Current Controversies in the Management of Cervical Cancer (2014)

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Has Chemoradiation fulfilled all its promises?

Green Meta-analysis (2001)

- 19 RCTs
- N=4850
- Significant benefit with CT-RT vs RT for both 5-yr OS (12% improvement) & PFS (16% improvement)
- Similar benefit with platinum vs non-platinum
- No effect of chemotherapy scheduling and dose
- Greater benefit for stage I-II
- Significantly more serious GI and hematological toxicities
- Little conclusive data on late toxicities

The Lancet, 2001

Green Meta-analysis Update (2005)

- 24 RCTs
- N=4921
- Significant benefit with CT-RT (+/- surgery) vs RT (+/- surgery) for both 5-yr OS (10% improvement) & PFS (13% improvement)
- Similar benefit with platinum vs non-platinum
- No effect of chemotherapy scheduling and dose
- Greater benefit for stage I-II
- Significantly more serious GI and hematological toxicities
- Little conclusive data on late toxicities

Cochrane Database

Cochrane Meta-analysis of Individual Patient Data (2010)- MRC (UK) group

- 18 RCTs (15 eligible)
- N=3452
- 5-yr OS improved by 6% (p<-0.001)
- DFS (8% improvement at 5 years) & local control (9% improvement at 5 years) also significantly improved
- Similar benefit for platinum (10 trials) vs non-platinum
- Greater benefit for adjuvant chemotherapy (2 trials, 19% OS benefit at 5 years)
- Trend towards greater benefit of OS for early stage disease: 10% improvement for IB-IIA, 7% for IIB, 3% for III-IV. No such trend for DFS.

Tierney et al. Cochrane Library Issue 1

- Considered RT (+/- surgery) vs CT-RT (+/- surgery)
- Did not consider trials using Hydroxyurea for the Control Arm in the main analysis, but considered them separately
- Did not consider trials using additional radiosensitisers or protectors in the experimental arm
- ITT analysis
- No difference based on RT dose (</> 45 Gy) & duration (</>8 weeks)
- No difference based on chemotherapy dose (</>25 mg/m^2 wkly) and dose-intensity

- No difference based on age, histology, grade & pelvic nodal involvement
- Significantly increased acute GI toxicities in trials of platinum (but not for non-platinum) chemotherapy
- Little available data on late toxicities
- No RCT has till date compared platinum vs non-platinum based chemoradiotherapy

Post-operative RT or CTRT for early disease: Cochrane Meta-analysis (2012)

- 2 RCTs
- N=397
- Stage IB disease
- Non-significant improvement of OS with PORT
- Significant improvement of PFS with PORT

Rogers et al. Cochrane Database

Summary

- Concurrent chemoradiation has maintained a significant overall survival advantage over RT alone, but better trial selection in analysis have shown the benefit to be lower than thought of earlier
- Platinum & non-platinum chemotherapy regimens are equivalent
- The overall survival benefit of CT-RT is more in early stage disease
- CT-RT in post-operative situations also has PFS, but not OS benefit over RT alone

Alternatives & add-ons for Concurrent Chemoradiation

- Adjuvant chemotherapy (after CTRT)

- Neo-adjuvant chemotherapy (followed by surgery)

Adjuvant chemotherapy for early stage disease: Meta-analysis (2012)

- Stage I-IIA disease (including bulky)
- RT +/- Adjuvant chemotherapy
- 3 trials
- N=368
- Adjuvant chemotherapy significantly reduces risk of death (HR=0.56) & disease progression (HR=0.47)
- No trials have till date assessed adjuvant chemotherapy after surgery

Rosa et al. Cochrane Library Issue 6

Neoadjuvant chemotherapy for locally advanced disease: Meta-analysis (2004): MRC (UK) group

- 18 trials
- IPD meta-analysis
- Included stage IB-IV disease
- Did not include trials with concurrent chemoradiotherapy

(1) NACT→ Local therapy vs Local therapy alone

- N=2074
- Significant survival benefit for NACT with cycles duration <14 days and using Cisplatin @ >25 mg/m^2/week
- No effect of age, stage, histology, grade and nodal involvement

Tierney et al. Cochrane Database

(2) NACT→ Surgery vs RT:

- 5 trials
- N=872
- Highly significant improvement in 5-year OS (14%) and DFS (13%)
- No change based on age, stage, histology, grade and nodal status

NACT→ Surgery vs Surgery alone for stage IB-IIA: Updated International Meta-analysis

- 5 RCTs and 4 observational studies
- N=1784
- NACT was related with smaller primary tumor size and lymph nodal involvement
- NACT reduced the need of adjuvant RT
- NACT reduced the distant metastasis rate
- NACT was NOT associated with OS/PFS benefit (in fact, in the observational studies, OS was worse).

Kim et al. Eur Surg Oncol 2013

GOG 141: NACT→S vs S for bulky IB

- N=288
- NACT= VCR + CDDP q10 days x 3 cycles→Surgery after 2-4 weeks

vs

- Upfront surgery
- Trial was prematurely closed due to slow accrual
- There were no differences in the recurrence rates or death rates in the 2 groups

Imaging : The Role of PET-CT

CT vs MRI vs PET-CT for determination of nodal disease: Meta-analysis

- 41 studies
- PET or PET-CT showed highest sensitivity (82%) and specificity (95%)
- CT sensitivity 50% and specificity 92%
- MRI sensitivity 56% and specificity 91%

Choi et al. Cancer Science (2010)

Histologic Results of Para-Aortic Lymphadenectomy in Patients Treated for Stage IB2/II Cervical Cancer With Negative [^{18}F]Fluorodeoxyglucose Positron Emission Tomography Scans in the Para-Aortic Area

Mathias Boughanim, Sophie Leboulleux, Annie Rey, Chi Tuan Pham, Yaelle Zafrani, Pierre Duvillard, Jean Lumbroso, Christine Haie-Meder, Martin Schlumberger, and Philippe Morice

ABSTRACT

Purpose
Histologic results of complete para-aortic lymphadenectomy were studied in patients treated for stage IB2/II cervical carcinoma who had no para-aortic uptake on [^{18}F]fluorodeoxyglucose positron emission tomography combined with integrated computed tomography (FDG-PET/CT).

Patients and Methods
Patients were treated between 2004 and 2006 for stage IB2/II cervical cancer. Magnetic resonance imaging of the abdomen and pelvis and FDG-PET/CT were initially performed. Patients with no para-aortic abnormalities were treated with external pelvic radiation therapy and concomitant chemotherapy followed by utero-vaginal brachytherapy. Para-aortic lymphadenectomy was then performed. FDG-PET/CT images were reviewed by two nuclear medicine specialists.

Results
Thirty-eight patients were studied. Three patients had histologically proven para-aortic involvement (metastatic nodes with capsular rupture in the para-aortic area), leading to a negative predictive value of 92% for para-aortic nodal involvement.

Conclusion
In this study, three of 38 patients with no para-aortic uptake on [^{18}F]FDG-PET/CT imaging had histologically proven para-aortic node involvement. PET/CT imaging without histologic examination of the para-aortic area used to determine radiation therapy fields in stage IB2/II cervical cancer would overlook 8% of patients with histologic para-aortic nodal involvement.

J Clin Oncol 26:2558-2561.

PET-CT, Para-aortics, Prognosis…

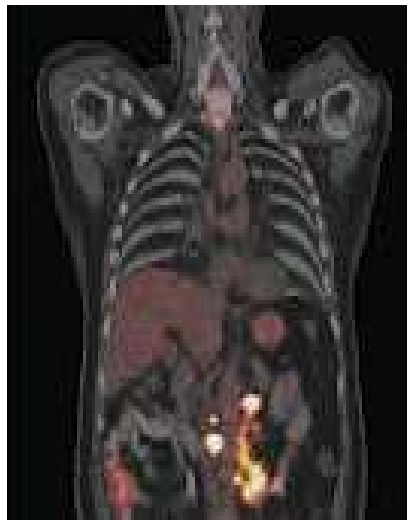
Prospective Multicenter Study Evaluating the Survival of Patients With Locally Advanced Cervical Cancer Undergoing Laparoscopic Para-Aortic Lymphadenectomy Before Chemoradiotherapy in the Era of Positron Emission Tomography Imaging

Sebastien Gouy, Philippe Morice, Fabrice Narducci, Catherine Uzan, Alejandra Martinez, Annie Rey, Enrica Bentivegna, Patricia Pautier, Desiree Deandreis, Denis Querleu, Christine Haie-Meder, and Eric Leblanc

J Clin Oncol 31:3026-3033. (2013)

Q1: picking up PA nodes

- N=237, IB-IVA disease, SCC/adeno /adenosquamous
- All patients underwent PET scan followed by laparoscopic para-aortic lymphadenectomy
- The false negativity rate for PET was 12%



Q2: addressing PA nodes

- Patients went on to receive radical CT-RT
- Patients with documented PA nodal involvement received EFRT & conc chemotherapy
- Event-free survival rates of patients with PA node <5mm and without PA node were similar
- Event free survival rates of patients with PA node>5mm were significantly worse than patients without PA node/ with PA node<5mm, despite EFRT & conc chemotherapy

Prophylactic PA nodal irradiation: RTOG 79-20

- N=367
- Bulky IB-IIA & IIB disease
- Pelvic only OR pelvic+para-aortic RT
- 10-yr OS 44% vs 55% (p=0.02)
- Similar local control & DFS rates
- Significantly increased incidence of grade 4-5 toxcities at 10 years for pelvic+PA RT
- Higher OS with similar DFS can be explained by lower incidence of distant failure & better salvage for pelvic+PA vs pelvic RT

Rotman et al. JAMA 1995

RTOG 90-01

- N=403
- High-risk patients: IIB-IVA, positive pelvic nodes, bulky IB-IIA
- Pelvic RT + conc chemotherapy (CCDP+FU)

vs

- Extended Field RT

- The EFRT arm was the control arm, established on the basis of the RTOG 79-20 trial

Eifel et al. J Clin Oncol 22:872-880 (2004)

- OS with CTRT was significantly greater than with EFRT (67% v 41% at 8 years; *P .0001).*
- Overall reduction in the risk of disease recurrence of 51% (95% CI, 36% to 66%) for patients who received CTRT.
- The rate of serious late complications of treatment was similar for the two treatment arms.
- Patients with stage IB to IIB disease who received CTRT had better OS and DFS than those treated with EFRT (*P .0001)*
- Patients with stage III to IVA disease had better DFS (*P .05)* and a trend toward better OS (P .07) if they were randomly assigned to CTRT.

So…

- Using concurrent chemotherapy is just as important as extending the RT fields in prophylactic treatment of PA nodes in high-risk disease

- Even with extended RT fields AND concurrent chemotherapy, involved PA nodes demand yet something more, possibly adjuvant chemotherapy

Screening: Benefits & Modalities

Screening: Meta-analysis

- 15,145 screened citations→ 27 papers (24 studies) included .
- A randomized controlled trial in India showed even a single lifetime screening test significantly decreased the risk of mortality from and incidence of advanced cervical cancer compared to no screening
- Cytology screening was shown to be beneficial in a cohort study that found testing significantly reduced the risk of being diagnosed with invasive cervical cancer compared to no screening .
- Pooled evidence from a dozen case–control studies also indicated a significant protective effect of cytology screening.
- No conclusive evidence for establishing optimal ages to start and stop cervical screening, or to determine how often to screen.
- Substantial protective effects for screening women 30 years and older and for intervals of up to five years.

Pearson et al. Systematic Reviews 2013

HPV testing vs repeat cytology for minor cervical lesions: Meta-analysis

- The pooled sensitivity of HC2 was significantly higher than that of repeat cytology at cut-off ASCUS+ to detect CIN2+ in both triage of ASCUS and LSIL .

- In ASCUS triage (39 studies), the pooled specificity of the triage methods did not differ significantly from each other .

- However, the specificity of HC2 was substantially, and significantly, lower than that of repeat cytology in the triage of LSIL (24 studies).

Arbyn et al. Cochrane Library Issue 3 (2013)

HPV for primary screening: Meta-analysis

- 7 trials were identified
- HPV was significantly more sensitive in picking up CIN3+ in the first round, and significantly less sensitive in the second round
- There were no differences in the pooled CIN3+/CIN2+ pick up rates
- Trend towards lower invasive carcinoma rates

Murphy et al. J Obstet Gynaecol Can 2012

The V word…

Safety and efficacy of cervical cancer vaccine: Meta-analysis

- 7 RCTs (2 bivalent, 1 monovalent, 4 quadrivalent)
- N=44,142
- Vaccines were highly efficacious against HPV 16/18 related CIN1+/CIN2+/persistent HPV infection (beyond 6 months)
- Limited efficacy against non-vaccine strain-HPV-associated CIN2+/persistent /HPV infection
- No significant difference in serious adverse events between vaccine & control groups
- Limited data regarding abnormal pregnancy outcomes

Lu et al. BMC Infectious Diseases 2011

Questions for a developing country

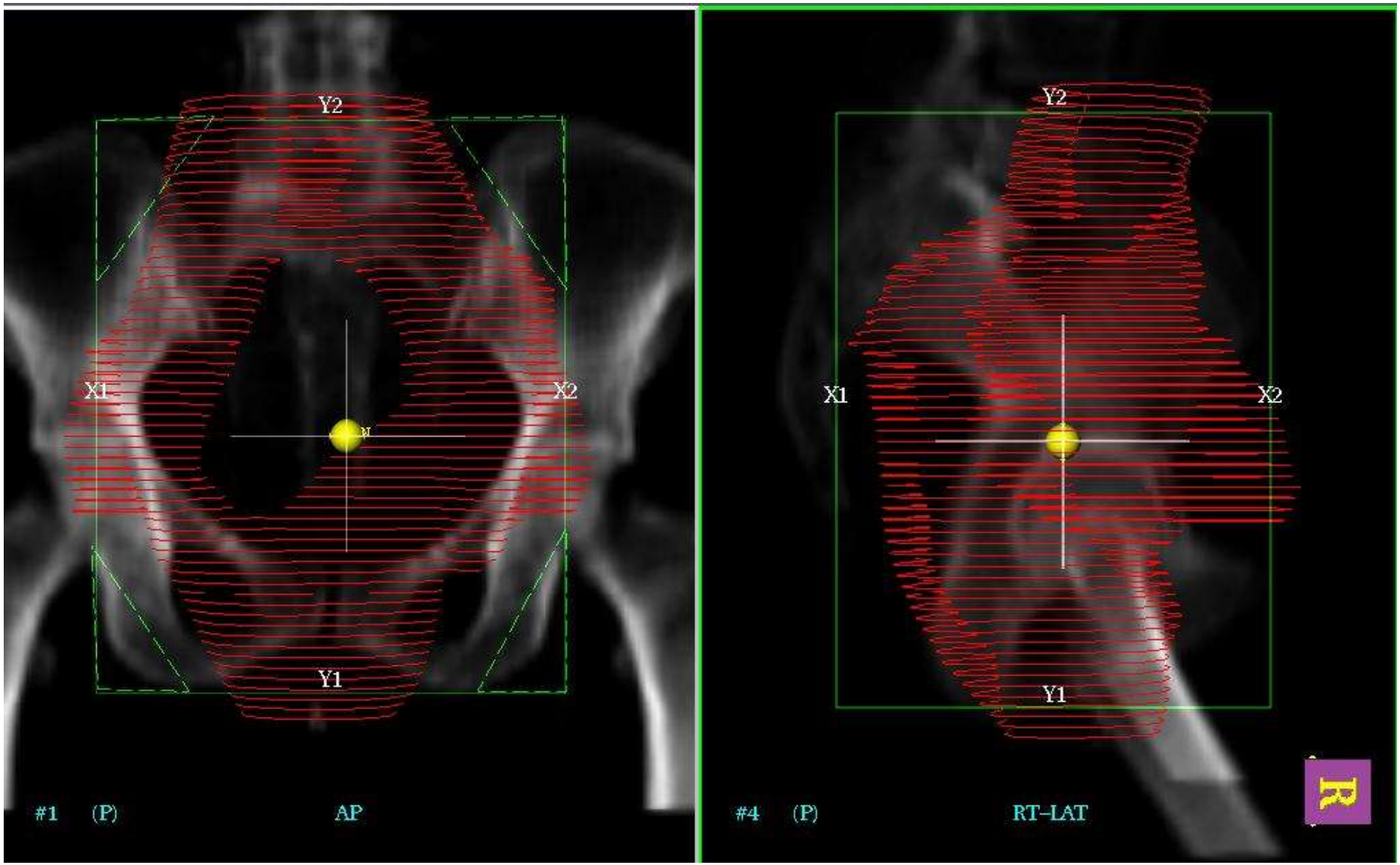
- Should the vaccine become a part of the Universal Immunisation Programme?

OR

- Should we rather invest more money & resources towards better screening?

Teletherapy

Is the X-ray planned 4 field box still acceptable EBRT?



- There is significant geographic miss superiorly (common iliac nodes) and laterally (external iliac nodes) in particular
- This correlates with the sites of intra-pelvic failures.
- Majority of failures are marginal. Of these most common is ABOVE the field.

Beadle et al. Int J Radiat Oncol Biol Phys (2010) 76:1396-1403

IMRT: For Extended Field RT

- N=36
- IB2-IVA
- EFRT with concurrent Cisplatin
- 34/36 had CR
- 2 yr LRC, DFS and OS were 80%, 51% and 65% respectively
- 2-year >=grade 3 GI toxicity rate was 10%

Beriwal et al. Int. J. Radiation Oncology Biol. Phys 2007 68;1,:166–171

IMRT: For Pelvic RT

- N=111
- Stage I-IVA
- Post-op patients included; extended field RT excluded
- 3-yr DFS and OS rates were 69% and 78% respectively
- Acute grade 3 or higher toxicity rate=2%
- Late grade 3 or higher toxicity rate=7%

Hasselle et al. Int. J. Radiation Oncology Biol. Phys 2011 80;5:1436–1445

Int J Radiat Oncol Biol Phys. 2013 Nov 1;87(3):542-8. doi: 10.1016/j.ijrobp.2013.06.2059.

Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study.

Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, Manigandan D, Laviraj MA, Kumar S, Thulkar S.

Author information

Abstract

PURPOSE: To evaluate the toxicity and clinical outcome in patients with locally advanced cervical cancer (LACC) treated with whole pelvic conventional radiation therapy (WP-CRT) versus intensity modulated radiation therapy (WP-IMRT).

METHODS AND MATERIALS: Between January 2010 and January 2012, 44 patients with International Federation of Gynecology and Obstetrics (FIGO 2009) stage IIB-IIIB squamous cell carcinoma of the cervix were randomized to receive 50.4 Gy in 28 fractions delivered via either WP-CRT or WP-IMRT with concurrent weekly cisplatin 40 mg/m(2). Acute toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, and late toxicity was graded according to the Radiation Therapy Oncology Group system. The primary and secondary endpoints were acute gastrointestinal toxicity and disease-free survival, respectively.

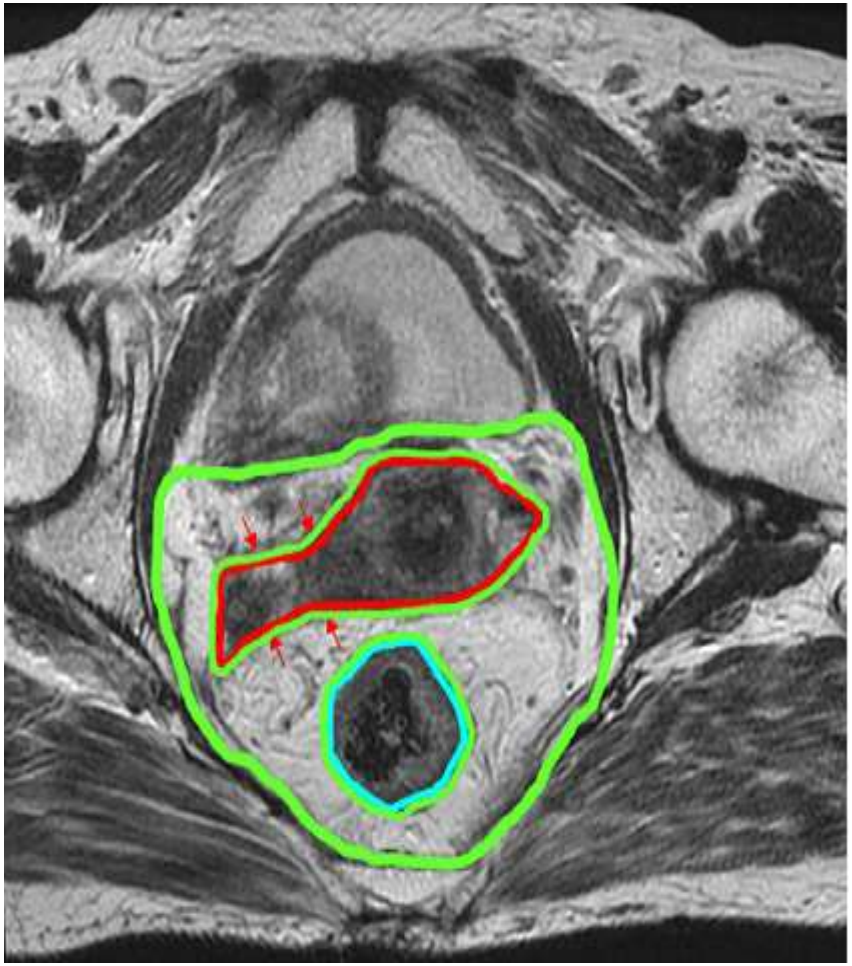
RESULTS: Of 44 patients, 22 patients received WP-CRT and 22 received WP-IMRT. In the WP-CRT arm, 13 patients had stage IIB disease and 9 had stage IIIB disease; in the IMRT arm, 12 patients had stage IIB disease and 10 had stage IIIB disease. The median follow-up time in the WP-CRT arm was 21.7 months (range, 10.7-37.4 months), and in the WP-IMRT arm it was 21.6 months (range, 7.7-34.4 months). At 27 months, disease-free survival was 79.4% in the WP-CRT group versus 60% in the WP-IMRT group (P=.651), and overall survival was 76% in the WP-CRT group versus 85.7% in the WP-IMRT group (P=.645). Patients in the WP-IMRT arm experienced significantly fewer grade ≥2 acute gastrointestinal toxicities (31.8% vs 63.6%, P=.034) and grade ≥3 gastrointestinal toxicities (4.5% vs 27.3%, P=.047) than did patients receiving WP-CRT and had less chronic gastrointestinal toxicity (13.6% vs 50%, P=.011).

CONCLUSION: WP-IMRT is associated with significantly less toxicity compared with WP-CRT and has a comparable clinical outcome. Further studies with larger sample sizes and longer follow-up times are warranted to justify its use in routine clinical practice.

Stop-press

- Trials are still ongoing at present
- Till now, control & survival rates have been comparable
- Potential benefits, especially with chemotherapy and when treating PA nodes are better GI toxicity profile and bone marrow sparing

Parametrial delineation for EBRT: Controversy



Care must be

taken to include the entire uterosacral ligaments if they are either clinically or radiologically involved with disease. If this is the case, an argument can be made to include the entire mesorectum as pararectal lymph nodes would also be at risk. In that case, parametrial volumes would extend up to the rectal contour (Fig. 5). Patients with Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stage 3B or greater disease and those with extensive nodal involvement should also have the entire mesorectum included in the parametrial volume. Laterally, the parametrial volume should ex-

Lim et al Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 2, pp. 348–355, 2011

Brachytherapy

Is LDR brachytherapy still viable?

HDR vs LDR brachytherapy: Meta-analysis

- 5 trials
- N=2065
- No difference in mortality, local recurrence or late complications for stage I-III

Viani et al. Journal of Experimental & Clinical Cancer Research 2009

HDR vs LDR brachytherapy: Cochrane Meta-analysis

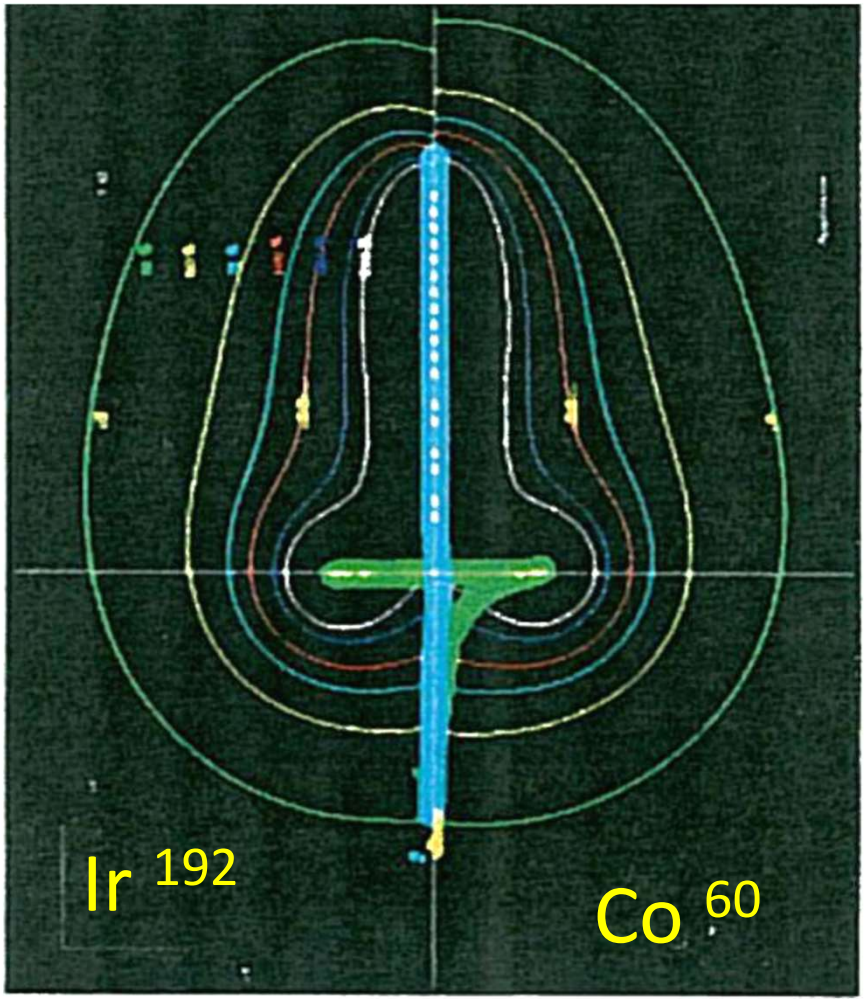
- 4 RCTs
- 1265 patients
- There were no differences in local control, survival or late rectal/bladder complications
- There was higher small bowel complication with HDR
- Due to potential advantages of HDR, such as better immobilisation, convenience, individualisation of treatment, the authors recommended HDR brachytherapy for all stages of cervical cancer.

Wang et al. Cochrane Library Issue 7 2010

HDR Brachytherapy: which isotope?

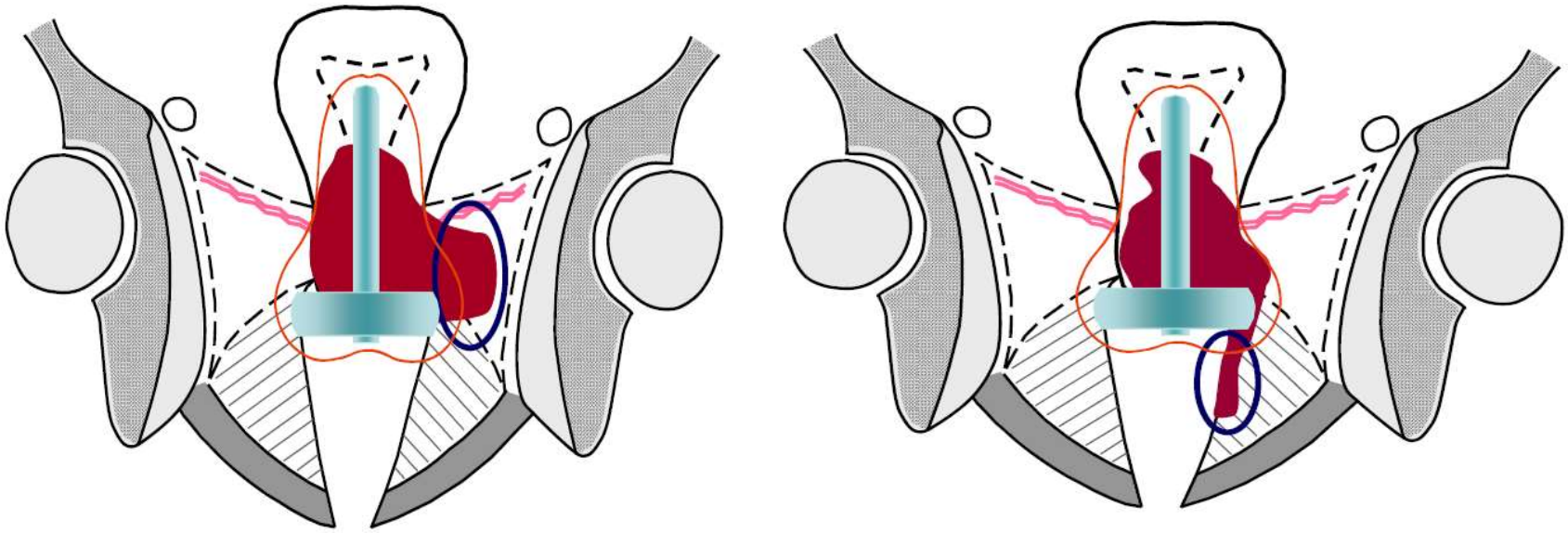
HDR Co^{60} vs Ir^{192}

- Co^{60} is dosimetrically equivalent
- Dose fall-off in non-target tissue (upto 22cm) is faster with Co^{60}
- Greater energy of Co^{60} (1.25MeV vs 0.375 MeV) demands greater bunker shielding
- The longer half-life of Co^{60} (5.26 years vs 74 days) makes it economically & logistically efficacious
- Clinical data is still forthcoming, but no trials till date have thrown up significant differences in outcomes



Interstitial Brachytherapy

Indications of interstitial implant



- Extensive parametrial disease
- Lower vaginal involvement
- Distorted anatomy

Interstitial brachytherapy regimens

Suggested doses for template-based HDR interstitial brachytherapy after 45–50.4 Gy of external beam.

Dose of EB radiotherapy	Brachytherapy dose*	EQD2 (Gy) to CTV
45 Gy/25 fractions	3.5 Gy × 9	79.7
	4.25 Gy × 7	79.6
	5 Gy × 5	75.5
50.4 Gy Gy/28 fractions	3 Gy × 9	78.8
	4.5 Gy × 5	76.7

*Twice a day treatments with approximately 6 hours between fractions (based on general radiobiological principles) over one week. The 9-fraction regimen is given over 4.5 days in one week with one insertion. Other regimens using other doses of external beam are also acceptable.

Vishwanathan et al. Brachytherapy 2012 ; 11(1): 47–52

Hybrid Intracavitary-Interstitial (Vienna) Applicator

Implications

- Interstitial implant allows better access and coverage of irregular anatomy tumors
- Optimal dose-schedule is still to be ratified, given the variety of institutional protocols
- One advantage of intracavitary brachytherapy, which should not be sacrificed with an implant, is the large central dose achievable
- Hence hybrid intracavitary & interstitial applicators, which use a central tandem AND peripheral needles, can be really useful

Dose –Volume Constraints & Clinical Outcomes

Optimal Target Doses using GEC-ESTRO guidelines

DOSE–VOLUME HISTOGRAM PARAMETERS AND LOCAL TUMOR CONTROL IN MAGNETIC RESONANCE IMAGE–GUIDED CERVICAL CANCER BRACHYTHERAPY

JOHANNES C. A. DIMOPOULOS, M.D.,* STEFAN LANG, PH.D.,* CHRISTIAN KIRISITS, D.SC.,* ELENA F. FIDAROVA, M.D.,* DANIEL BERGER, M.SC.,* PETRA GEORG, M.D.,* WOLFGANG DÖRR, D.V.M., PH.D.,† AND RICHARD PÖTTER, M.D.*

* Department of Radiotherapy, Medical-University of Vienna, Vienna, Austria; and † Department of Radiotherapy and Radiation Oncology, Medical Faculty Carl Gustav Carus, University of Technology, Dresden, Germany

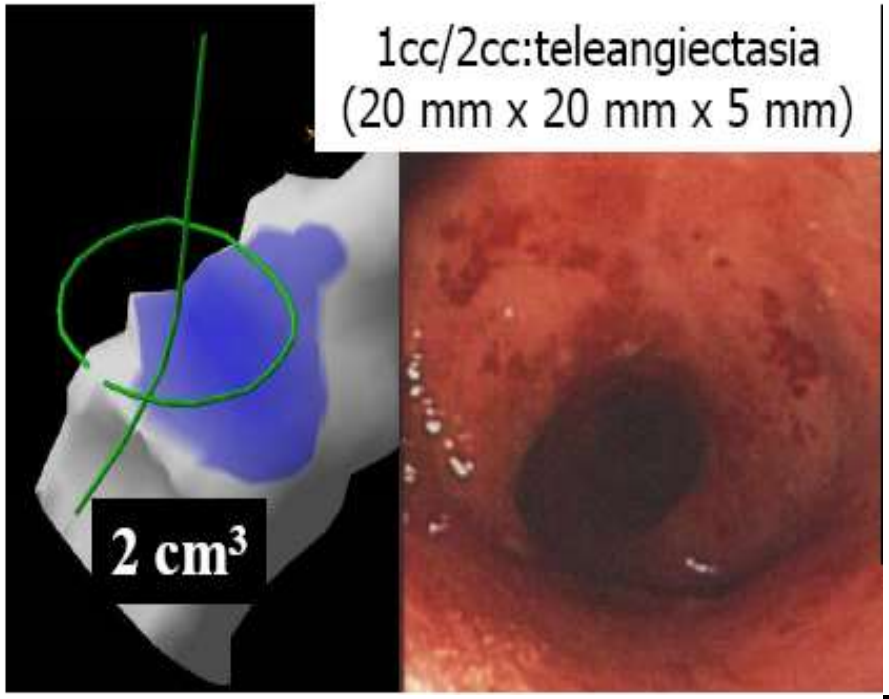
Purpose: To investigate the value of dose–volume histogram (DVH) parameters for predicting local control in magnetic resonance (MR) image-guided brachytherapy (IGBT) for patients with cervical cancer.

Methods and Materials: Our study population consists of 141 patients with cervical cancer (Stages IB–IVA) treated with 45–50 Gy external beam radiotherapy plus four times 7 Gy IGBT with or without cisplatin. Gross tumor volume (GTV), high-risk clinical target volume (HRCTV), and intermediate-risk clinical target volume (IRCTV) were contoured, and DVH parameters (minimum dose delivered to 90% of the volume of interest [D90] and D100) were assessed. Doses were converted to the equivalent dose in 2 Gy (EQD2) by applying the linear quadratic model ($\alpha/\beta = 10$ Gy). Groups were defined for patients with or without local recurrence (LR) in the true pelvis for tumor size at diagnosis (GTV at diagnosis [GTVD] of 2–5 cm (Group 1) or greater than 5 cm (Group 2) and for tumor size response at IGBT (HRCTV) of 2–5 cm (Group 2a) or greater than 5 cm (Group 2b).

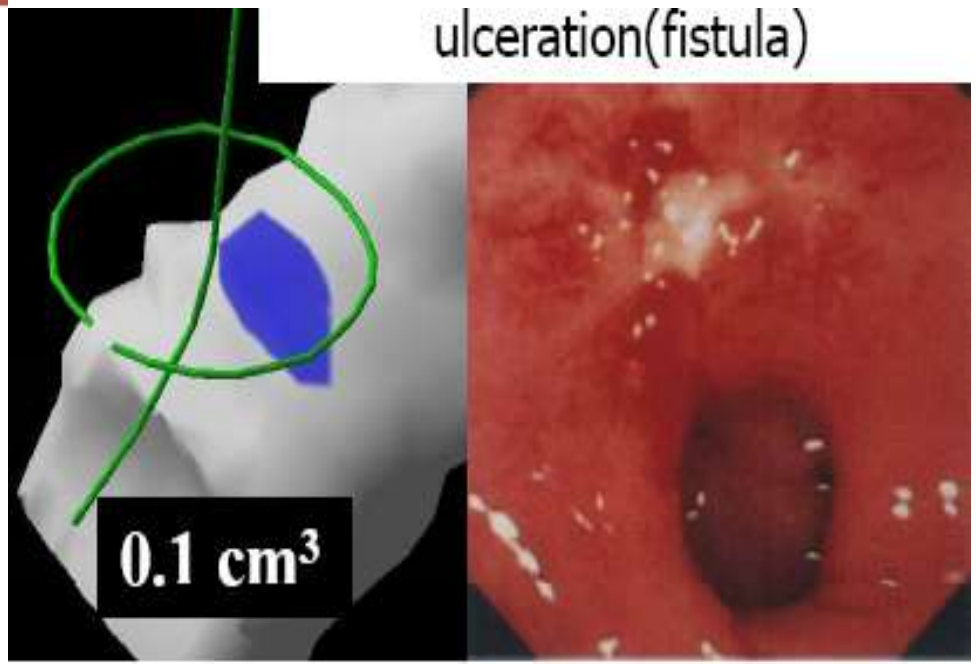
Results: Eighteen LRs were observed. The most important DVH parameters correlated with LR were the D90 and D100 for HRCTV. Mean D90 and D100 values for HRCTV were 86 ± 16 and 65 ± 10 Gy, respectively. The D90 for HRCTV greater than 87 Gy resulted in an LR incidence of 4% (3 of 68) compared with 20% (15 of 73) for D90 less than 87 Gy. The effect was most pronounced in the tumor group (Group 2b).

Conclusions: We showed an increase in local control in IGBT in patients with cervical cancer with the dose delivered, which can be expressed by the D90 and D100 for HRCTV. Local control rates greater than 95% can be achieved if the D90 (EQD2) for HRCTV is 87 Gy or greater.

Dimopoulos et al. Int. J. Radiation Oncology Biol. Phys. 2009 75;1:56–63



Volumes & Clinical Outcomes



Dose Volume Constraints

Bladder : D2cc < 90Gy EQD2

Rectum : D2cc < 70 Gy EQD2

Sigmoid : D2cc < 70 Gy EQD2

Vagina : ???

Thank You