The Optimal Treatment for Locally Advanced Cervical Cancer

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My personal view

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University Hospitals Birmingham
NHS Foundation Trust


John Lewis

- It is rare in epithelial cancer to achieve curative treatment using radiotherapy or chemotherapy as the sole modality of treatment

Cervical Cancer- the myths

IB2/IIA(early) Carcinoma of the cervix

Landoni Lancet 1997 vol 350, 9077 535-540

S v RTO

Post op RT (High risk)*

- Surgery vs Radical Radiotherapy (n=343, p-15% difference)

- *High risk Surgery (+ve nodes, <3 mm margin or +ve margins, pIIB, cut-through) given post op RT (54% of Ib1 and 84% of Ib2)

- DFS (>4 cm) at 5 years
- 63%(S) vs 57% (RT)
- OS (>4cm) at 5 Years
- 70% vs 72% at 5 years (No Systemic chemotherapy !)

Pelvic Recurrence (>4cm)

- Surgery followed by RT
- 9/46(19%)
- Radiotherapy alone
- 16/54(30%) Dose of radiotherapy 76 Gy to point A

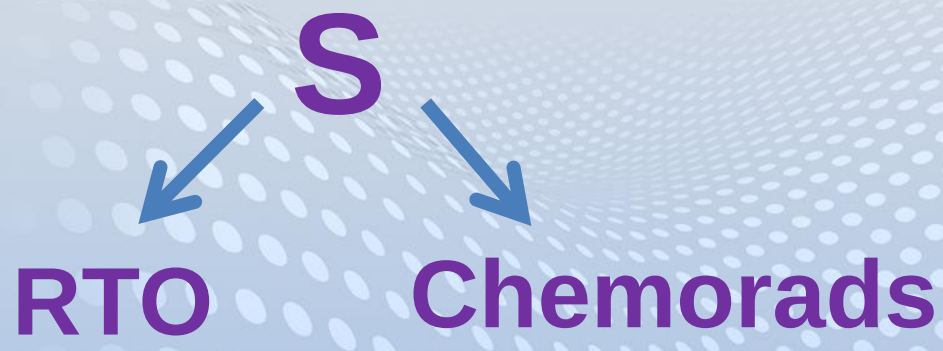
Significant Survival benefit for Surgery in Adenocarcinoma of the cervix

- DFS at 5 Years
- 66%(S) vs 47% (RT) p=0.02
- Overall Survival at 5 years
- 70%(S) vs 59% p=0.05
- 20 year follow-up 71% vs 47% p=0.09

Morbidity

- 28% (S) vs 12%(RTO) - Lower Dose than 2016
- 31% (S) vs 27% (S followed by RT)
- Acute (0.6 % mortality)
  - Vascular
  - Fistula
  - PE
- Late
  - Bladder
  - Chronic neuralgic bladder
  - Hydroureteropyelonephrosis (10%)
  - Pelvic lymphocysts (18%)

Peters (2000) JCO, 18, 8,1606-1613



- Ia2, IB, IIA Surgery followed by RTO or Chemorads
- Involved nodes (90%)
- Positive margins (10%)
- Microscopic parametrial involvement (68%)

Overall Study Protocol

268 patients –

Radiotherapy dose 49.3 Gy in 29 fractions with 4 field brick (No shielding) +/- PA Node irradiation if +ve common illiac nodes

Chemotherapy (CIS + 5FU)

Results

- 4 Year PFS : 80%(CRT) versus 63% (RTO)
- 4 Year OS (81% versus 71%)
- Reduction in both pelvic(5% vs17%) and extrapelvic recurrence
- Adenocarcinomas and adenosquamous tumours did just as well as squamous tumours for CRT arm but did worse in RTO arm

Toxicity

- Predominantly haematological or related to chemotherapy
- Rectal grade3/4/5: 0
- Bladder3/4/5: 0
- Desquamation /4/5: 0
- Small bowel3/4/5: 2/122 (1.6%) patients small bowel obstruction requiring surgery in CRT arm 0/112 in RTO (excluded patients not having radiotherapy).
- NB PA node irradiation would not be given as standard with involved common iliac nodes in modern practice.

Conformal radiotherapy or IMRT not used

Birmingham 2015 (Yahya et al) 1999-2006

Anticancer Research 35:5567-5574 (2015)

- Largest UK Audit for Cervical Cancer 1999- 2016 Treatment by Chemoradiation (175 patients)
- 73% Primary Chemorads
- 27% Post op Chemorads
- Median BED 90 Gy (77-99.6)

- OS 74% at 3 years
- Stage 1(89%), stage2(76%), stage3 (51%)

Patterns of recurrence

- 9% local failure rate at primary site 3% pelvic nodal relapse (12%)
- local control by stage 99% (stage1), 95% (stage2), 84%(stage 3)

Toxicity

- Grade3/4 late bowel/bladder/bone for primary chemoradiation 16%

- Grade3/4 late bowel/bladder/bone for surgery followed by CRT 4% (p=0.03)

Surgery followed by Chemoradiation had less toxicity than up front Chemoradiation

Vale et al RCR audit of all UK centres 2010

Clinical Oncology vol 22, 7, 588-602

- OS 68% at 3 years for CRT
- Stage1(74%), stage2 (71%) stage3 (51%)
- Local pelvic recurrence rates for CRT: 22%
- Grade3/4 Late effects CRT: 10%
- Grade3/4 Late effects surgery and post op RT or CRT :5%

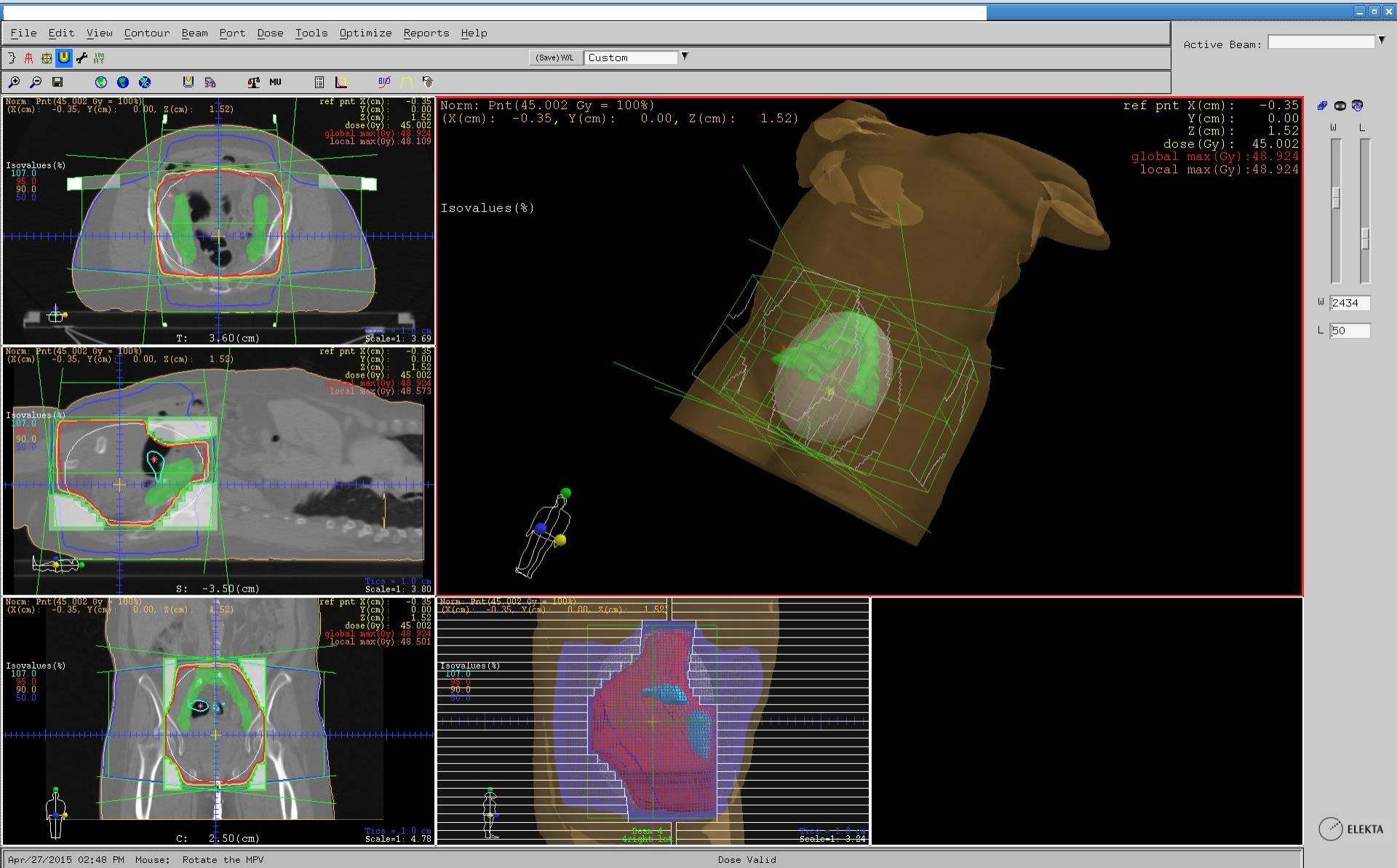
Other advantages of Post operative Chemoradiation in Stage 1B2

- Knowledge of the Histology and in some cases avoiding Radiotherapy completely
- Use of omental spacer at time of surgery to reduce bowel volume (Omentoplasty)

Logmans et al Radiotherapy Oncology (1994, 33 269-271) 60% reduction in bowel volume during radiotherapy

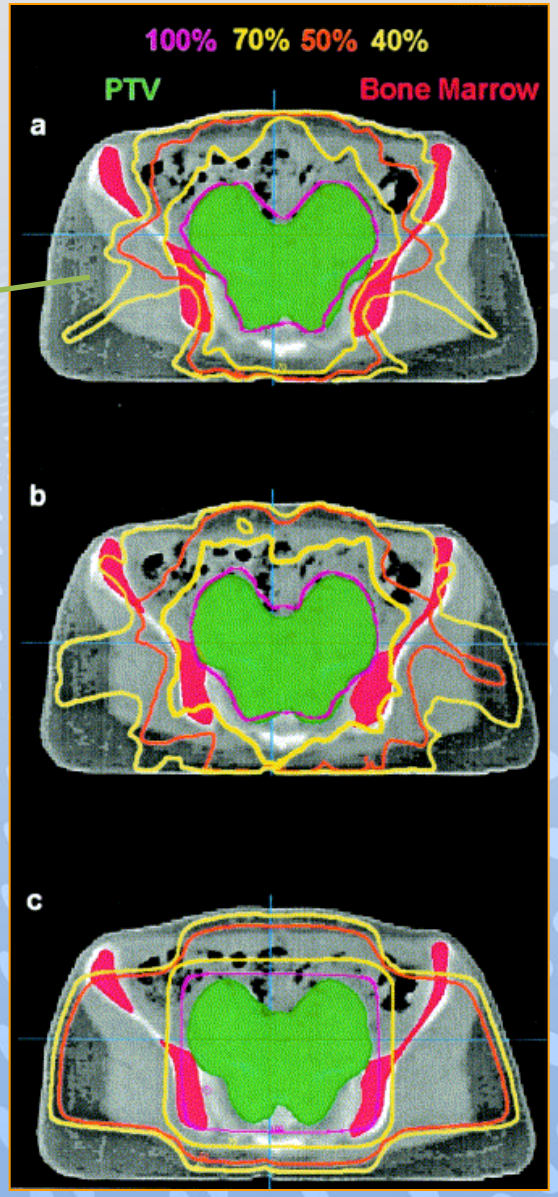
- Use of IMRT (more favourable post op)

Conformal radiotherapy



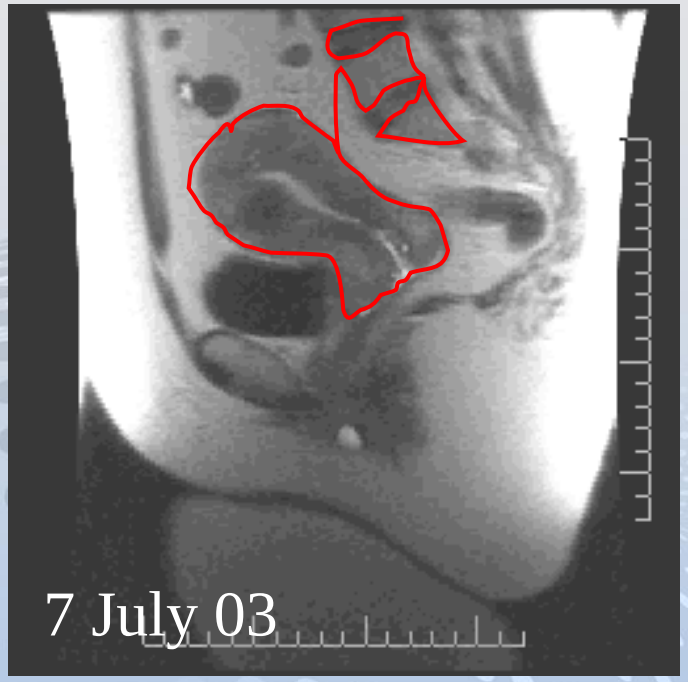
What can IMRT do ?

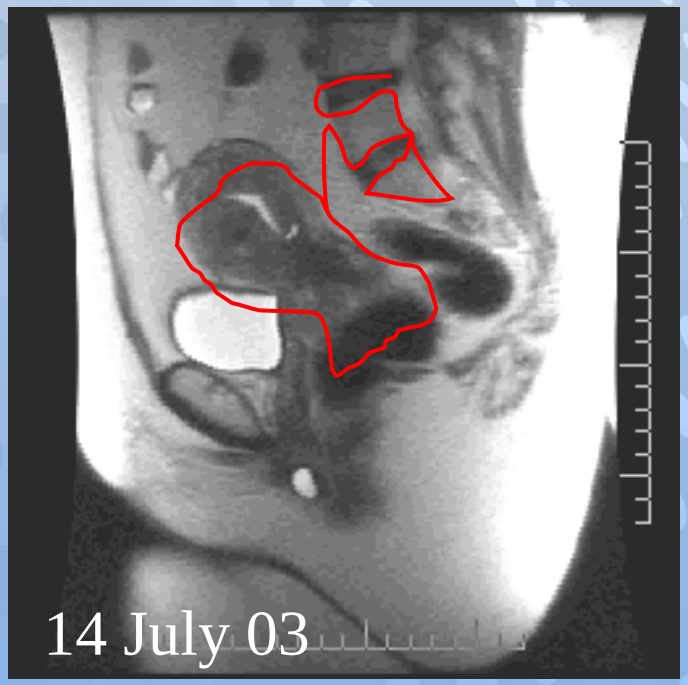
- Reduction of dose to normal structures - ‘conformal avoidance’
- Deliver multiple dose levels at one time
  - simultaneous in-field boost
  - mimicking brachytherapy distributions

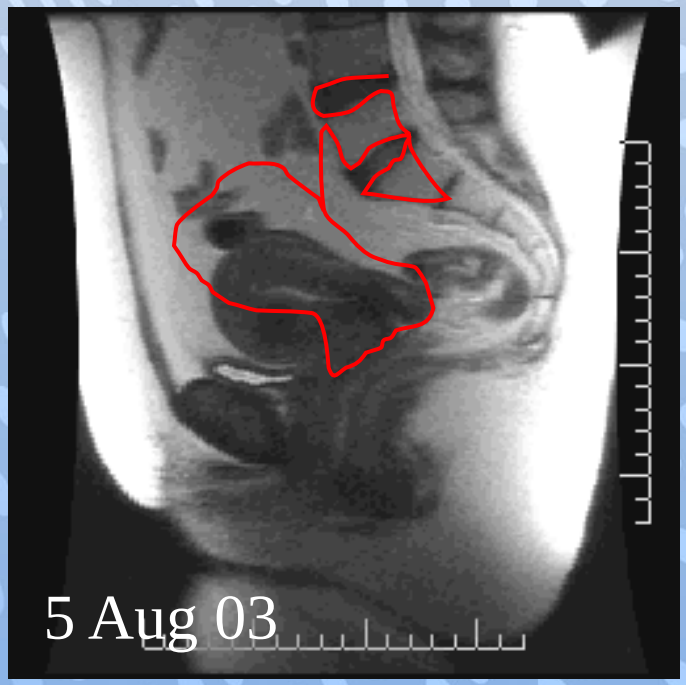


Lujan et al IJROBP 57 (2003) 516

Inter-fraction Organ Motion

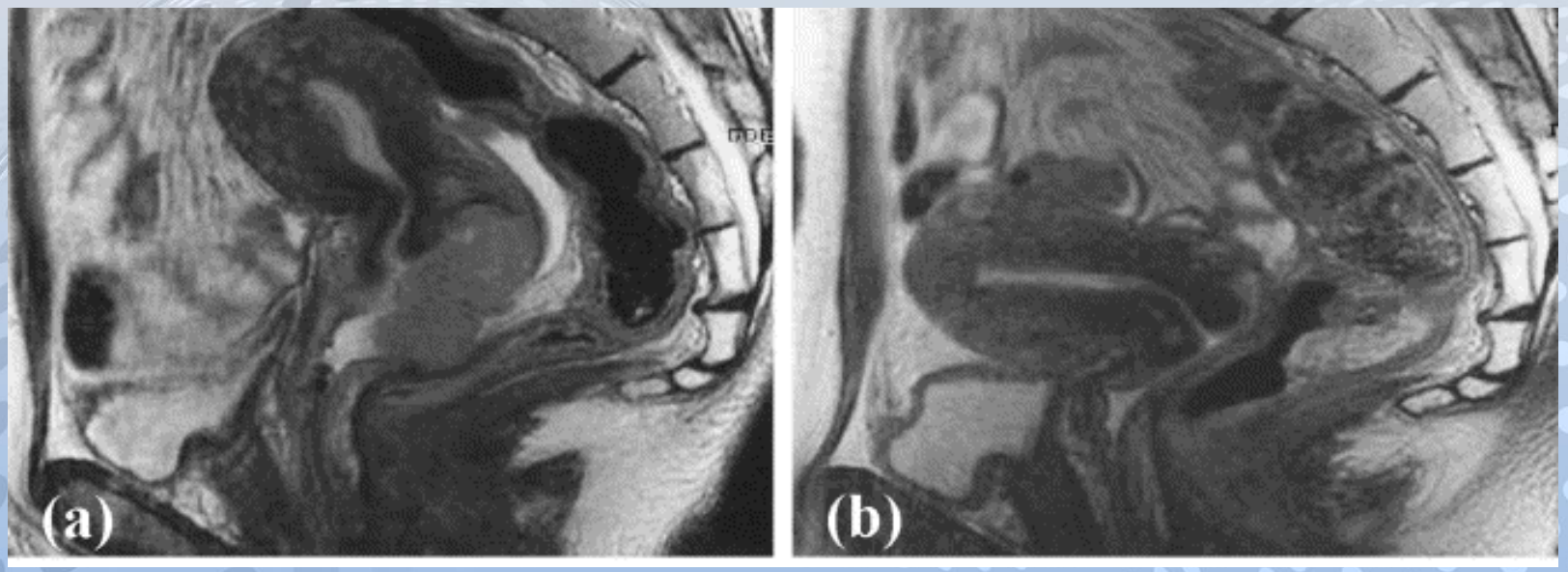




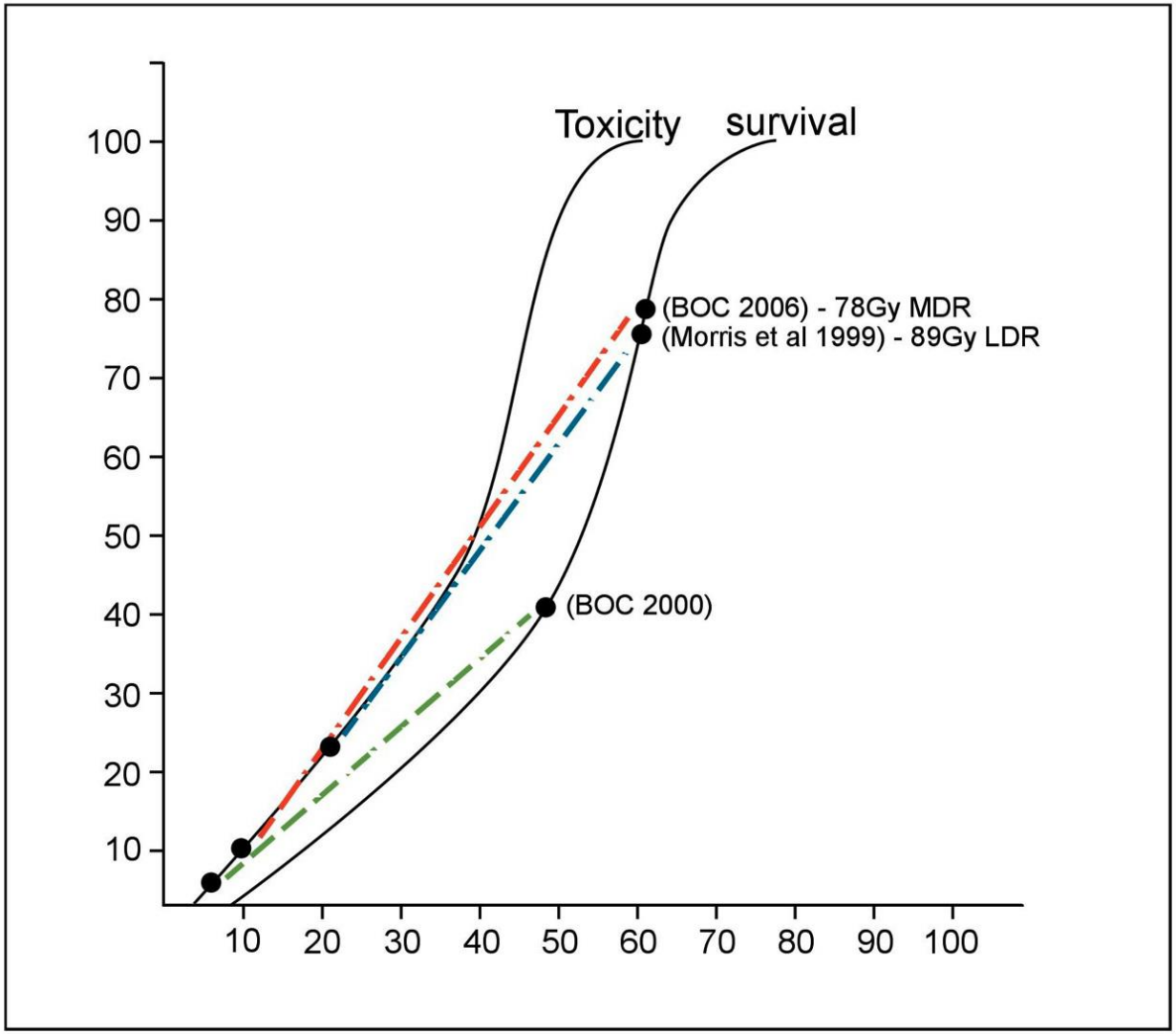


Courtesy A Fyles

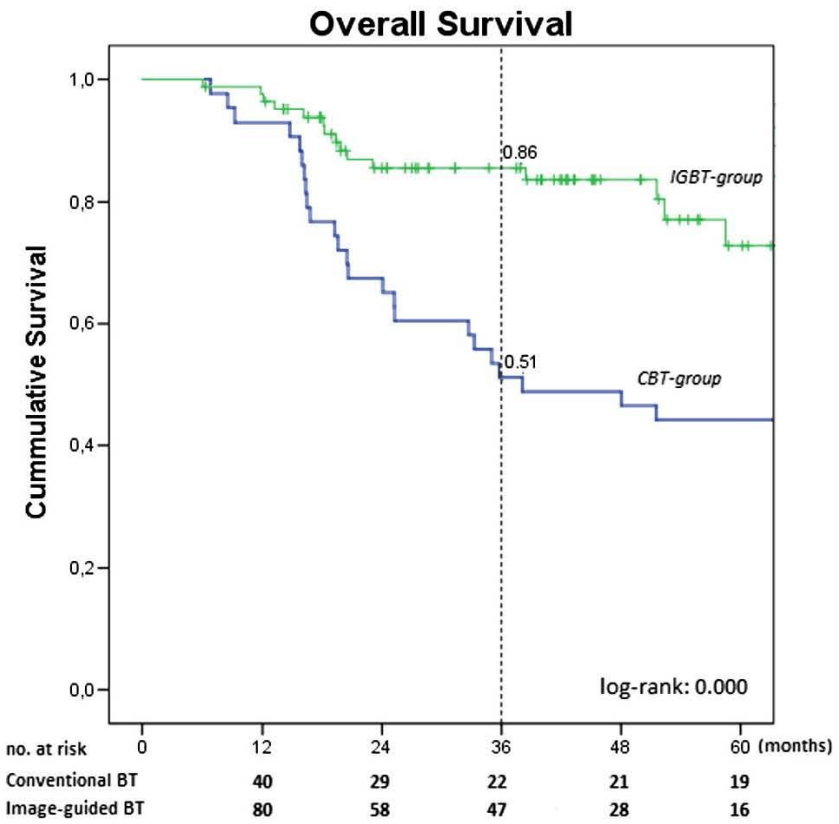
…is it constant?

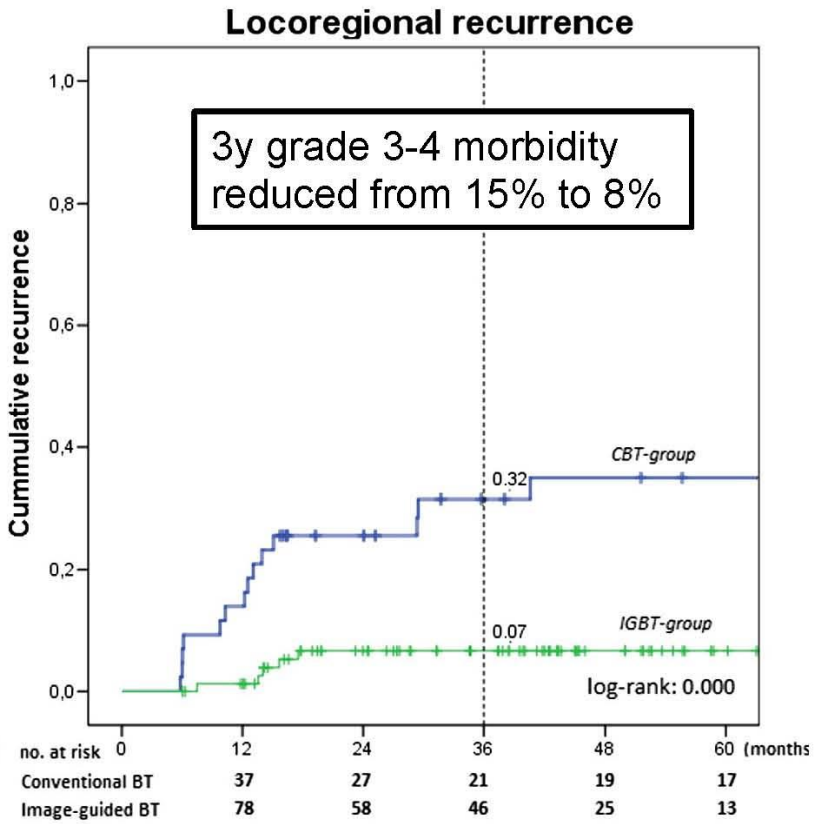


From Huh, SJ et al Radiother. Oncol. 71 (2004) 73
2 MRI T2 weighted images of the same patient 4 weeks and 35Gy apart


Toxicity
survival
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
60
70
80
90
100
(BOC 2006) - 78Gy MDR
(Morris et al 1999) - 89Gy LDR
(BOC 2000)

Leiden experience





Rijkmans et el Gyn Oncol 2014

Neoadjuvant Chemotherapy followed by Radical Surgery vs Chemoradiation in Stage IB2, IIA, IIB Squamous Carcincoma

- Gupta *et al* (JCO 2018)
- No difference in OS but difference in late toxicity

	Bladder	Rectum	Vagina
NC-Surgery-RT/CRT	1.6%	3.5%	12%
CCRT	3.5%	2.2%	25%

- Therapeutic gain

‘ Avoid combination treatment as you get double the toxicity ‘

With modern Radiotherapy especially with IMRT significant benefit in terms of toxicity and local control for post op Chemorads verses up front Chemorads

Surgery should be considered for cases of Adenocarcinoma / Adenosquamous /? Clear cell of the cervix

Patients should be warned as to toxicity of Chemorads including Brachytherapy

‘Standard treatment should be Chemoradiation’

There needs to be more discussion with the patient regarding the pros and cons of surgery + Chemorads verses Chemorads

‘Why should I operate just to reduce the side effects of the radiation therapy’

As oncologists, our role must be to consider the ‘whole package of treatment’ to decide which is best for the patient

Is There A Role For Adjuvant Hysterectomy After Suboptimal Concurrent Chemoradiation In Cervical Carcinoma

Results of retrospective study of external beam versus external beam + brachytherapy in advanced cervical cancer		
	FIGO stage III	> 1096 pt
	EBRT only	EBRT + IBRT
5yrs DFS	27% (>50% local failure)	53% (p<0.0001)
Complications Toxicity	57%	20% (p<0.0001)

Reference:
Lodgson MD Eifel PJ, IJROBP 1999; 43: 49-55

<table>
<tr><th colspan="3">Management of patients with failed brachytherapy for cervical cancer at QEHB</th></tr>
<tr><td colspan="2">1999 - 2007</td><td>19 cases</td></tr>
<tr><td colspan="2">2 policies department</td><td rowspan="2">eg, Uterine perforation, stenosed cervical os</td></tr>
<tr><td>Further External Beam Radiotherapy (for all cases)</td><td>Further external beam radiotherapy followed by Adjuvant Hysterectomy (if sufficient response to make the tumour operable by clinical and radiological imaging)
IF/KKC/KS</td></tr>
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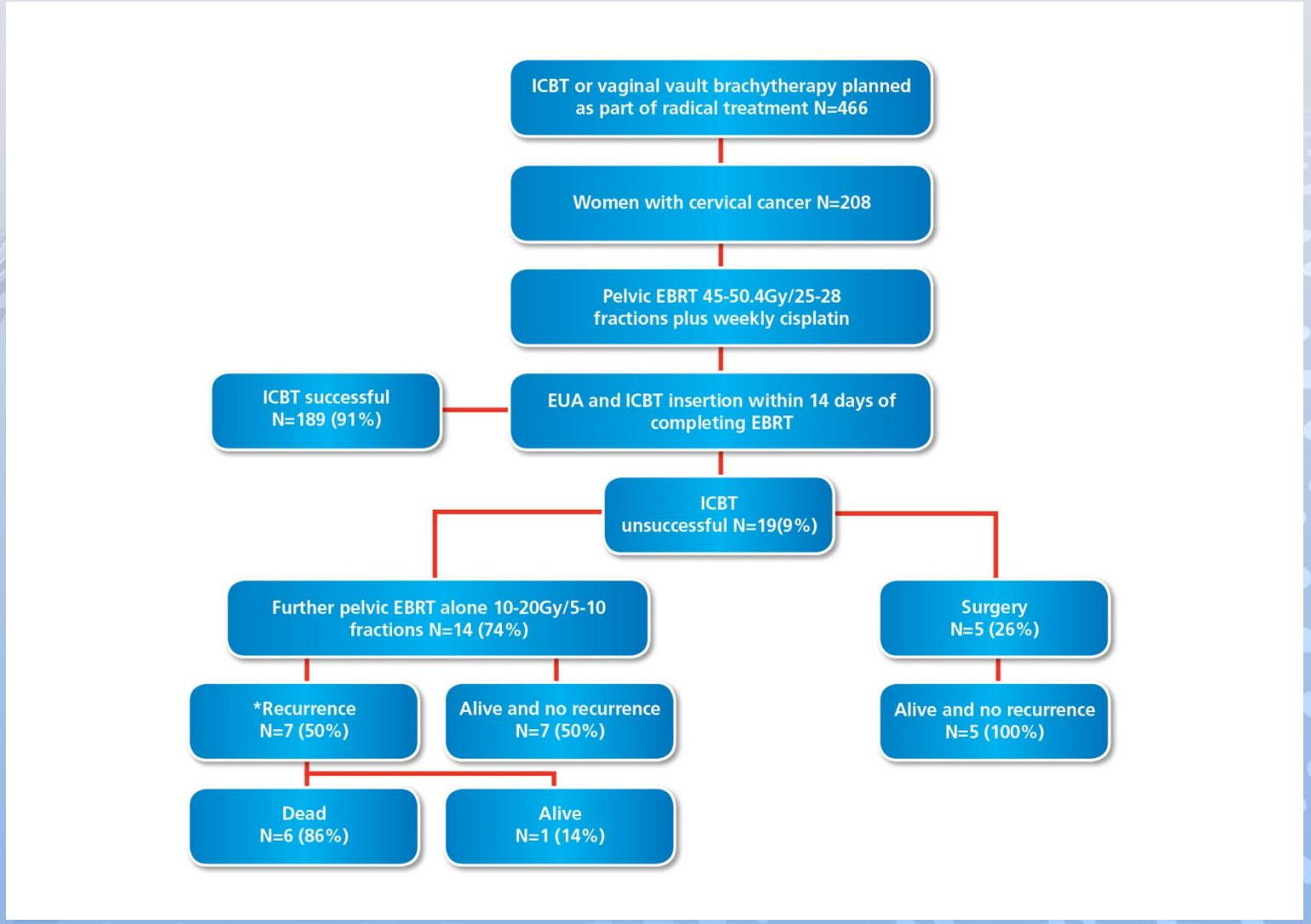
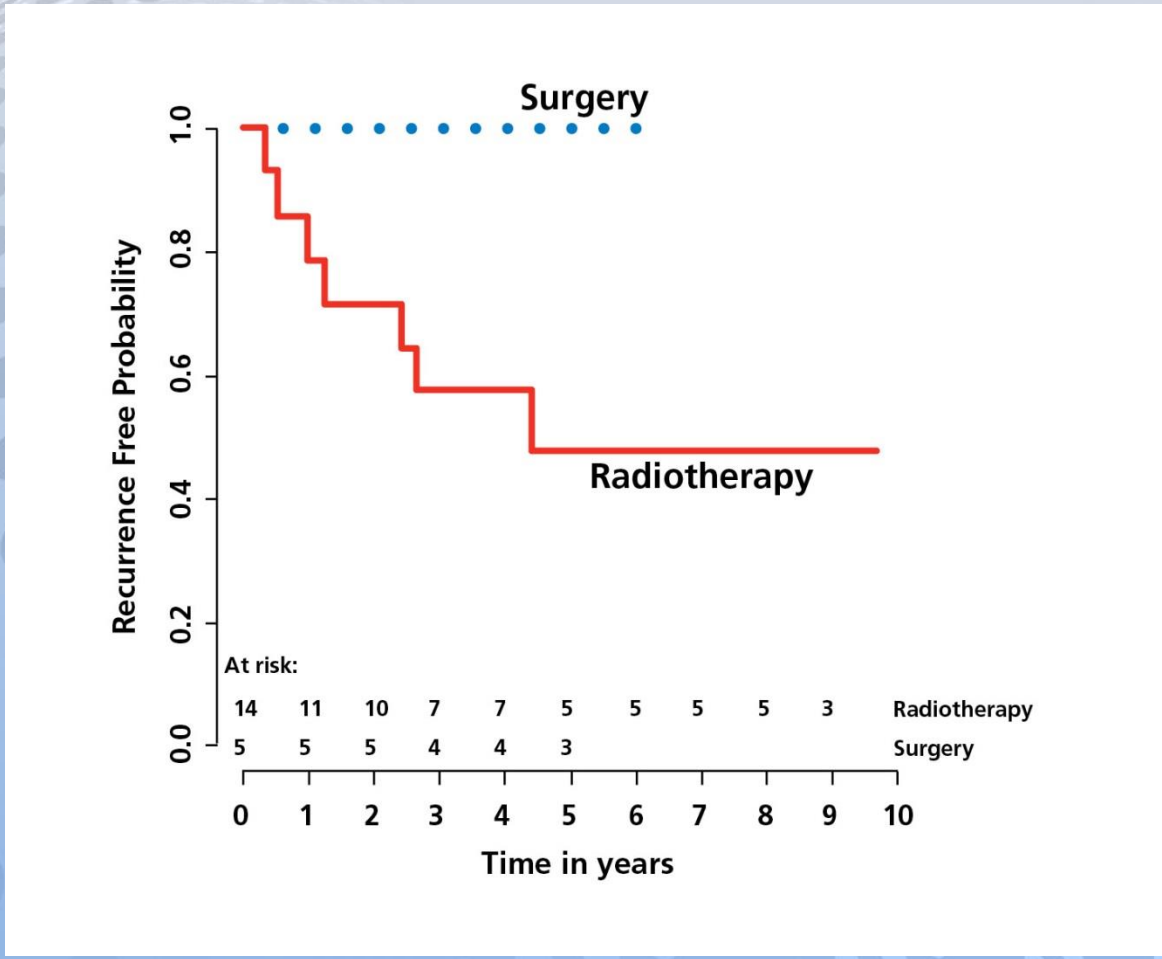
Failed Brachytherapy Audit

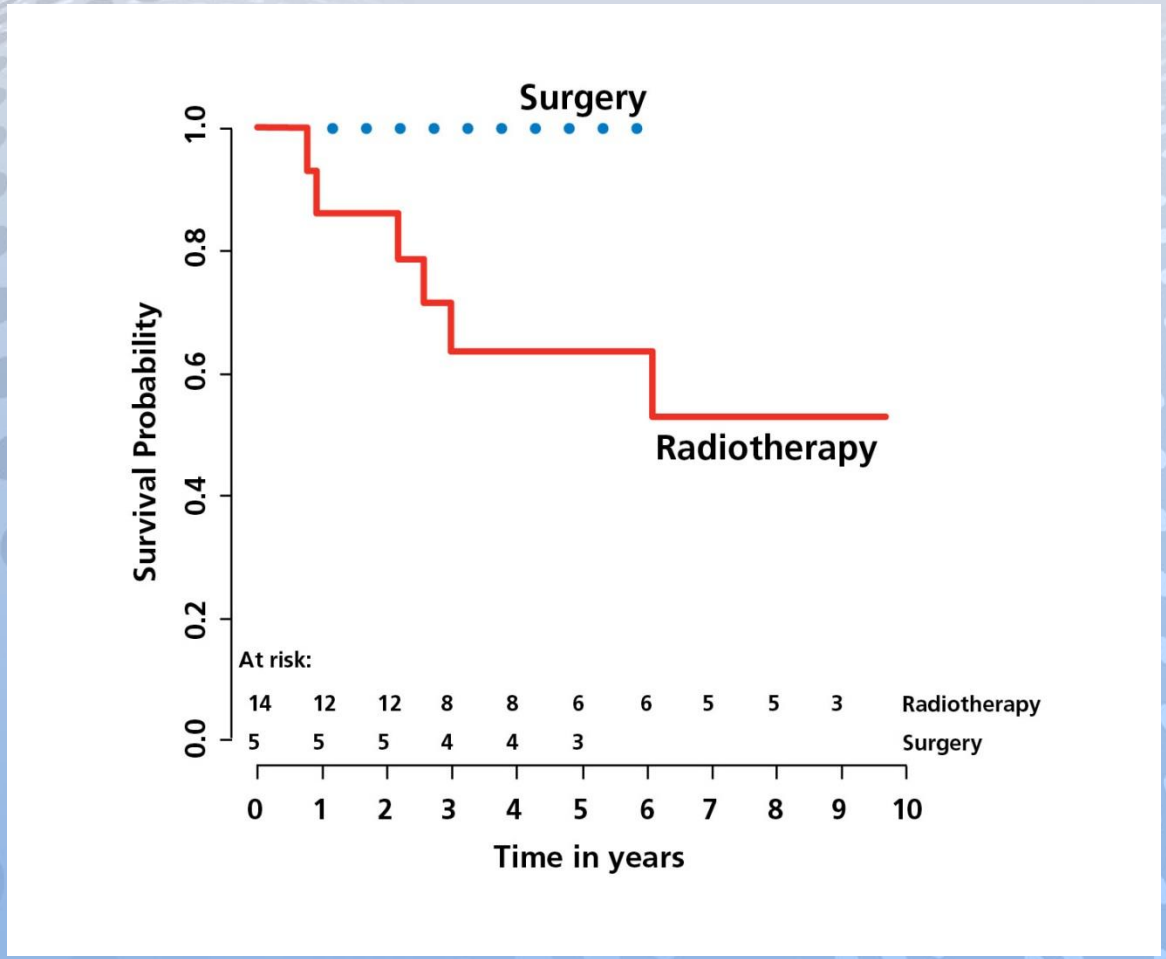


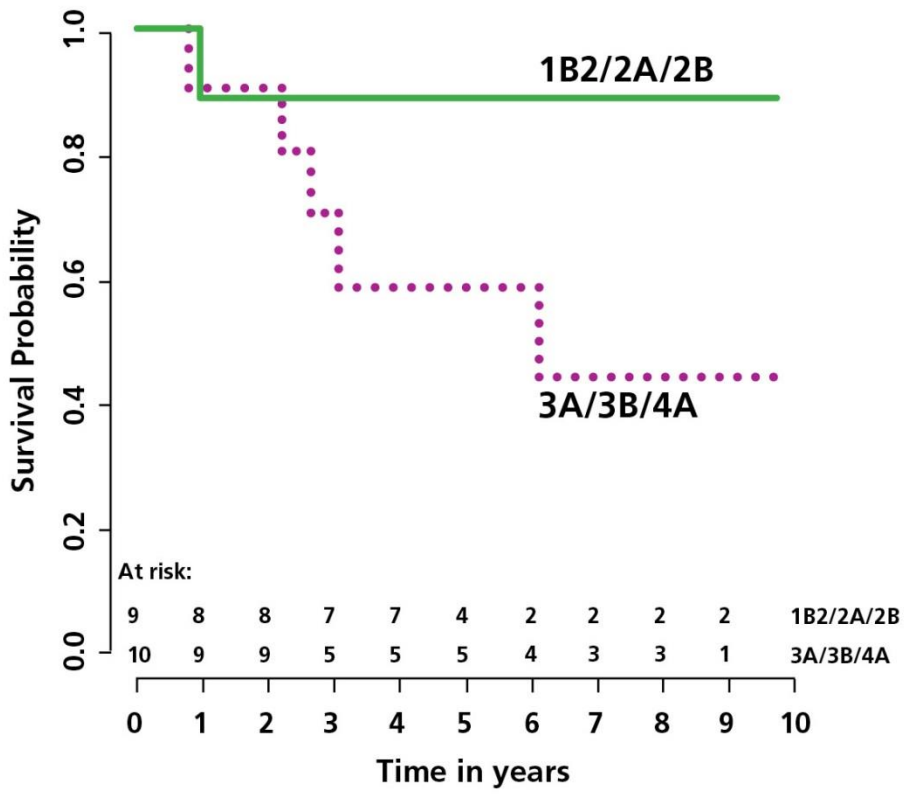
*3 cases operable by MRI & clinical

Reference: Is there a role for adjuvant hysterectomy after suboptimal concurrent chemoradiation in cervical carcinoma? Clinical Oncology 22 (2010) 140-146 Walji et al

P=0.068


Surgery
Radiotherapy
Recurrence Free Probability
1.0
0.8
0.6
0.4
0.2
0.0
At risk:
14 11 10 7 7 5 5 5 5 3 Radiotherapy
5 5 5 4 4 3 Surgery
0 1 2 3 4 5 6 7 8 9 10
Time in years


Surgery
Radiotherapy
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
At risk:
14 12 12 8 8 6 6 5 5 3 Radiotherapy
5 5 5 4 4 3 Surgery
0 1 2 3 4 5 6 7 8 9 10
Time in years


1B2/2A/2B
3A/3B/4A
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
At risk:
9 8 8 7 7 4 2 2 2 2 1B2/2A/2B
10 9 9 5 5 5 4 3 3 1 3A/3B/4A
0 1 2 3 4 5 6 7 8 9 10
Time in years

Toxicity

- Blood loss 200-250ml
- 1 wound infection
- No late grade 3 or 4 toxicity in terms of fistula, dehiscence

Compared to pelvic exanteration

20-40% 5 yr survival with 40-50% grade 3,4 effects and 100% colostomy ± urostomy

- This is now part of our departmental policy to consider patients for salvage hysterectomy if failed selectron (brachytherapy)
- Continue audit and follow up (Miss Kavita Singh)
- Walji Clinical Oncology 22 (2010) 140-146