6th CONGRESS OF THE
MEDITERRANEAN MULTIDISCIPLINARY ONCOLOGY FORUM
&
3rd INTERNATIONAL CONGRESS ON ONCOLOGICAL SCIENCES

28 November - 1 December 2019
Regnum Carya Convention Center
Antalya, Turkey

Gynecologic Oncology: Advances in Radiotherapy

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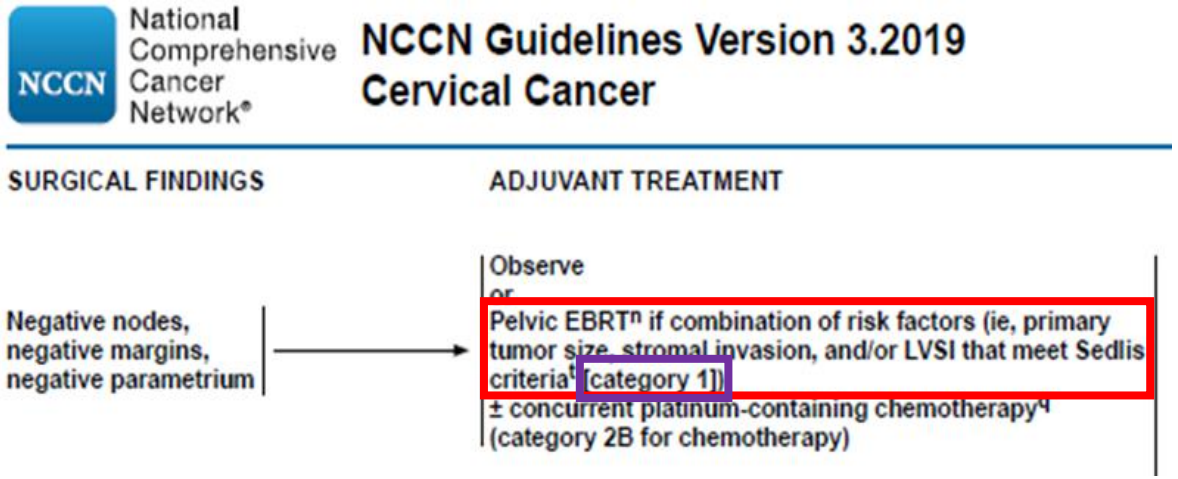
Treatment Options of Cervical Cancer

FIGO Stage	Treatment
IA1	Conization Extrafascial Hysterectomy Radical Trachelectomy
IA2, IB1, IIA1	Modified Radical Hysterectomy + LND RT/CRT
IB2, IIA2, III, IVA	Definitive CRT
IVB	Chemotherapy ± Palliative RT

After Radical Hysterectomy …

- **Intermediate risk: Pelvic EBRT**
  - If 2 of the following: **Deep stromal invasion**, **≥4 cm tumor, LVSI, adenoCa, adenosquamous Ca**
    - **GOG 92** (Sedlis 1999, Rotman 2006)
    - **KGOG 1021** (Ryu 2014)



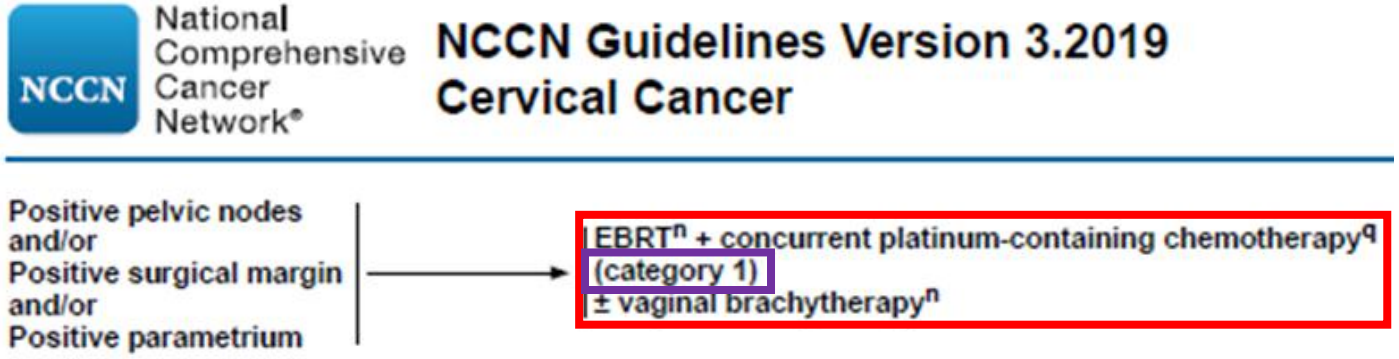
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Cervical Cancer

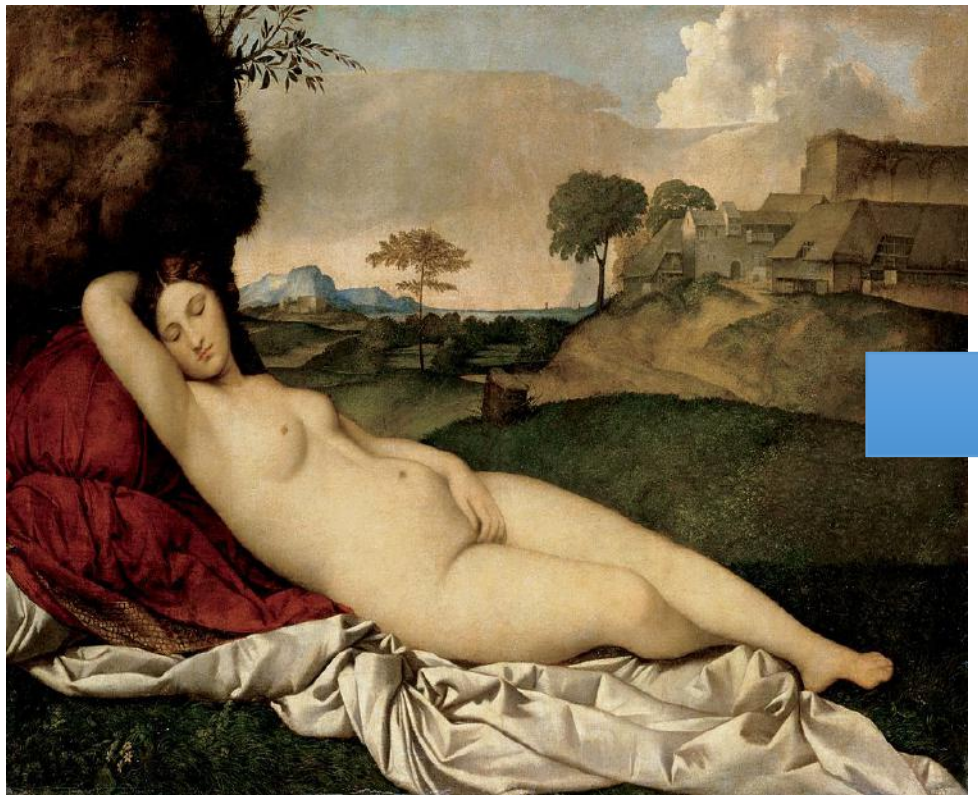
SURGICAL FINDINGS	ADJUVANT TREATMENT
Negative nodes, negative margins, negative parametrium	Observe or Pelvic EBRT[n] if combination of risk factors (ie, primary tumor size, stromal invasion, and/or LVSI that meet Sedlis criteria[t] [category 1]) ± concurrent platinum-containing chemotherapy[q] (category 2B for chemotherapy)

After Radical Hysterectomy …

- **High risk: Concurrent CRT**
  - If 1 of the following: **Positive margin**, **parametrial invasion**, **positive node**
    - **GOG 109** (Peters 2000)
  - No difference in **cisplatin** vs. combined schemes



Cervical Cancer



Is it time to change the classical treatment policy?

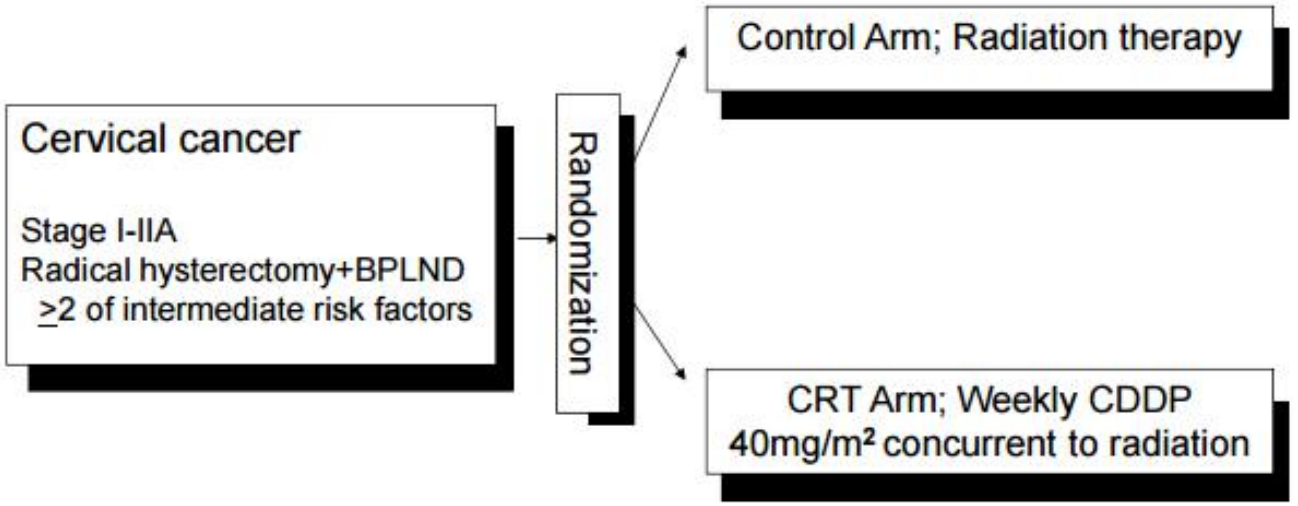
Pts with intermediate risk factors
Do we need concomitant chemo?

- **Intermediate risk group**
  - **RT vs. CRT**
  - Cisplatin 1/wk
    40 mg/m^2

GOG 263/KGOG 1008

PI; Sang Young Ryu, MD

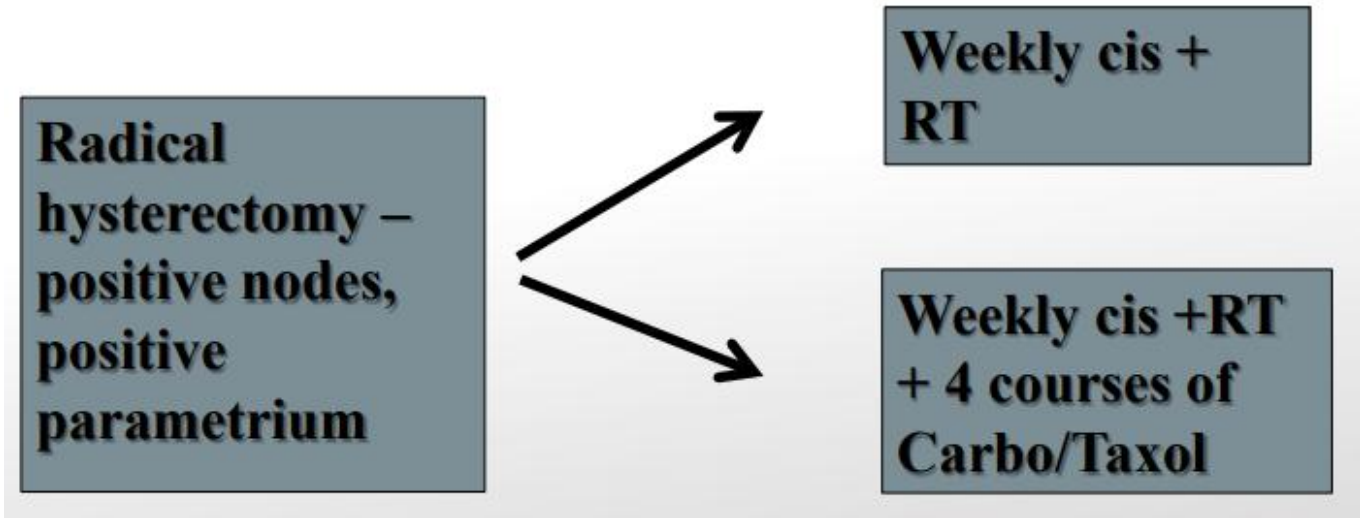
Randomized Phase III Clinical Trial of Adjuvant Radiation vs Chemoradiation In Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy



Pts with high risk factors
Do we need aduvant chemo?

- **High risk group**
  - **CRT** ± adjuvant chemo
    - 4 cycles carbo/taxol

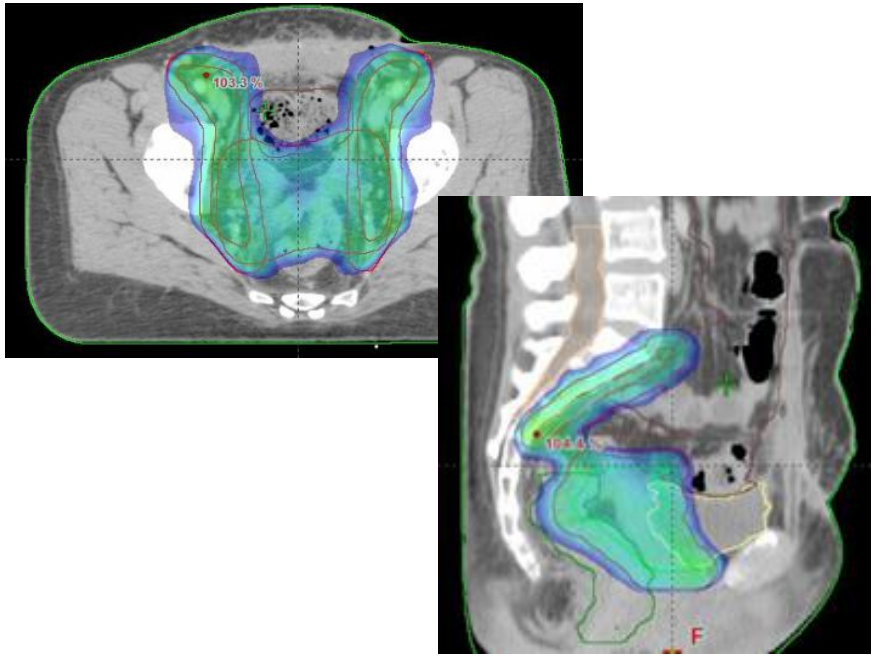
RTOG/GOG 0724 – for high- risk Cervical Carcinoma

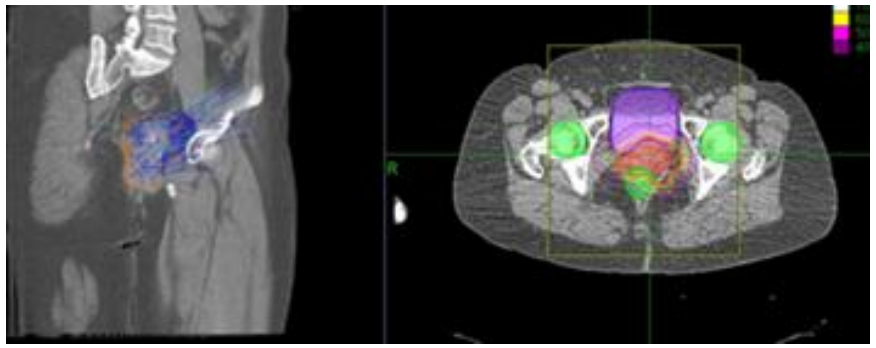


Advances in EBRT Techniques

- **Intensity modulated radiotherapy (IMRT)**
- **Volumetric modulated arc therapy (VMAT)**
- **Stereotactic ablative radiotherapy (SABR)**
- **Image-guided RT (IGRT)**

- **High doses to the target volumes**
- **Sparing of normal tissues in the vicinity**





3D-CRT vs. IMRT

- **RTOG 1203 (TIME-C)**
  - 281 pts (postoperative cervical/endometrial Ca)
  - Median f/u: 37.8 months

	2yr LRF	2yr DFS	2yr OS
IMRT	2.6%	89.1%	95.1%
4 Field	1.4%	86.1%	99.3%
HR (95% CI)	0.82 (0.20, 3.27)	1.39 (0.82, 2.35)	0.76 (0.32, 1.79)
p-value	0.81 (Gray's test)	0.21 (log-rank)	0.53 (log-rank)

Yeung AR, et al. ASTRO, 2019

RTOG 1203 (TIME-C)

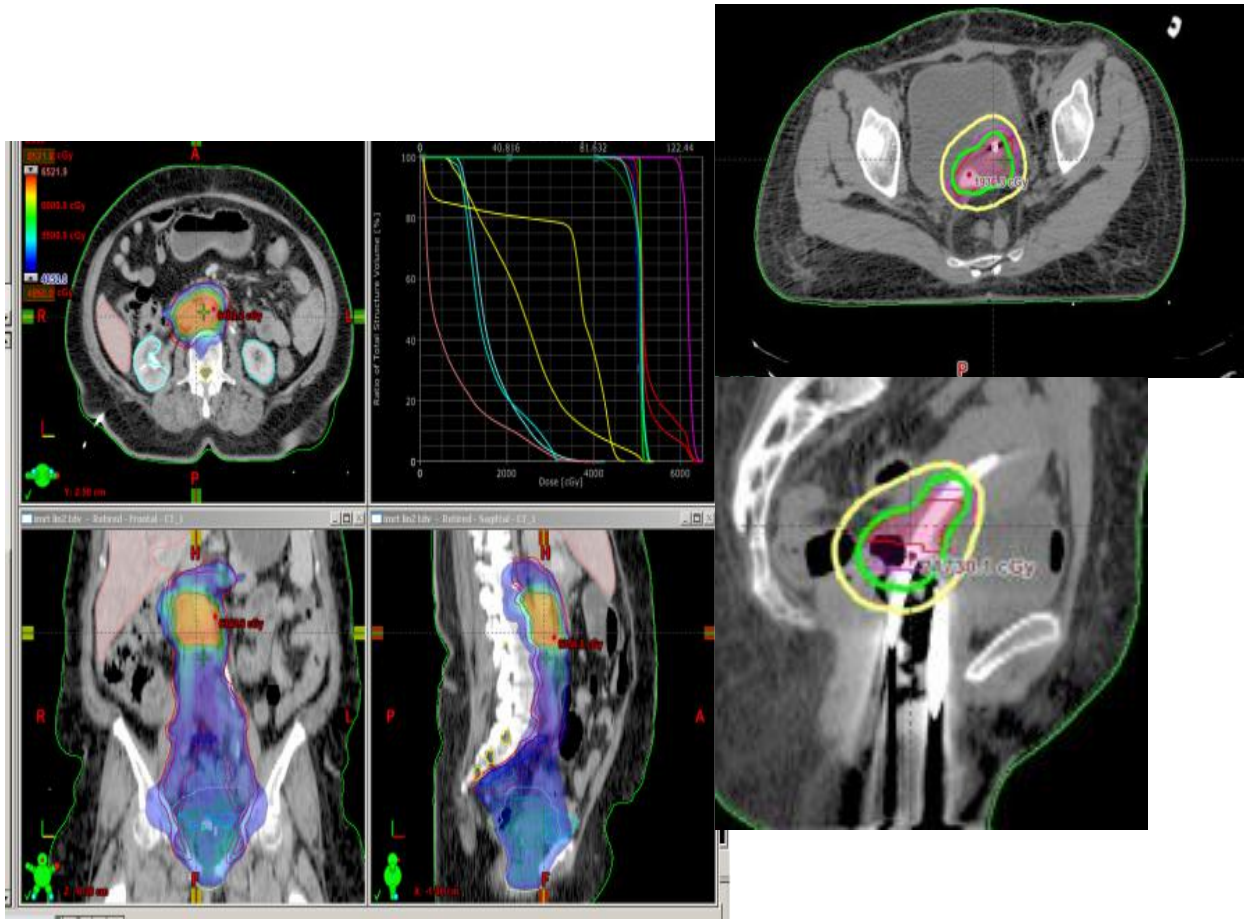
- In comparison with 3DCRT, **IMRT reduces patient-reported**:
  - Acute GI adverse events (at 5 weeks of RT)
  - Acute urinary adverse events (at 5 weeks of RT)
  - Some late GI adverse events (diarrhea at 1 year post-RT)
  - **Late urinary adverse events (at 3 years post-RT)**

- No effects on physician reported late toxicity

Yeung AR, et al. ASTRO, 2019

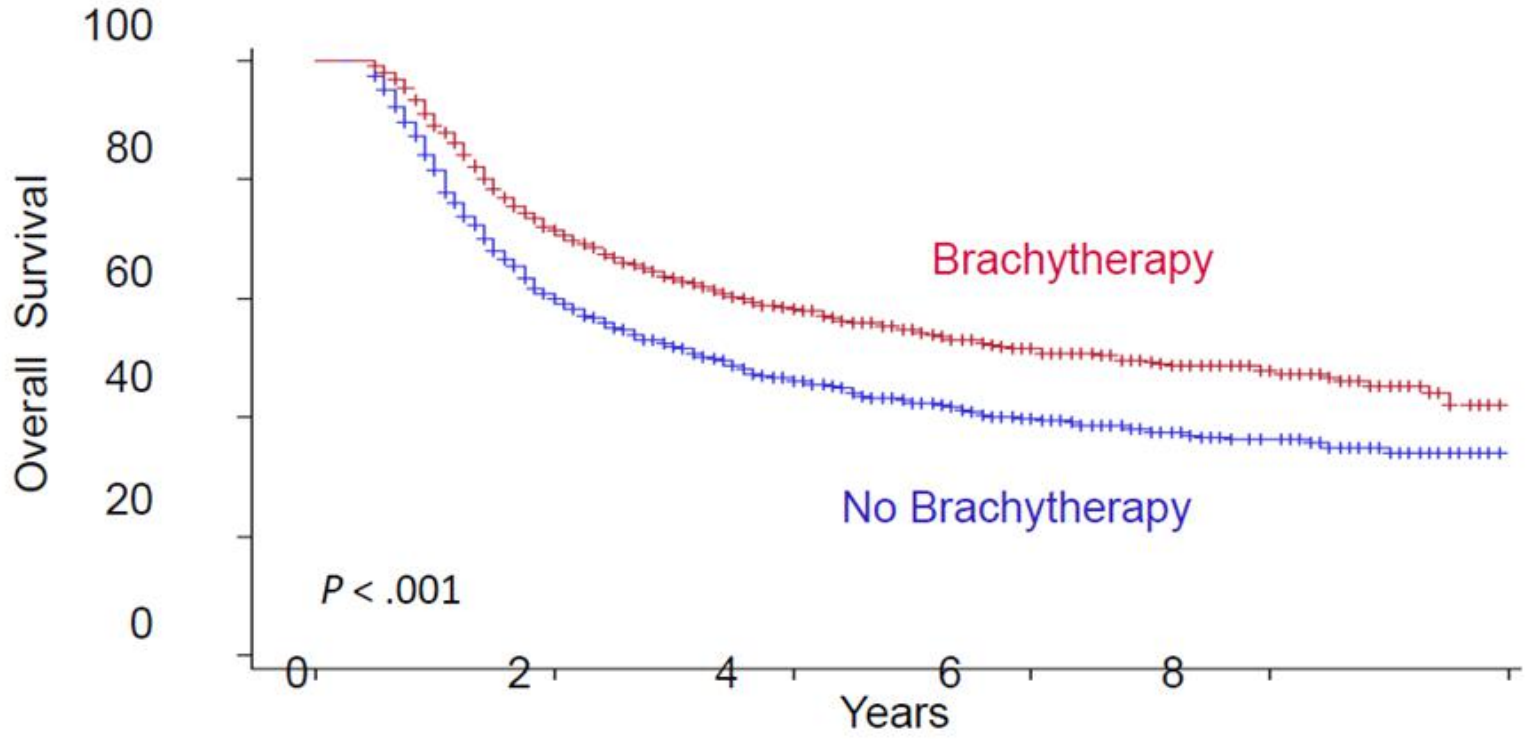
Locally Advanced Cervical Cancer IB2-IVA

- **EBRT and BRT**
  - EBRT (1.8 Gy/45 Gy)
  - BRT (85-90 Gy to HRCTV)
- **Concurrent cisplatin chemo**
  - Cisplatin 40 mg/m^2
  - Max dose 70 mg, IV q wk
  - During EBRT (6 wks)



Locally Advanced Cervical Cancer: BRT

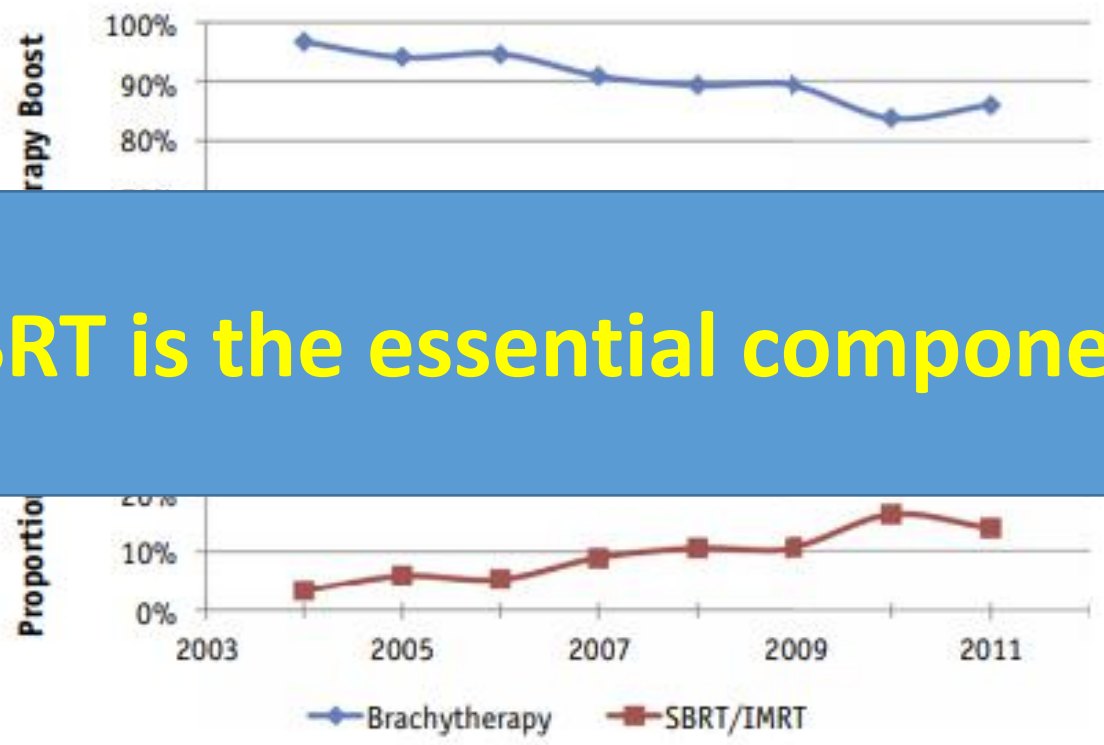
- Dose escalation
- **OS ↑** (HR 0.66)

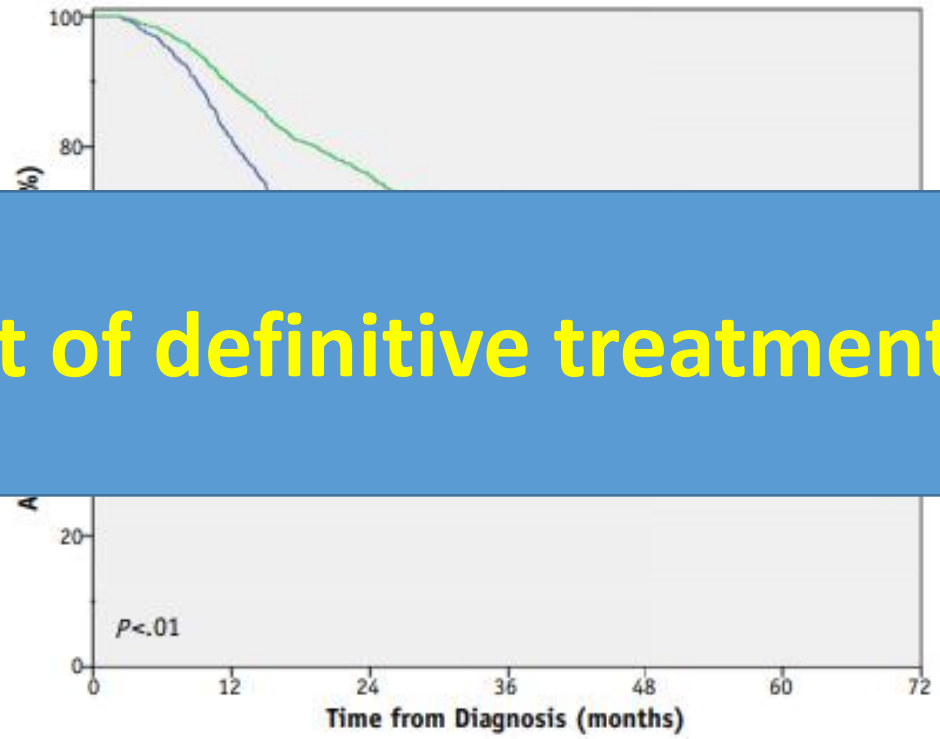


Han K, et al. Int Radiat Oncol Biol Phys 2013

Pts with locally advanced disease
Can SBRT/IMRT replace BRT?

- NCDB, 2004-2011, 7654 pts





BRT is the essential component of definitive treatment!

Gill BS, et al. Int Radiat Oncol Biol Phys 2014

Advances in Brachytherapy

2D Point-Based BRT → 3D Volume-Based BRT (CT/MRI) → 4D Image-Guided Adaptive BRT

- **↑ Local control and Survival**
- **↓ Toxicity**
- **↑ QOL**

Sturdza A, et al. Radiat Oncol 2016
Tanderup K, et al. Radiat Oncol 2016
Fokdal L, et al. Radiat Oncol 2016

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Image guided brachytherapy in cervical cancer

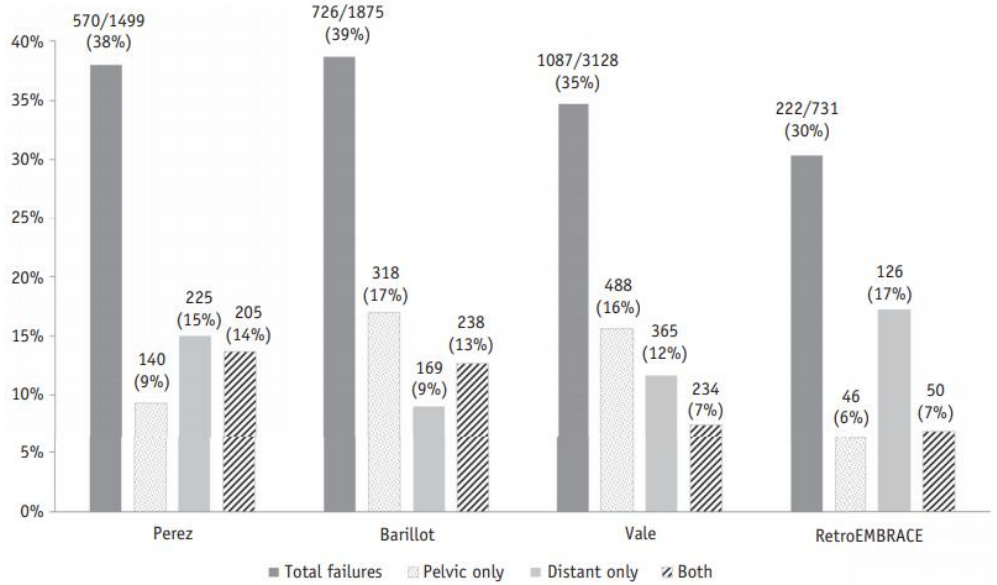
Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

FIGO stage	Number of patients	Total number of local failures	Total number of pelvic failures	Number of patients with any failure	Number of patients with no evidence of disease	Mean D90 HRCTV in Gy (±SD)	Actuarial local control at 3/5 years	Actuarial pelvic control at 3/5 years	Actuarial overall survival at 3/5 years	Actuarial cancer specific survival at 3/5 years
1A	2	0	0	0	2	-	100%	100%	100%	100%
1B	123	2	4	19	104	93 ± 17	98%/98%	96%/96%	88%/83%	93%/90%
2A	42	3	4	9	33	89 ± 16	97%/94%	95%/92%	83%/80%	87%/84%
2B	368	28	42	97	271	88 ± 14	93%/91%	89%/87%	78%/70%	83%/77%
3A	23	5	6	13	10	83 ± 12	71%/71%	66%/66%	54%/42%	54%/48%
3B	145	28	36	68	77	83 ± 13	79%/75%	73%/67%	56%/42%	65%/53%
4A	23	3	3	13	10	78 ± 13	76%/76%	76%/76%	43%/32%	53%/ 40%
4B	5	0	1	3	2	78 ± 2	-	-	-	
Total	731	69	96	222	509	87 ± 15	91%/89%	87%/84%	74%/65%	79%/73%

Sturdza A, et al. Radiother Oncol 2016

What we learned from new studies…

- 731 pts
- 12 institutions
- CRT and image-guided BRT
- Treatment failure: 222 pts
  - 21% pelvic failure alone
  - **57% distant failure alone**
  - 23% pelvic and distant failure



Clinical Investigation

Change in Patterns of Failure After Image-Guided Brachytherapy for Cervical Cancer: Analysis From the RetroEMBRACE Study

Tan L, et al. Int Radiat Oncol Biol Phys 2019

Pts with locally advanced disease
Do we need adjuvant chemo?

- 515 pts, stg IIB-IVA

	CRT	CRT + Chemo	
	(40mg/m² CDDP)	(CDDP/Gem + 2 CDDP/Gem)	p value
3-y PFS (%)	65	74	0.029
3-y OS (%)	70	81	0.024
LRF (%)	16	11	0.09
DM (%)	16	8	0.05
Gr 3-4 toxicity (%)	46	87	<0.001

Duenas-Gonzales A, et al. J Clin Oncol 2011

Ongoing Trial: Outback

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: THE OUTBACK TRIAL (*ANZGOG 0902*)

IB2, II, IIIB or IVA cervical cancer
ANZGOG 0902
GOG0724
RTOG1174

45-50.4 Gy/1.8 Gy
Cisplatin 40 mg/m2 weekly x 5
brachytherapy

Concurrent chemoradiation→
Adjuvant carbo AUC 5
paclitaxel 155 mg/m2 x 4

Pts with Stage IB2-IIB disease

Can neoadjuvant chemo and surgery replace CRT?

- **No significant difference in OS**
- **Neoaduvant chemotherapy:**
  - **Stage IIB: Decreased DFS**
  - **Adjuvant RT need ~20-36%**
  - **More acute toxicity**

EORTC 55994
Kenter G, et al. ASCO, 2019

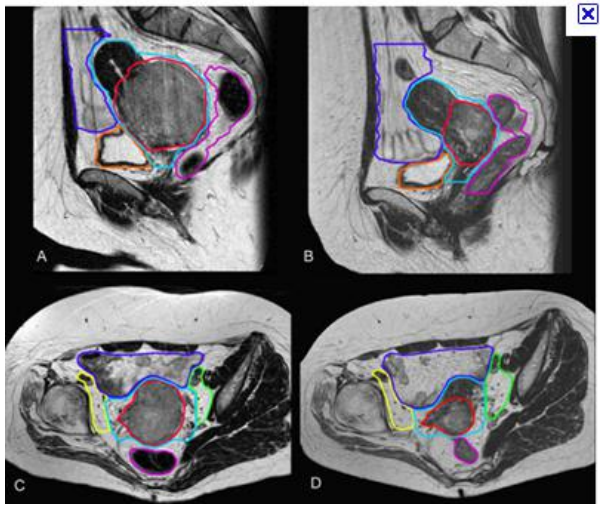
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

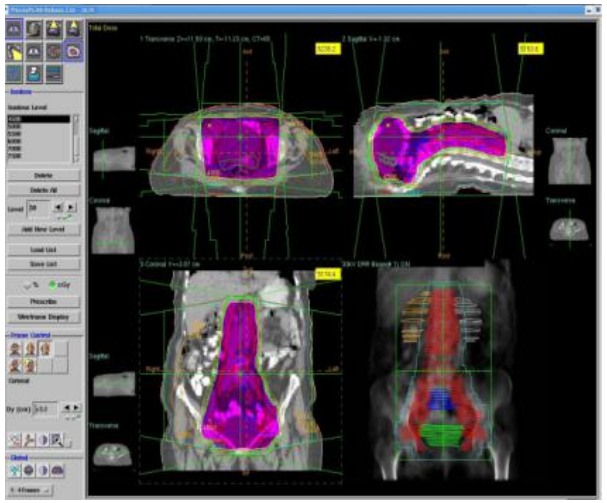
Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

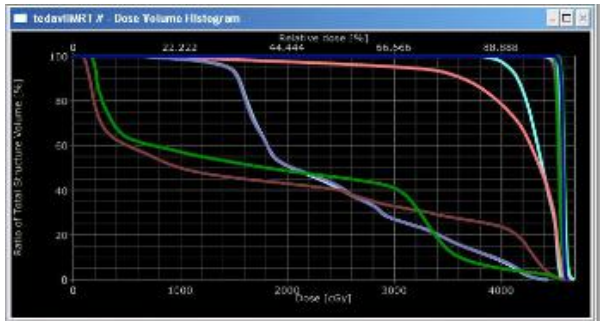
Gupta S, et al. J Clin Oncol 2018

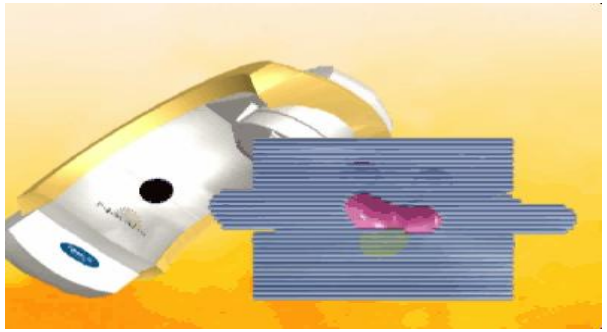
EBRT Process

- **Immobilization and CT simulation**
- **Contouring**
- **Treatment Planning**
- **Plan evaluation and QA**
- **Treatment**
  - **Set-up and imaging**



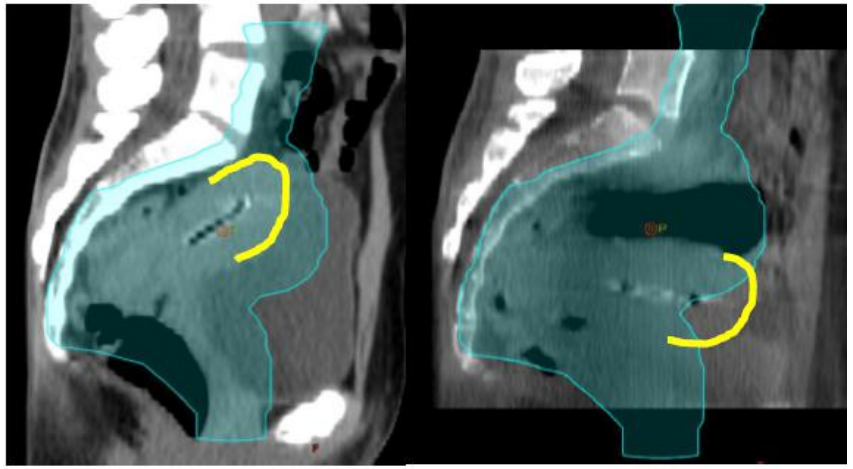


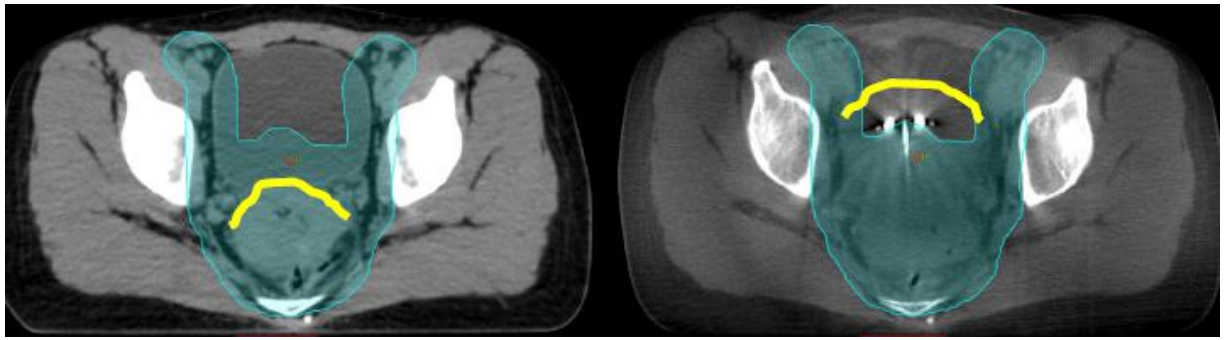




EBRT Technique in LACC

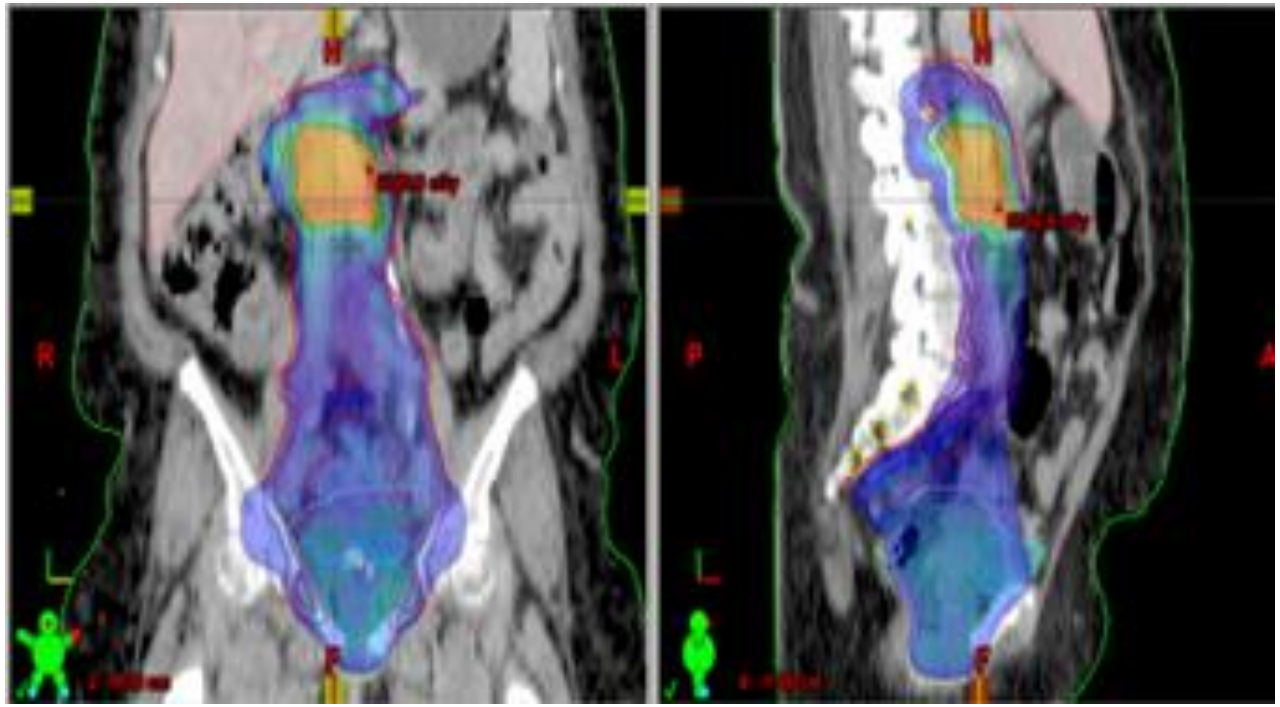
- Simulation
  - Bladder full and bladder empty
- Contouring
- Organ motion
  - Uterus, bladder, rectum, etc.
- Treatment
  - **Daily soft tissue imaging!!!!**
- **Adaptive and IGRT!!!!!!**





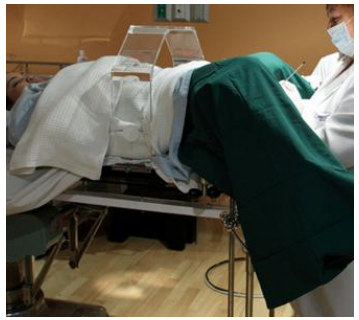
EBRT Technique in LACC

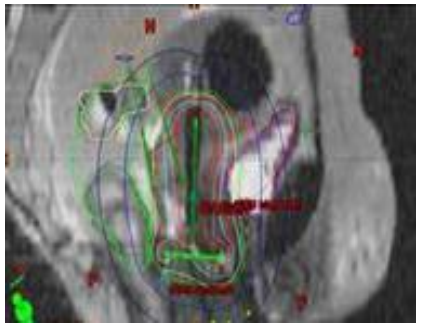
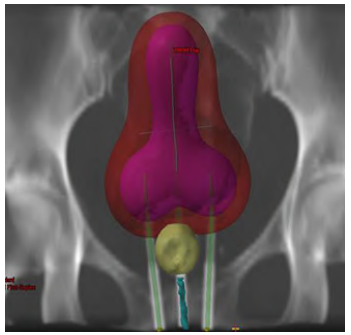
- **Simultaneous integrated boost (SIB)**
  - **Nodes/Pelvic sidewalls**

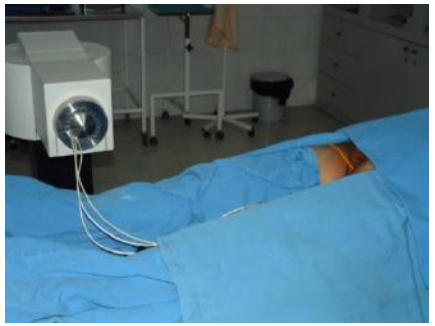


BRT Process

- Sedation
- Gynecologic examination
- Application of T/O, ring, needles etc.
- Imaging
  - MRI-based (gold standard) or CT-based
- Contouring
- Treatment planning
- Treatment





Endometrial Cancer

Classical approach vs. Contemporary approach

Standard Approach: Surgery

- **Adjuvant treatment**
  - **Clinicopathological risk factors and risk grouping**
    - Stage, grade, depth of MI, LVSI, histology

Risk group	Description	LOE
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Non-endometrioid (serous or clear-cell or undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

VOLUME 33 · NUMBER 28 · SEPTEMBER 10 2015
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Postoperative Radiation Therapy for Endometrial Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline

Larissa A. Meyer, Kari Bohlke, Matthew A. Powell, Amanda N. Fader, Gregg E. Franklin, Larissa J. Lee, Daniela Matei, Lourie Coallier, and Alexi A. Wright

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

N. Colombo[1*], C. Creutzberg[2], F. Amant[3,4], T. Bosse[5], A. González-Martín[6,7], J. Ledermann[8], C. Marth[9], R. Nout[10], D. Querleu[11,12], M.R. Mirza[13], C. Sessa[14] & the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group[‡]

Annals of Oncology 27: 16–41, 2016
doi:10.1093/annonc/mdv484

Low Risk: Stage IA, Gr 1-2, no LVSI

- **Surgery: TAH + BSO**

Recommendation 5.5: Patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, and two RCTs did not show a survival benefit. Therefore, lymphadenectomy is not recommended for these patients

Level of evidence: II
Strength of recommendation: A
Consensus: 100% yes (37 voters)

- ***Recurrence Risk: ≤5%***
- ***Do not require adjuvant treatment***

ESMO-ESGO-ESTRO, 2016
ASCO/ASTRO 2015

Intermediate Risk: IB, Gr 1-2, no LVSI
HIR: IA, Gr 3 or IA-B, Gr 1-2, LVSI

- **Intermediate Risk:**
  - **Vaginal BRT**
  - **NFT is an option in pts <60y**

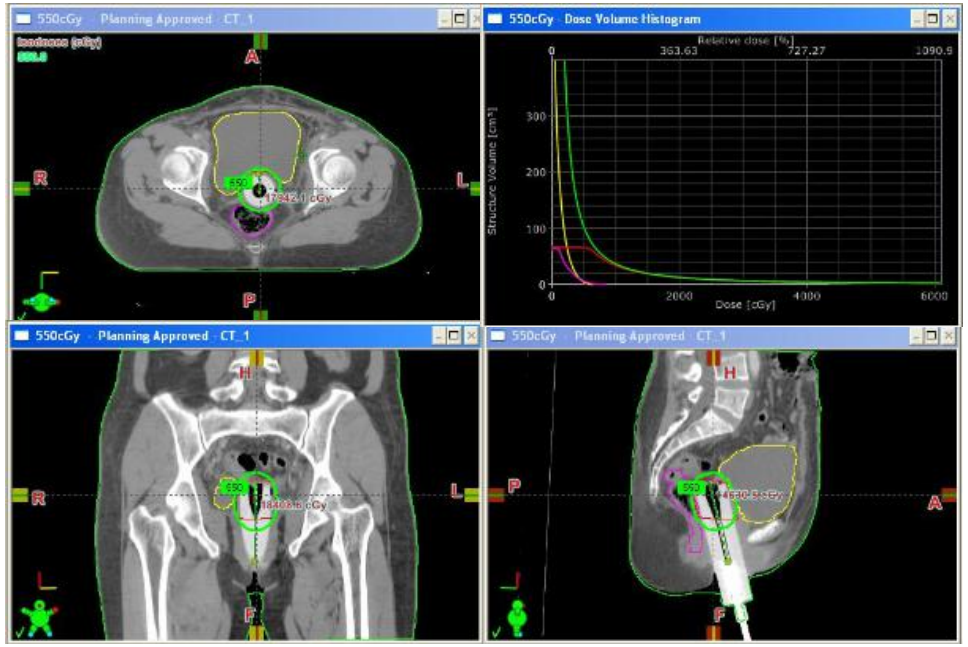
- **HIR:**
  - **Vaginal BRT when no LVSI or when LND (+)**
  - **EPRT when LVSI (+) and no LND**

ESMO-ESGO-ESTRO, 2016
ASCO/ASTRO 2015

RT Technique

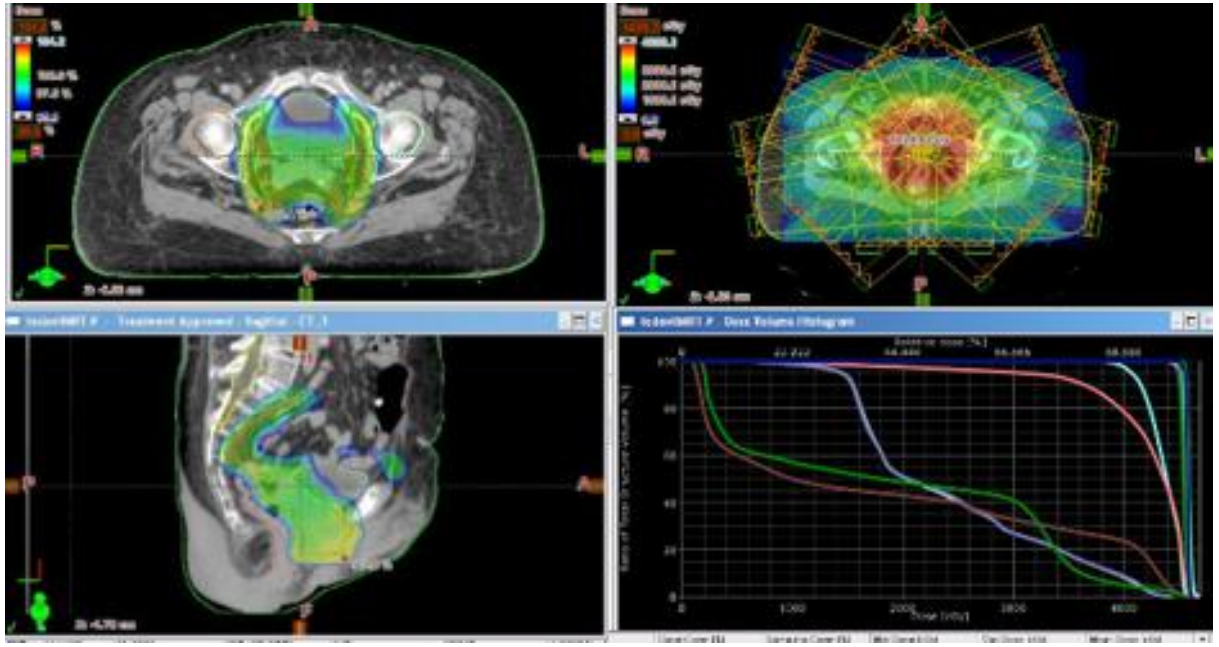
Vaginal Cuff BRT

- ***Image-guided BRT***



EPRT: 1.8-2 Gy/45-50.4 Gy

- ***IMRT***: Similar to cervical cancer



What is new in endometrial cancer?

- 4 different molecular subgroups
  - **POLE ultramutated**…… best prognosis
  - **MSI or MMRd hypermutated**
  - **Copy number low**
  - **Copy number high (TP53 mutation)** ……. worst prognosis

ARTICLE OPEN

doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

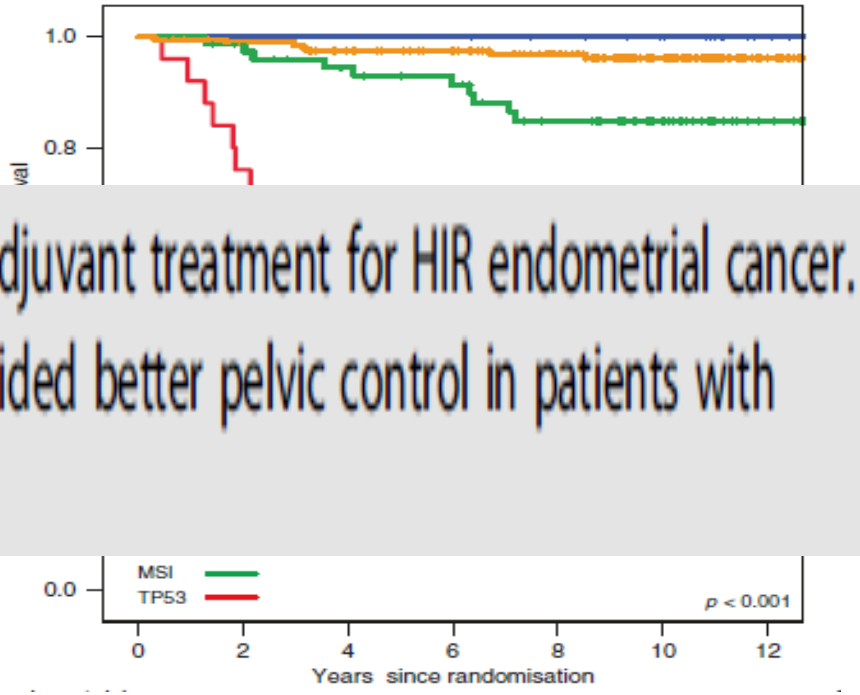
The Cancer Genome Atlas Research Network, Nature, 2013

BJC British Journal of Cancer www.nature.com/bjc

ARTICLE
Clinical Study

Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy

- **HIR**, central pathology review (n=416)



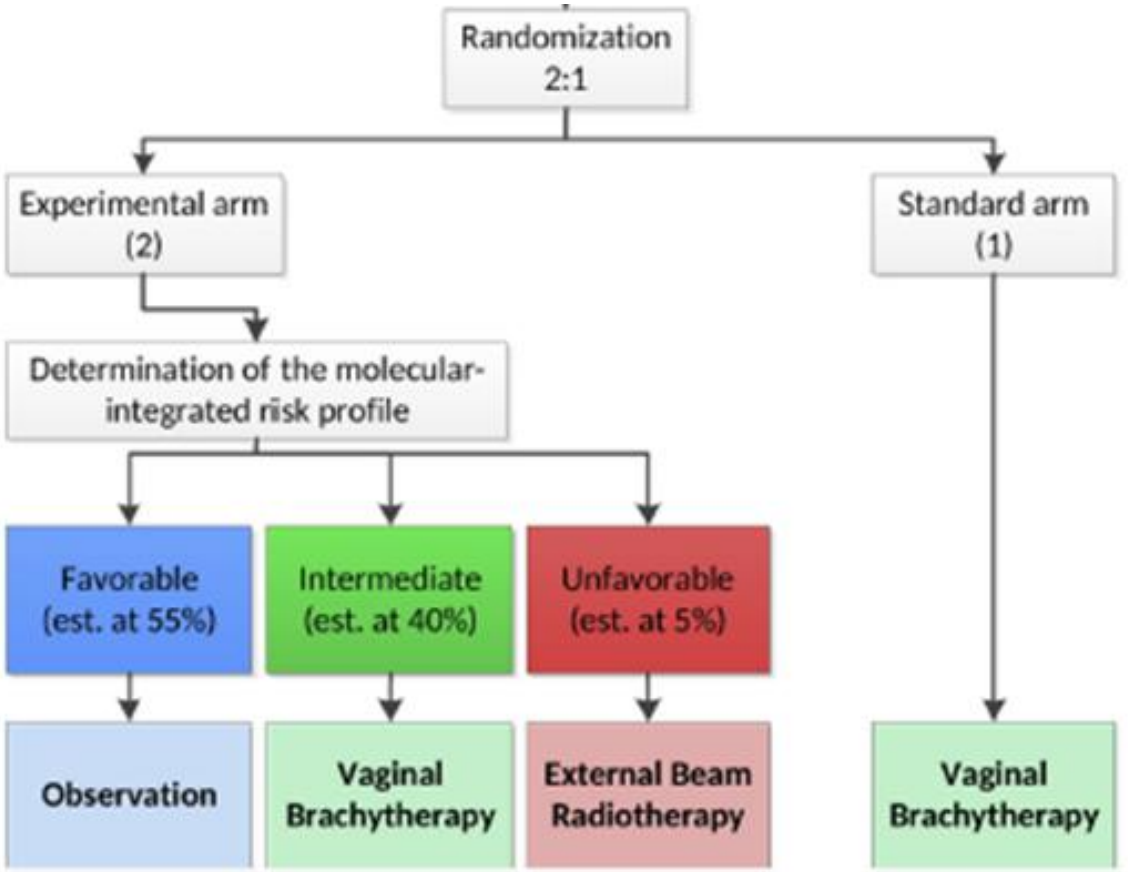
CONCLUSION: Long-term results of the PORTEC-2 trial confirm VBT as standard adjuvant treatment for HIR endometrial cancer. Molecular risk assessment has the potential to guide adjuvant therapy. EBRT provided better pelvic control in patients with unfavourable risk factors.

MSI	**85**
p53mutant	**62**

Wortman BG, et al. Br J Cancer 2018

Ongoing PORTEC 4a

- Surgical and pathologic diagnosis
- **HIR**
  - IA, Gr 3
  - IB, Gr 1-2; ≥60 y or LVSI+
  - IB, Gr 3, no LVSI
  - II (microscopic), Gr 1



*High-intermediate risk (HIR) endometrial cancer: stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

High Risk: IB-Gr 3; II; IIIEC-no residue; non-endometrioid

- **Adjuvant Treatment?**
  - EPRT only?
  - Chemo?
  - CRT?

  - ***PORTEC-3***
  - ***GOG 249***

original report

Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/ Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer

Eligibility:

Stage I endometrioid type
Age ≥ 18 with 3 RF
Age ≥ 50 with 2 RF
Age ≥ 70 with 1 RF

Stage II
Stage I-II serous and clear cell

RANDOMIZE

- Pelvic RT only
  46 Gy/2 Gy fx
- VBT
  Carboplatin/paclitaxel

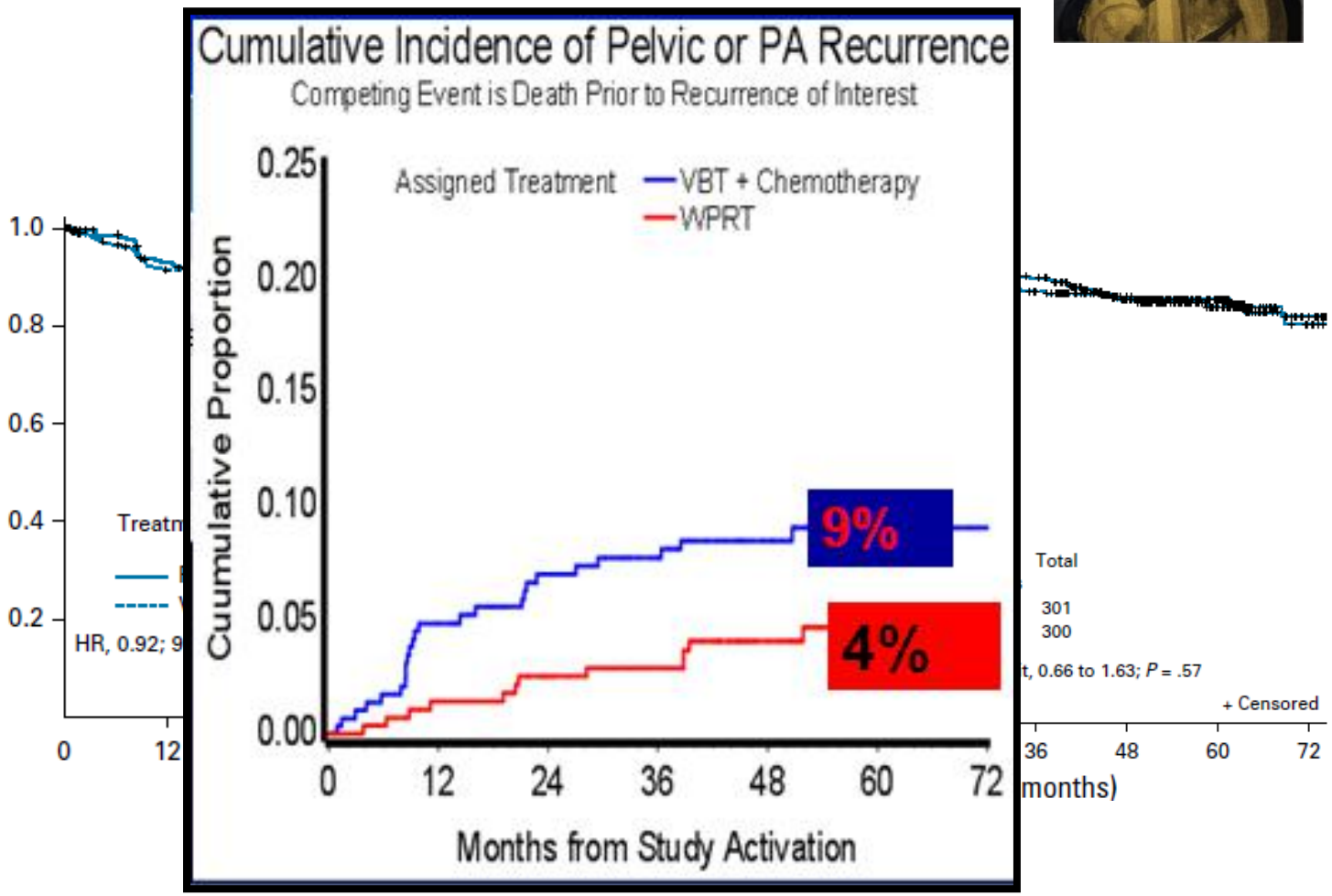
*high-intermediate risk uterine risk factors (endometrioid):
G2-3, outer ½ depth of MI, LVSI
89% lymphadenectomy

Randall ME, et al. J Clin Oncol 2019

GOG 249

- **527 pts**
- **Median f/u: 53 mos**

- **5-y OS, RFS, LR, DR: NSD**
- **Acute toxicity (≥Gr 3)**
  - **11% vs. 64%**
- Late toxicity (≥Gr3)
  - 13% vs. 12%



Randall ME, et al. J Clin Oncol 2019

GOG 249

- **No evidence that addition of chemotherapy improves survival.**
- ***Pelvic RT alone remains an appropriate (and probably preferable) treatment for high risk, early stage endometrial cancers of all histologies.***
- **Better treatment strategies to address the risk of systemic disease will be necessary to further improve outcomes in this patient group.**

Randall ME, et al. J Clin Oncol 2019

Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial

- **103 centers (n=686)**

Eligibility:

EAC
- Stage IAg3 with LVSI
- Stage IBg3
- Stage II or III
- Stage I-III USC/CC(>25%)

RANDOMIZE

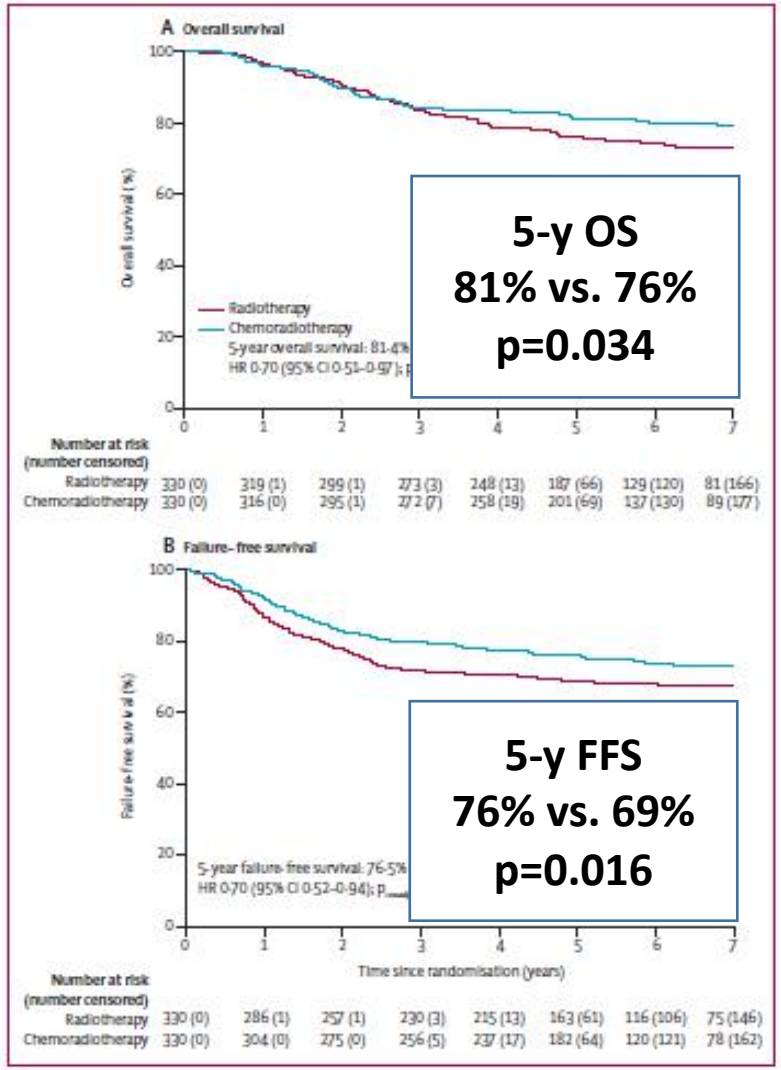
- Pelvic RT only
  48.6 Gy/1.8 Gy fx
- 48.6 Gy/1.8 Gy w/cis 50 mg/m2 x2
  Carbo AUC5/paclitaxel 175 mg/m2
  X 4 cycles

*No residual macroscopic tumor after surgery

de Boer SM, et al. Lancet Oncol 2019

PORTEC-3

- **Median f/u: 72 mos**
- **CRT-4 CT vs. EPRT**
  - **5-y OS and FFS ↑**
    - ***Stage III or serous cancers***
  - DM: 22% vs. 29%, p=0.057
  - Pelvic RR: 6% vs. 9%, p=0.11



de Boer SM, et al. Lancet Oncol 2019

By the guidance of PORTEC 3: take home messages……

- **Stage IB, gr3 or II disease usually treated with EPRT ± chemotherapy**
- **If pts had stage III disease or serous cancers, combined chemotherapy and EPRT should be considered**
- ***Most recurrences were at distant sites, suggesting that new systemic treatment approaches are needed to improve survival outcomes***
- **Molecular analysis has the potential to improve risk stratification and to guide adjuvant treatment**

ELSEVIER

Invited Review

Immunoth
A potentia

Larissa Lee [a,*]

Table 3
Ongoing clinical trials of definitive radiation with concurrent and adjuvant immunotherapy for locally advanced cervical cancer.

Identifier	Phase	N	Title	Disease	Treatment	Radiation details	Primary outcome	Secondary outcomes
NCT03298893	I	21	Nivolumab in Association with Radiotherapy and Cisplatin in Locally Advanced Cervical Cancers Followed by Adjuvant Nivolumab for up to 6 Months (NiCOL)	Locally advanced cervical cancer (stages IB2-IVA)	Nivolumab every 2 weeks (240 mg or 1 mg/kg) with CRT and 5 months thereafter	IMRT with or without nodal boost and weekly cisplatin followed by brachytherapy	Incidence of DLTs	• ctDNA heterogeneity • DFS • Incidence of AEs • Incidence of SAEs • ORR • PFS • Tumor molecular analysis • Tumor PD-L1 expression
NCT03738228	I	40	Anti PD-L1 (Atezolizumab) as an Immune Primer and Concurrently with Extended Field Chemoradiotherapy for Node Positive Locally Advanced Cervical Cancer	Stage IB/IIA cervical cancer with PALN or stage IIB/III/IVA cervical cancer with pelvic and/or PALN	Randomized to day −21 or day 0 atezolizumab with CRT every 3 weeks for 3 cycles	Extended field RT with weekly cisplatin, image-guided brachytherapy	Measurements in T-cell receptor clonal expansion in peripheral blood	• Correlation of PD-L1 expression and post--treatment PET-CT • 2-year DFS • Frequency and severity of AEs • Incidence of DLTs • Serial measurements of T-cell clonality and diversity • Incidence of distant metastasis • Metabolic RR by PET/CT at 12 weeks • OS • PFS
NCT02635360	II	88	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer	Locally advanced cervical cancer	Randomized to concurrent or sequential pembrolizumab with CRT every 21 days for 3 months	EBRT with weekly cisplatin followed by brachytherapy	Changes in immunologic markers at 6 and 12 weeks Incidence of DLTs	–
NCT03612791	II	190	Trial Assessing the Inhibitor of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab (ATEZOLACC)	Stage IB2-IIA cervical cancer with positive pelvic nodes, stage IIB-IVA, or stage IVB with para-aortic nodes	Randomized to CRT alone or CRT with concurrent and adjuvant atezolizumab every 21 days for up to 20 cycles	Pelvic +/− para-aortic EBRT with nodal boost and weekly cisplatin followed by brachytherapy	PFS	

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Thanks for your attention

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