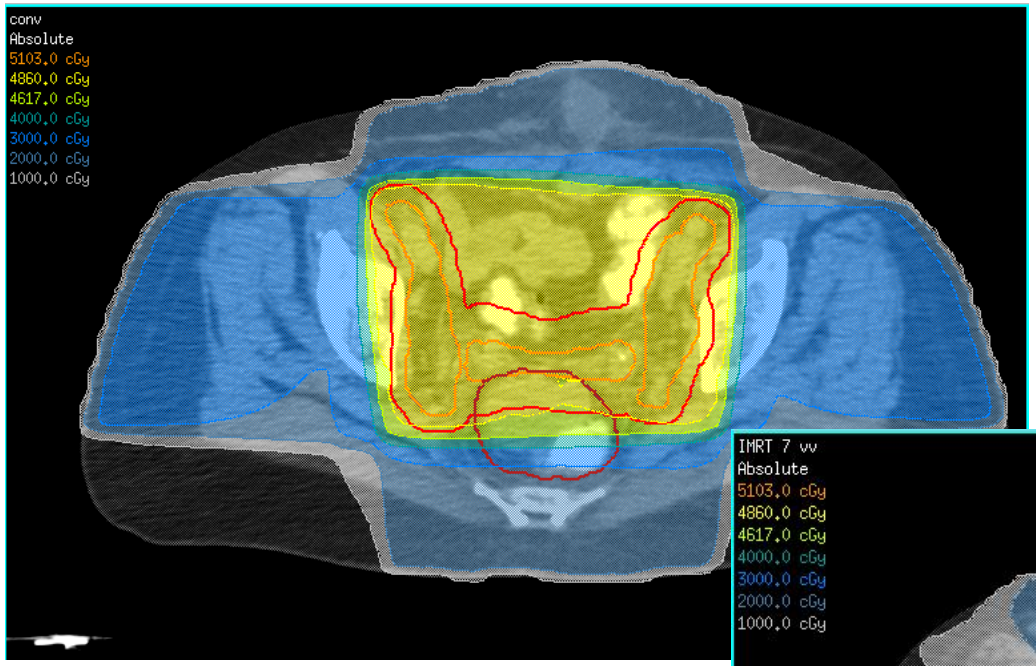
Morbidity & QOL

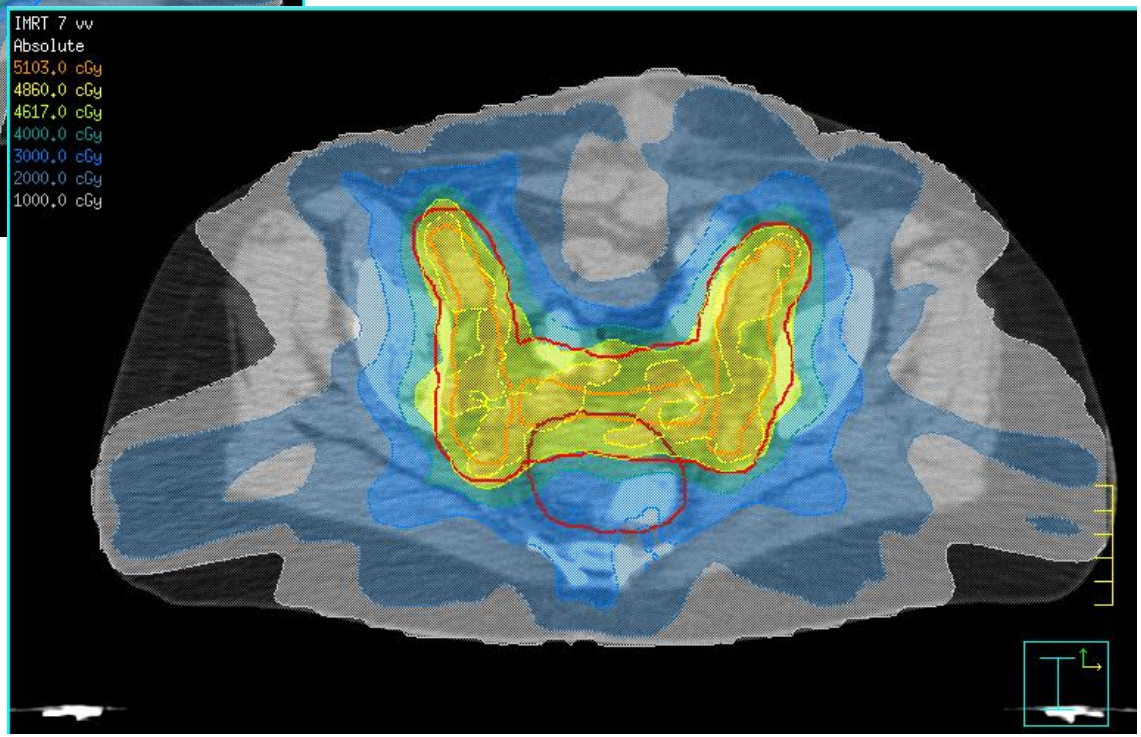
Frequency and range of GI symptoms reported after pelvic RT in Gyn patients

	Gynaecological cancer	
	Reported frequency (%)	Proportion who reported symptom affects quality of life (%)
Rectal bleeding	23–26%	11%
Bloating	32–45%	NA
Change in bowel habit	75–89%	49–79%
Constipation	21%	79%
Abdominal cramps	12%	NA
Diarrhoea (loose or soft stool)	52%	57–67%
Faecal incontinence	25–47%	30–89%
Excessive flatulence	23–50%	NA
Increased frequency of defaecation	56%	NA
Inability to differentiate solid from liquid stool or gas	NA	NA
Lactose intolerance	NA	6%
Mucus discharge	NA	NA
Nausea	10%	NA
Nocturnal defaecation	NA	NA
Pain (abdominal, rectal, anal, or perineal)	34–52%	28–77%
Sexual activity curtailed by bowels	11%	NA
Tenesmus	14–31%	NA
Defaecation urgency	48–53%	21–79%
Vomiting	14%	NA
Weight loss	0–83%	NA

Modified from Andreyev Lancet Oncology 2007;8(11):1007

3D CRT and IMRT



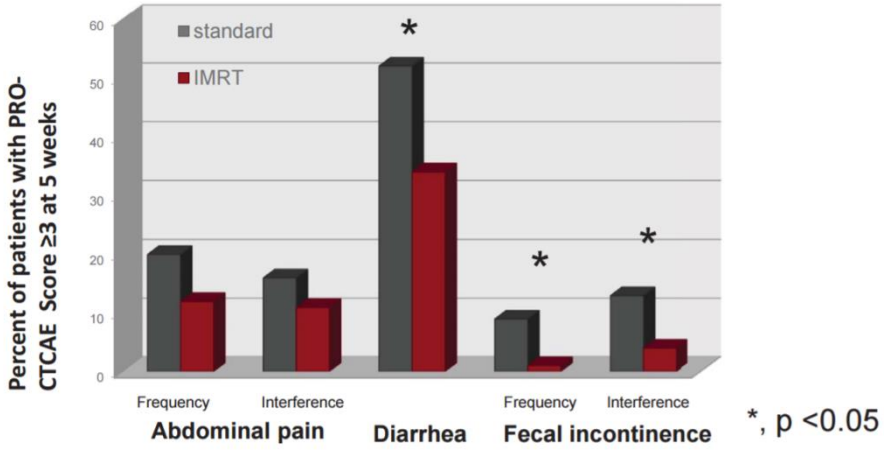


3D CRT vs IMRT

NRG – RTOG Time-C trial (presented at ASTRO 2016)

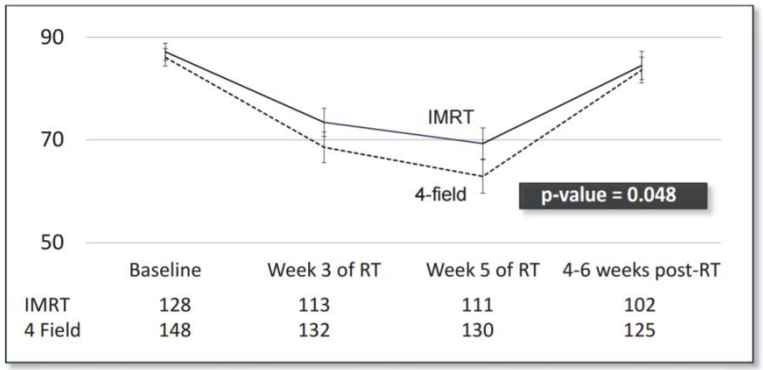
- Randomised trial of IMRT vs 4-field pelvic radiotherapy
- IMRT reduces acute GI and GU toxicity at 5 wks
- IMRT improved QOL with regard to physical functioning

Pro-CTCAE Results



*, p <0.05

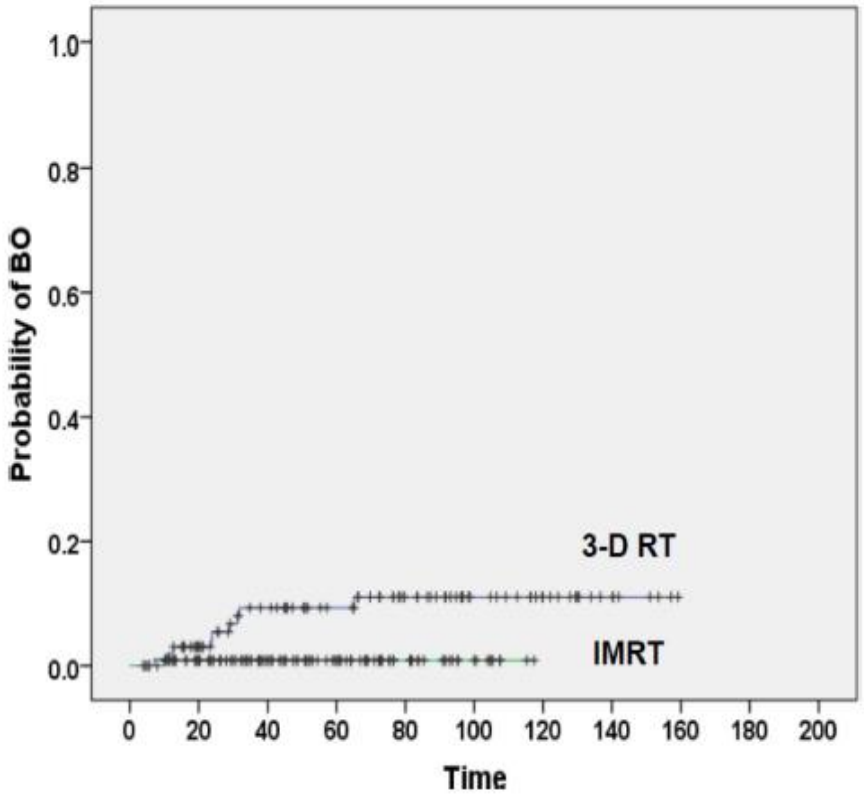
EPIC Bowel Score



Klopp et al, ASTRO 2016

3D CRT and IMRT

Bowel obstruction



- Retrospective review 224pts/12years
- Overall 5yr actuarial rate BO 4.8%
- 5 yr rate 9.3% (3D CRT) & 0.9% IMRT

Shih et al Gynae Oncol 2016

Morbidity with IGABT

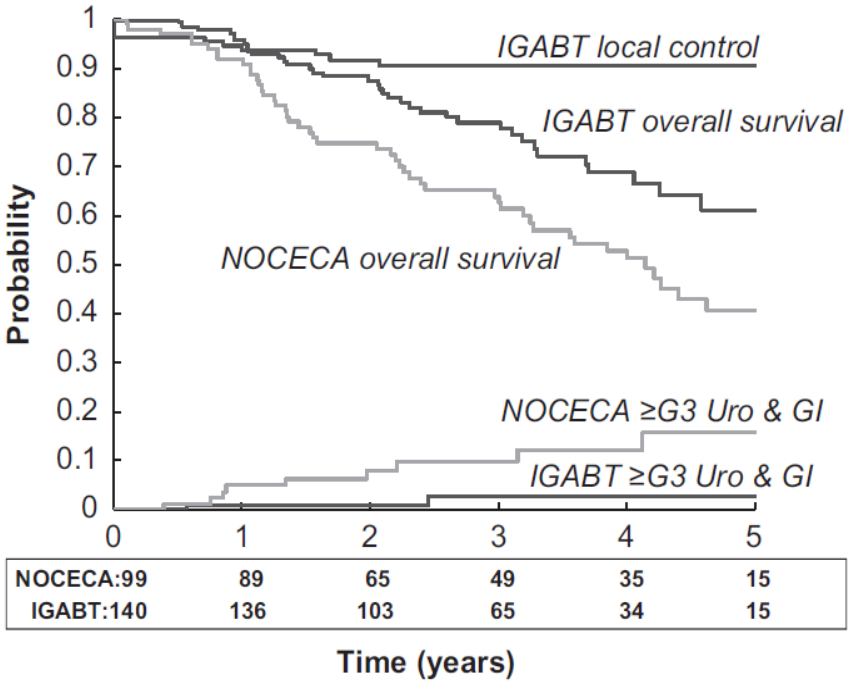


Table IV. Outcome in terms of actuarial three-year disease control, survival and morbidity in 140 consecutive patients treated with MRI-guided IGABT compared with 99 patients treated with x-ray-based BT (NOCECA).

Cohort	IGABT	NOCECA	p-value	Hazard ratio
Local control	91%	–	–	–
Pelvic control	85%	76%	0.12	1.6 (0.9–2.8)
Cancer-specific survival	87%	68%	0.001	5.0 (2.8–8.9)
Overall survival	79%	63%	0.005	1.8 (1.2–2.8)
Overall survival IIB–IV	77%	63%	0.01	1.7 (1.1–2.6)
G2 ≥ urological	17%	18%	0.29	1.4 (0.7–2.7)
G2 ≥ gastrointestinal	18%	35%	<0.001	2.9 (1.6–5.2)
G2 ≥ vaginal	33%	87%	<0.001	4.8 (2.7–8.4)
G2 ≥ overall	55%	90%	<0.001	4.3 (2.9–6.4)
G3 ≥ urological	1%	2%	0.23	3.6 (0.5–26.0)
G3 ≥ gastrointestinal	3%	8%	0.08	3.8 (0.9–15.5)
G3 ≥ vaginal	4%	9%	0.08	2.8 (0.9–8.7)
G3 ≥ overall	7%	15%	0.02	3.0 (1.2–7.3)

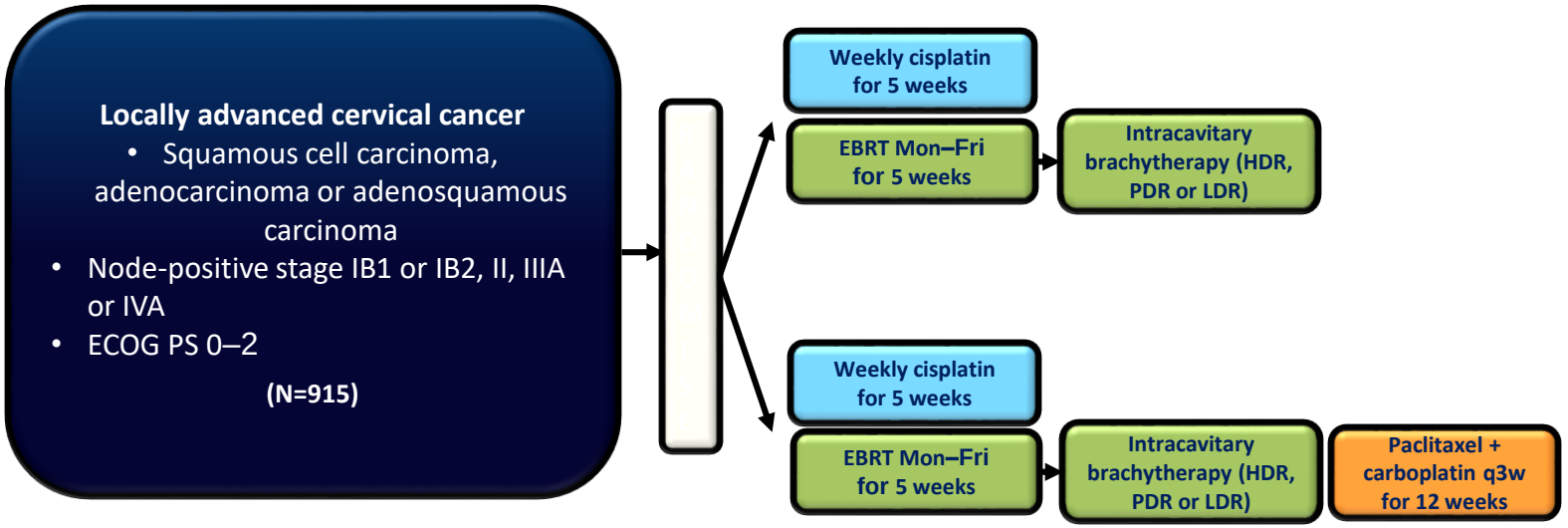
Lindegaard et al Acta Oncologica 2013

OUTCOME

OUTBACK (GOG 0274/RTOG 1174/ANZGOG 0902

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP

OUTBACK



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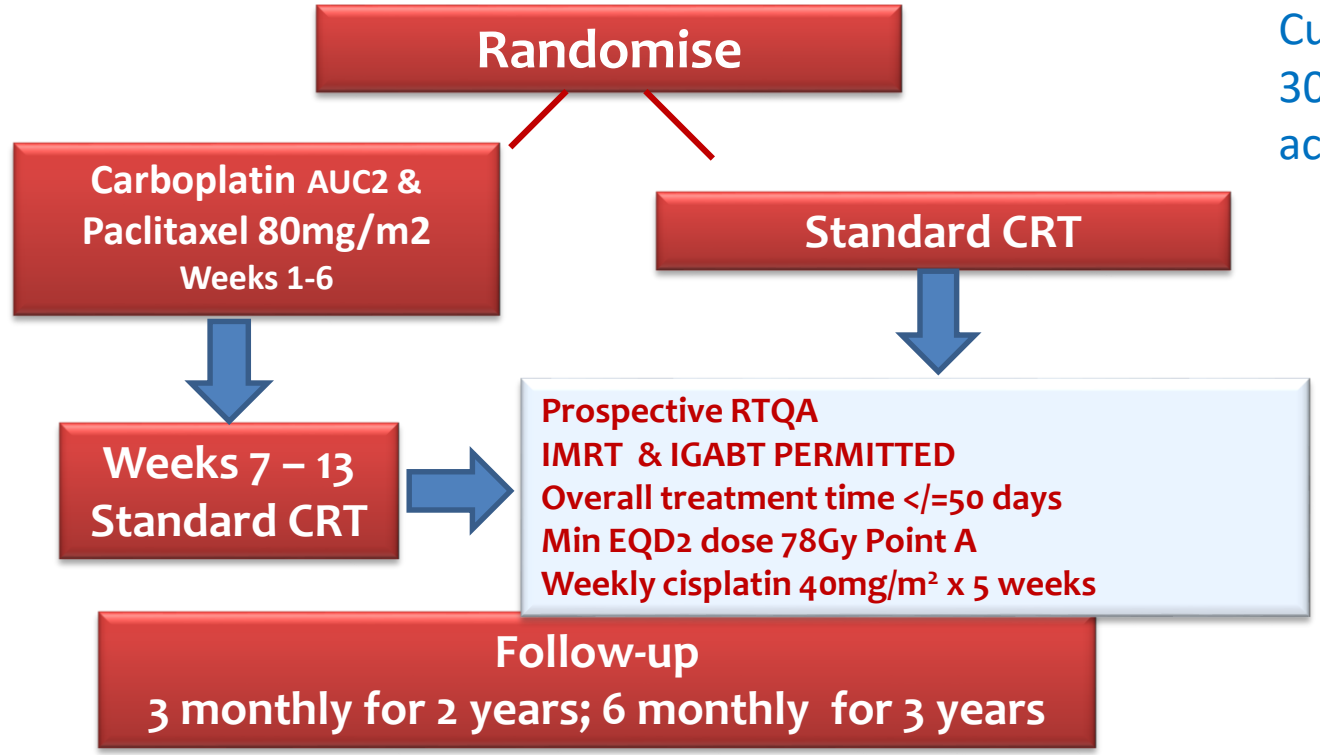
INTERLACE



Current status
300/500 pts
accrued

Conclusions

- Radiation therapy come along way since

Chicago physician early-1900s: "I believe this treatment is an absolute cure for all forms of cancer. I do not know what its limitations are."

- Urgent need to improve survival further-on going trials chemo

- Define role of immunotherapy in this disease

- Survivorship and QOL of paramount importance