3d CRT Vs IMRT In Carcinoma Cervix: Lessons Learnt From PARCER Trial And Beyond

Presenter :

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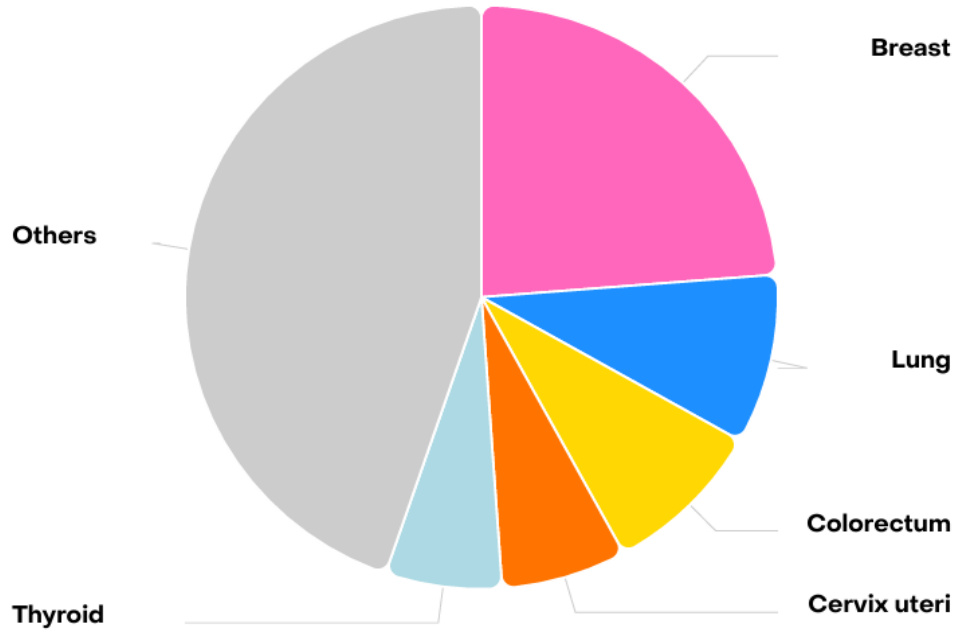
Cervical Cancer Incidence

Females

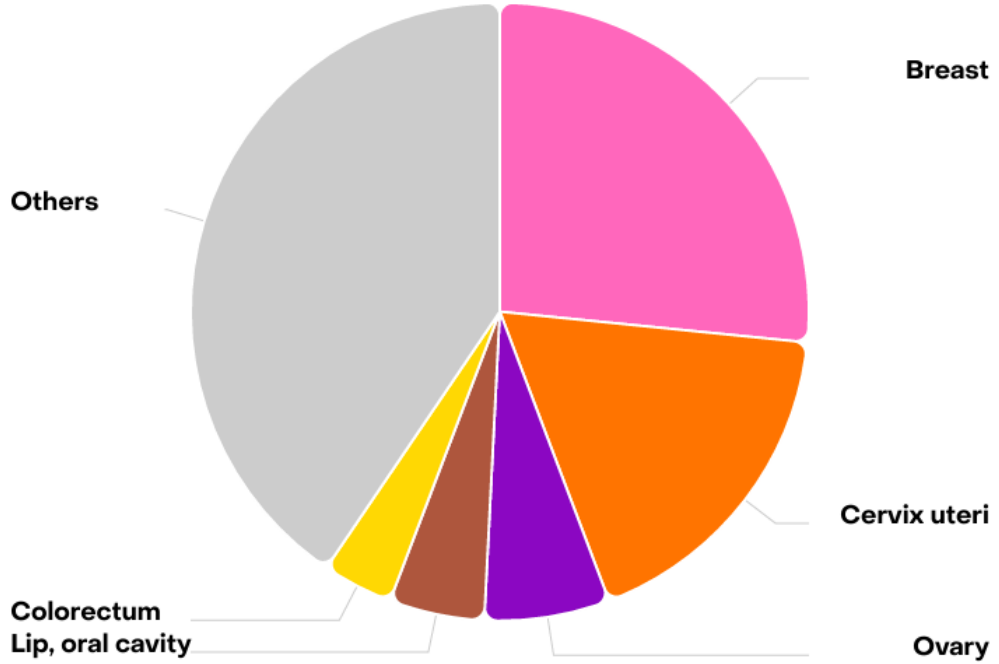
Worldwide 604,000



Total: 9 664 889

Females

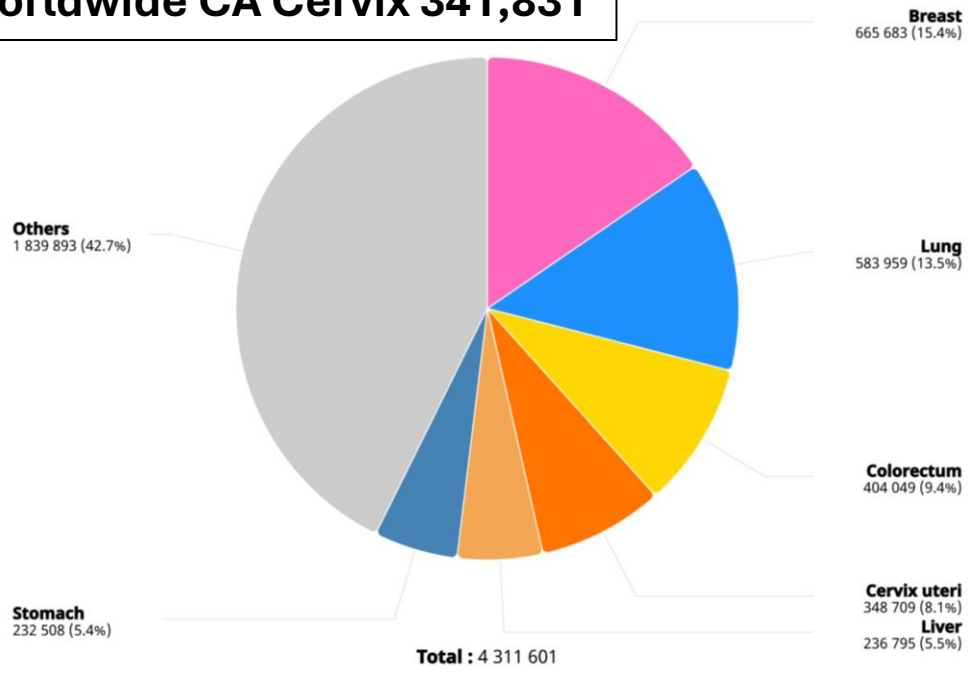
India 123,907



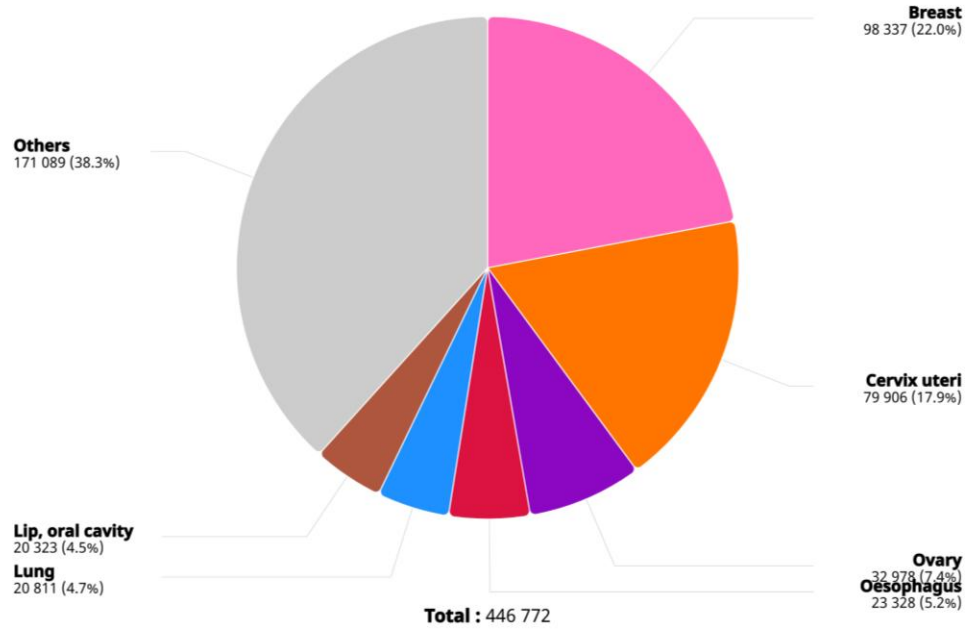
Total: 722 138

Mortality Worldwide Vs India

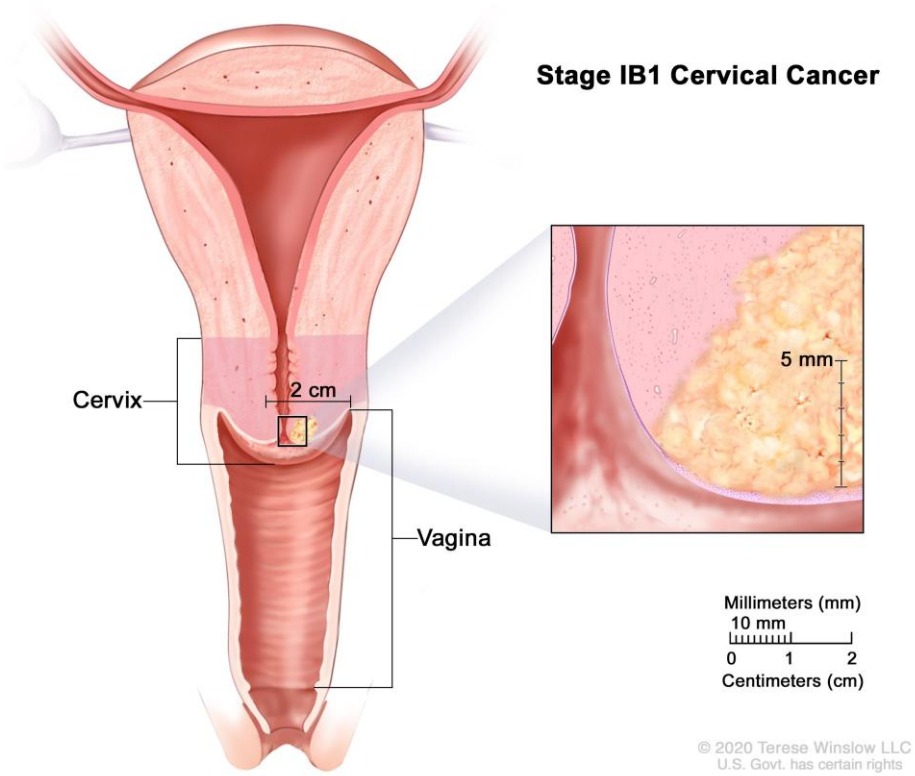
Worldwide CA Cervix 341,831

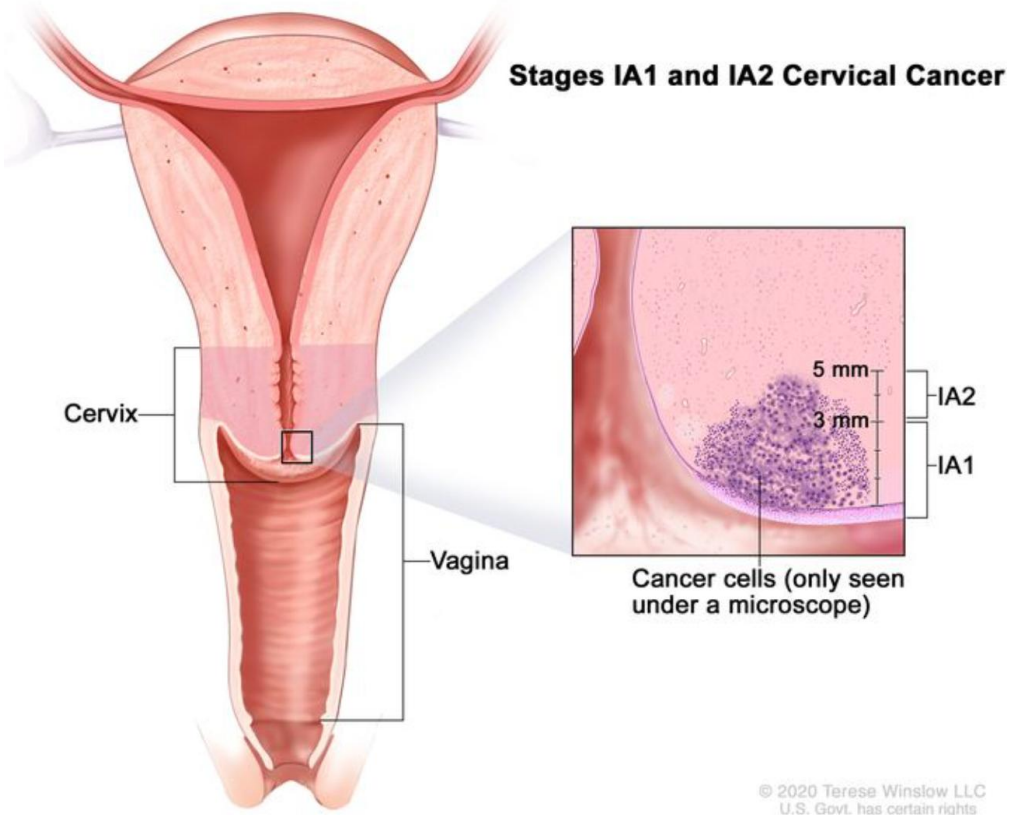


India CA Cervix 77,348



Early Stage Carcinoma Cervix





Treatment Approach for Early Cancer

- **Early-stage:** Radical hysterectomy ± adjuvant therapy.
- Adjuvant RT reduces locoregional recurrence in high/intermediate risk.
- CTRT improves OS , given for positive nodes/margins or parametrial involvement.

SEDLIS CRITERIA FOR EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE CASES[a-c,1,2]

LVSI	Stromal Invasion	Tumor Size (cm) (determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or deep 1/3	≥4

LVSI: Lymphovascular space invasion

Footnotes

[a] Modified with permission from Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology study group. Gynecol Oncol 1999;73:177-183.

[b] Risk factors may not be limited to the Sedlis criteria.

[c] Sedlis criteria were developed primarily for squamous cell carcinoma. Histology-specific nomograms for squamous and adenocarcinoma lesions may provide a more contemporary tool to model the risk of recurrence and base adjuvant recommendations. Depth of invasion is an important risk factor of recurrence for squamous lesions. Tumor size is an important risk factor for cervical adenocarcinoma, and this risk becomes more pronounced with the presence of LVSI.[3]

Histology Specific Nomogram

Contents lists available at ScienceDirect

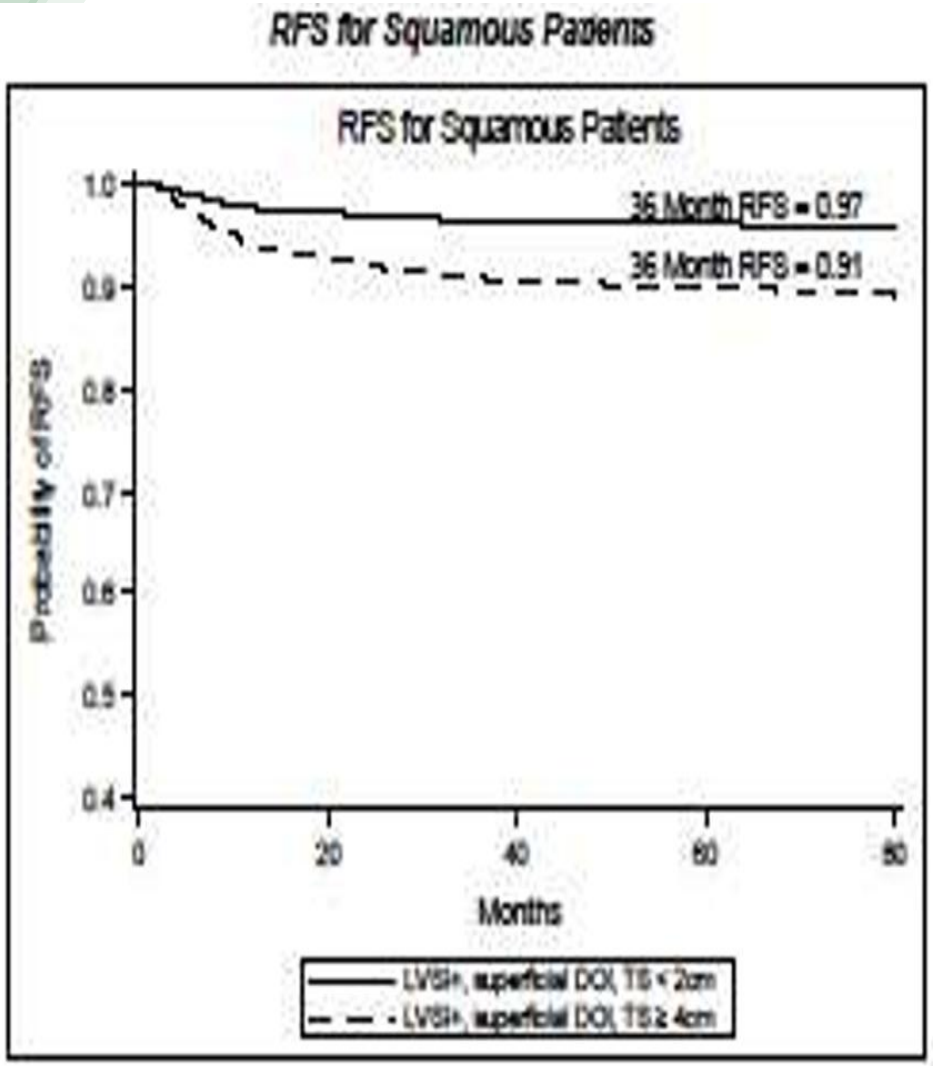
Gynecologic Oncology

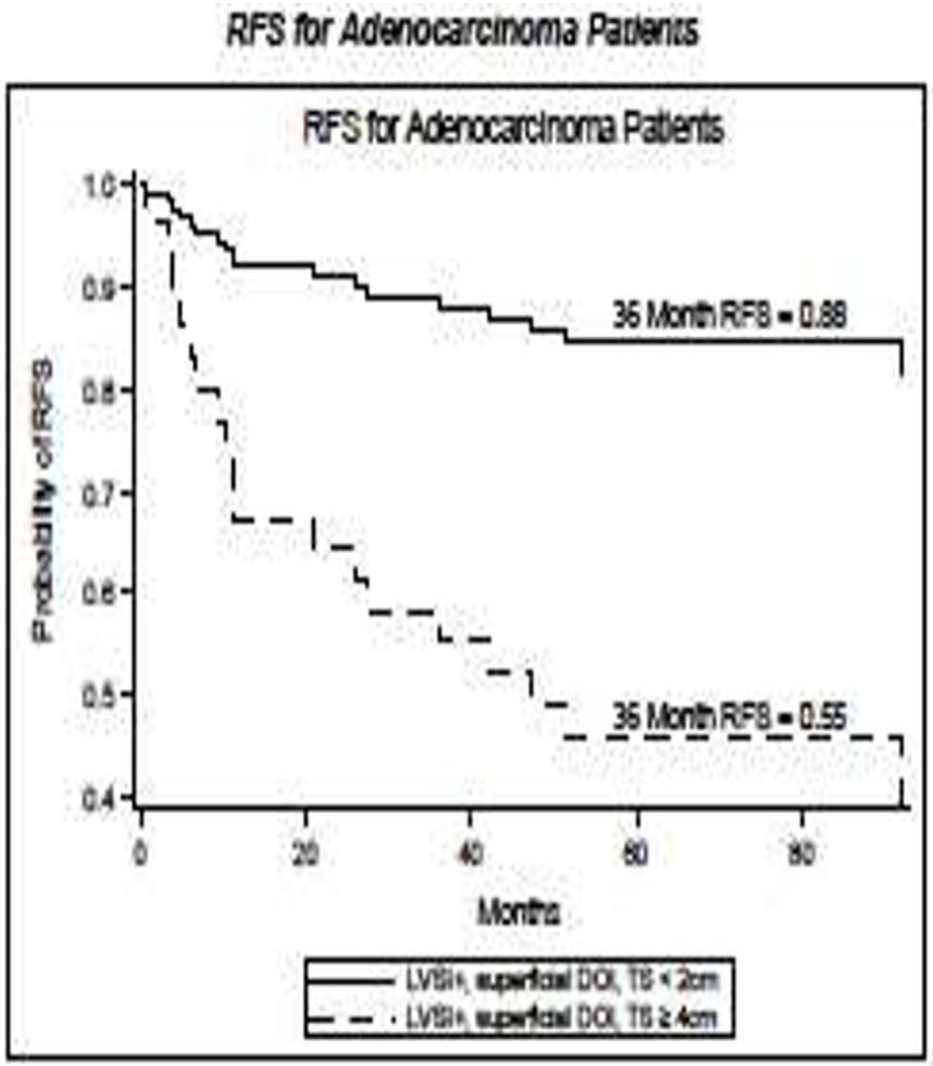
journal homepage: www.elsevier.com/locate/ygyno

Beyond Sedlis—A novel histology-specific nomogram for predicting cervical cancer recurrence risk: An NRG/GOG ancillary analysis

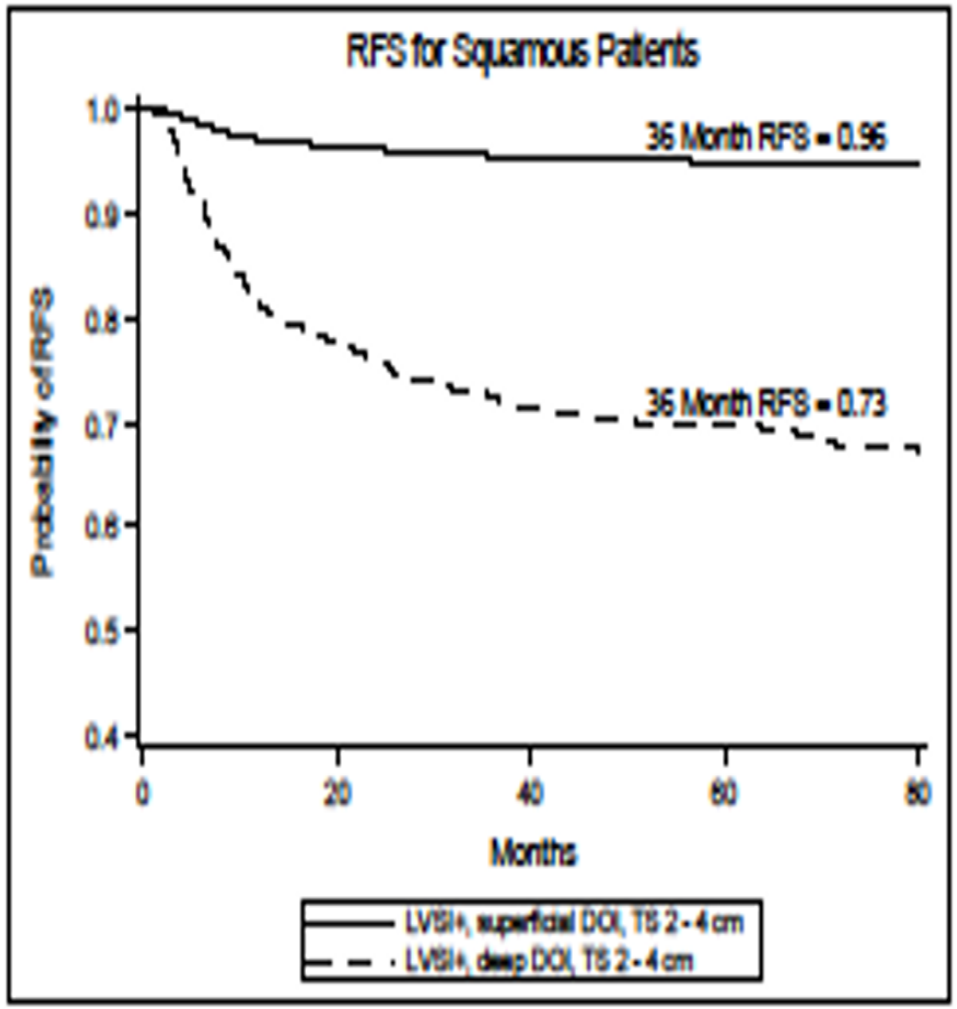
Kimberly Levinson [a,*], Anna L. Beavis [a], Christopher Purdy [b], Anne F. Rositch [c], Akila Viswanathan [a], Aaron H. Wolfson [d], Michael G. Kelly [e], Krishnansu S. Tewari [f], Leah McNally [g], Saketh R. Guntupalli [h], Omar Ragab [i], Yi-Chun Lee [j], David S. Miller [k], Warner K. Huh [l], Kelly J. Wilkinson [m], Nicola M. Spirtos [n], Linda Van Le [o], Yovanni Casablanca [p], Laura L. Holman [q], Steven E. Waggoner [r], Amanda N. Fader [a]

Need for looking beyond Sedlis

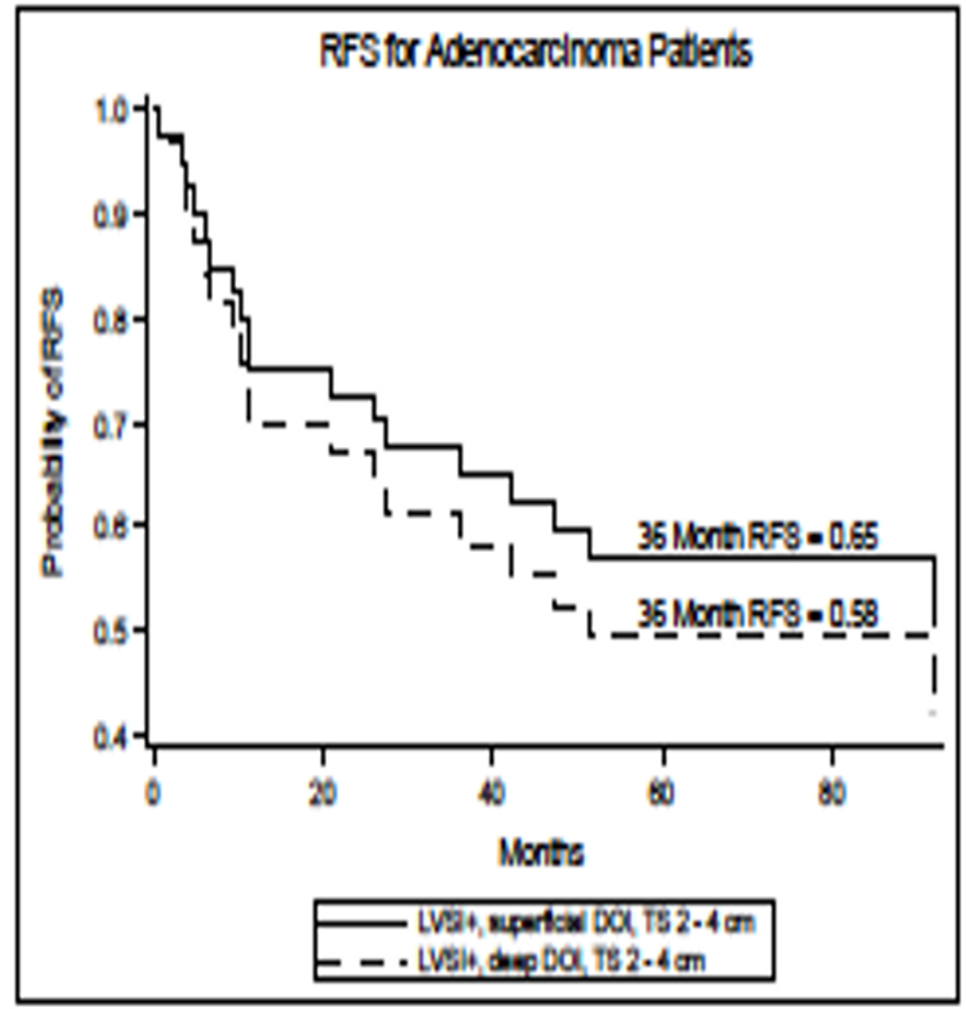




RFS for Squamous Patients



RFS for Adenocarcinoma Patients



Comparison of 3 yr RFS, nomogram recurrence risk, and Sedlis criteria for predictor variable combinations.

Vascular Invasion	Invasion Depth	Tumor Size	SCC			AC		
			RFS (3 yr, CI)	Sedlis Criteria (+/−)	Nomogram recurrence risk	RFS (3 yr, CI)	Sedlis Criteria (+/−)	Nomogram recurrence risk
N	Superficial	(<2 cm)	0.98 (0.96, 1)	−	<5%	0.96 (0.90, 1.00]	−	<5%
N	Middle	(<2 cm)	0.91 (0.87, 0.95)	−	9%	0.97 (0.92, 1.00]	−	<5%
N	Deep	(<2 cm)	0.86 (0.79, 0.93)	−	16%	0.95 (0.87, 1.00]	−	7%
N	Superficial	(2–4 cm)	0.97 (0.95, 1)	−	<5%	0.86 (0.70, 1.00]	−	14%
N	Middle	(2–4 cm)	0.88 (0.84, 0.93)	−	11%	0.89 (0.77, 1.00]	−	11%
N	Deep	(2–4 cm)	0.82 (0.75, 0.89)	−	18%	0.83 (0.66, 1.00]	−	17%
N	Superficial	(≥4 cm)	0.94 (0.9, 0.99)	−	10%	0.81 (0.59, 1.00]	−	19%
N	Middle	(≥4 cm)	0.78 (0.7, 0.86)	+	18%	0.85 (0.70, 1.00]	+	16%
N	Deep	(≥4 cm)	0.66 (0.58, 0.75)	+	25%	0.77 (0.56, 1.00]	+	22%
Y	Superficial	(<2 cm)	0.97 (0.94, 0.99)	−	<5%	0.88 (0.71, 1.00]	−	15%
Y	Middle	(<2 cm)	0.86 (0.8, 0.92)	−	12%	0.91 (0.78, 1.00]	−	12%
Y	Deep	(<2 cm)	0.78 (0.7, 0.88)	+	20%	0.85 (0.70, 1.00]	+	18%
Y	Superficial	(2–4 cm)	0.96 (0.92, 1)	−	6%	0.65 (0.32, 1.00]	−	32%
Y	Middle	(2–4 cm)	0.82 (0.76, 0.89)	+	14%	0.71 (0.48, 1.00]	+	29%
Y	Deep	(2–4 cm)	0.73 (0.65, 0.81)	+	21%	0.58 (0.36, 0.96]	+	35%
Y	Superficial	(≥4 cm)	0.91 (0.84, 0.99)	+	16%	0.55 (0.19, 1.00]	+	39%
Y	Middle	(≥4 cm)	0.67 (0.57, 0.79)	+	24%	0.63 (0.37, 1.00]	+	36%
Y	Deep	(≥4 cm)	0.52 (0.43, 0.64)	+	31%	0.47 (0.24, 0.95]	+	42%

3 yr recurrence risk predicted by the histology specific nomogram for tumors meeting Sedlis criteria.

Sedlis intermediate risk factor combinations	SCC Predicted 3-yr Recurrence Risk	AC Predicted 3-yr recurrence risk
LVSI positive Deep 1/3 invasion Any tumor size	38%	22%
LVSI positive Middle 1/3 invasion Tumor size ≥2 cm	23%	**39%**
LVSI positive Superficial 1/3 invasion Tumor size ≥5 cm	18%	**45%**
LVSI negative Middle/deep 1/3 invasion Tumor size ≥4 cm	28–40%	**30–38%**

Evolution of Treatment

- Surgery alone → RT → Concurrent CTRT → Advanced RT (3D-CRT, IMRT, IG-IMRT).

- Technological advancements aimed at reducing toxicity while maintaining efficacy.

- Long term follow of Prospective trials guide us on what toxicities to expect

- **1990s-2000s: Establishment of Adjuvant Therapy**
- GOG 49 (1999): Established role of adjuvant RT for intermediate-risk features
- Peters et al. (2000): Demonstrated survival benefit of concurrent chemoradiation for high-risk features

2000s-2010s: Recognition of Toxicity Burden

- Landoni Trial 20-year follow-up: Surgery alone had fewer adverse events than RT
- Multiple studies documented long-term GI toxicity rates:
  - Rotman: 6.6% vs 2.1% late Grade III-IV GI toxicity (RT vs Surgery alone)
  - Keys: 8% vs 0.4% late Grade III-IV GI toxicity (RT vs Surgery alone)
  - Peters: 10% vs 5% late Grade III-IV GI toxicity (CT/RT vs RT alone)

- **2010s-Present: Advanced Radiation Techniques**
- Development of IMRT and image guidance
- Early phase II studies showed promise for reduced acute toxicity

Long term Toxicity: 20 year follow up Landoni

Table 5. Complications related to the actual treatment

Type of complication	Surgery	Surgery+RT	RT
No. of patients	61	108	158
Urologic			
Hydroureteronephrosis*	2 (3.3)	11 (10.1)	9 (5.6)
Ureteral fistula	1 (1.6)	-	-
Urinary incontinence	2 (3.3)	4 (3.7)	-
Atonic bladder	8 (13.1)	5 (4.6)	1 (0.6)
Actinic cystitis	-	7 (6.4)	9 (5.6)
Vascular			
Pulmonary embolism	2 (3.3)	1 (0.9)	-
Legs edema	-	12 (11.1)	1 (0.6)
Lymphocyst	5 (8.2)	5 (4.6)	1 (0.6)
Vascular lesion	1 (1.6)	-	-
Intestinal			
Rectal fistula	-	-	1 (0.6)
Bowel obstruction	-	6 (5.5)	2 (1.2)
Proctitis	-	-	14 (8.8)
Others			
Wound abscess	-	-	-
Abdominal hernia	4 (6.6)	4 (3.7)	2 (1.2)
Bone necrosis	-	1 (0.9)	-
Vaginal necrosis	-	-	1 (0.6)
Vaginal stenosis	-	1 (0.9)	2 (1.2)
Pelvic fibrosis	-	4 (3.7)	3 (1.8)
Uterine perforation	-	-	1 (0.6)
Peritonitis	-	1 (0.9)	-
Total	25 (40.7)	62 (56.4)	47 (29.0)

Why refine and improve the techniques of treatment

- A significant proportion of patients survive for long term

- Morbidities and QOL Changes are real life issue with the long tem survival

Toxicity Concerns with Adjuvant RT

Late Gastrointestinal Toxicity Rates:

- **Rotman:** Surgery + RT: 6.6% vs Surgery alone: 2.1%
- **Keys:** Surgery + RT: 8% vs Surgery alone: 0.4%
- **Peters:** Surgery + RT + CT: 10% vs Surgery + RT: 5%
- **Chen:** Surgery + RT + BT: 19.2% Grade I-IV (non-rectal GI)

Patient Reported Quality of Life Impact

- **PORTEC I and II Endometrial Trials (EBRT vs Vaginal BT):**
- Diarrhea
- Fecal urgency
- Fecal leakage
- Limitation of activities of daily living

Early Trials of IMRT and Favorable Toxicity Profile

Study	N	Follow-up	Grade II-IV Toxicity
Grigsby (2009)	20 EBRT	19 months	35% (Acute)
Kabarriti (2009)	26 EBRT only	18 months	15.4% (Acute)
Barrilott (2013)	49	Week 15	<30%
RTOG 0418 (2009)	98 EBRT+BT	30 months	3.2%
Folker MR (2013)	34 EBRT+Chemo	44 months	Late: 3%

Why need more studies ?

Limitations of Early Studies
Key Issues:
- Small sample sizes
- No randomized comparators
- Short follow-up periods
- Heterogeneous patient populations
- **Long-term benefit for IG-IMRT was not clear**
- **NRG 1203 Study (TIME-C)**
- **Results:**
- Early impact on RT quality of life
- **No benefit at long-term follow-up** (Klopp JCO 2018, Yeung JCO 2020)
- Focused primarily on patient-reported outcomes
- Limited physician-reported toxicity assessment

Need for IMRT

- Toxicity profile

- OAR at higher risk due to a changed anatomy

Early IMRT Trials & Toxicity Profile

- Phase II studies suggested reduced acute GI toxicity.
- No robust phase III evidence for late GI toxicity before PARCER.

PARCER Trial – Hypothesis
Postoperative Adjuvant Radiation in CERvical Carcinoma

- IG-IMRT will reduce late GI toxicity compared to 3D-CRT in adjuvant setting.

PARCER Trial – Study Design

- Phase III RCT, N=300, post-op cervical cancer.
- Stratified by surgery type & CTRT use.
- Primary endpoint: 3-year Grade ≥2 late GI toxicity.
- IG-IMRT vs 3D-CRT; 50 Gy/25 fractions + HDR BT.

original reports

Late Toxicity After Adjuvant Conventional Radiation Versus Image-Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial

Supriya Chopra, MD, DNB[1]; Sudeep Gupta, DM[2]; Sadhana Kannan, MSc[3]; Tapas Dora, MD[4]; Reena Engineer, DNB[5]; Akshay Mangaj, MD[5]; Amita Maheshwari, MD[6]; T. Surappa Shylasree, MD[6]; Jaya Ghosh, MD, DM[2]; Siji N. Paul, MSc[1]; Reena Phurailatpam, MSc[1]; Mayuri Charnalia, MSc[1]; Mitali Alone, BSc[7]; Jamema Swamidas, PhD[1]; Umesh Mahantshetty, MD[5]; Kedar Deodhar, MD[8]; Rajendra Kerkar, MD[6]; and Shyam K. Shrivastava, MD, DNB[5]

- **Study:** NCT01279135/CTRI2012/120349
- **Publication:** Journal of Clinical Oncology, 2021
- **Principal Investigator:** Dr. Supriya Chopra, MD
- Department of Radiation Oncology, Tata Memorial Centre, Mumbai, India

Scientific Rationale

- Correlation established between bowel dose and GI toxicity
- Phase II studies suggested reduced acute GI toxicity with IMRT
- Technological advancement allows superior dose distribution
- Opportunity to reduce long-term morbidity while maintaining cure rates

Objectives

Primary Objective:

- Demonstrate 13% reduction (18% to 5%) in late Grade ≥II GI toxicity at median follow-up of 36 months

Secondary Objectives:

- Compare acute toxicity between 3D-CRT and IG-IMRT
- Compare quality of life between treatment arms
- Identify dose-volume characteristics predicting late GI toxicity
- Assess disease control outcomes

Patient Eligibility

Inclusion Criteria:	**Exclusion Criteria:**
Cervical cancer patients aged >18 years Type III (Wertheim's) hysterectomy with intermediate or high-risk features Type I/II hysterectomy necessitating adjuvant chemoradiation therapy	Positive para-aortic nodes or indication for extended field RT History of multiple previous abdominal surgeries/radiation Medical conditions predisposing to bowel toxicity

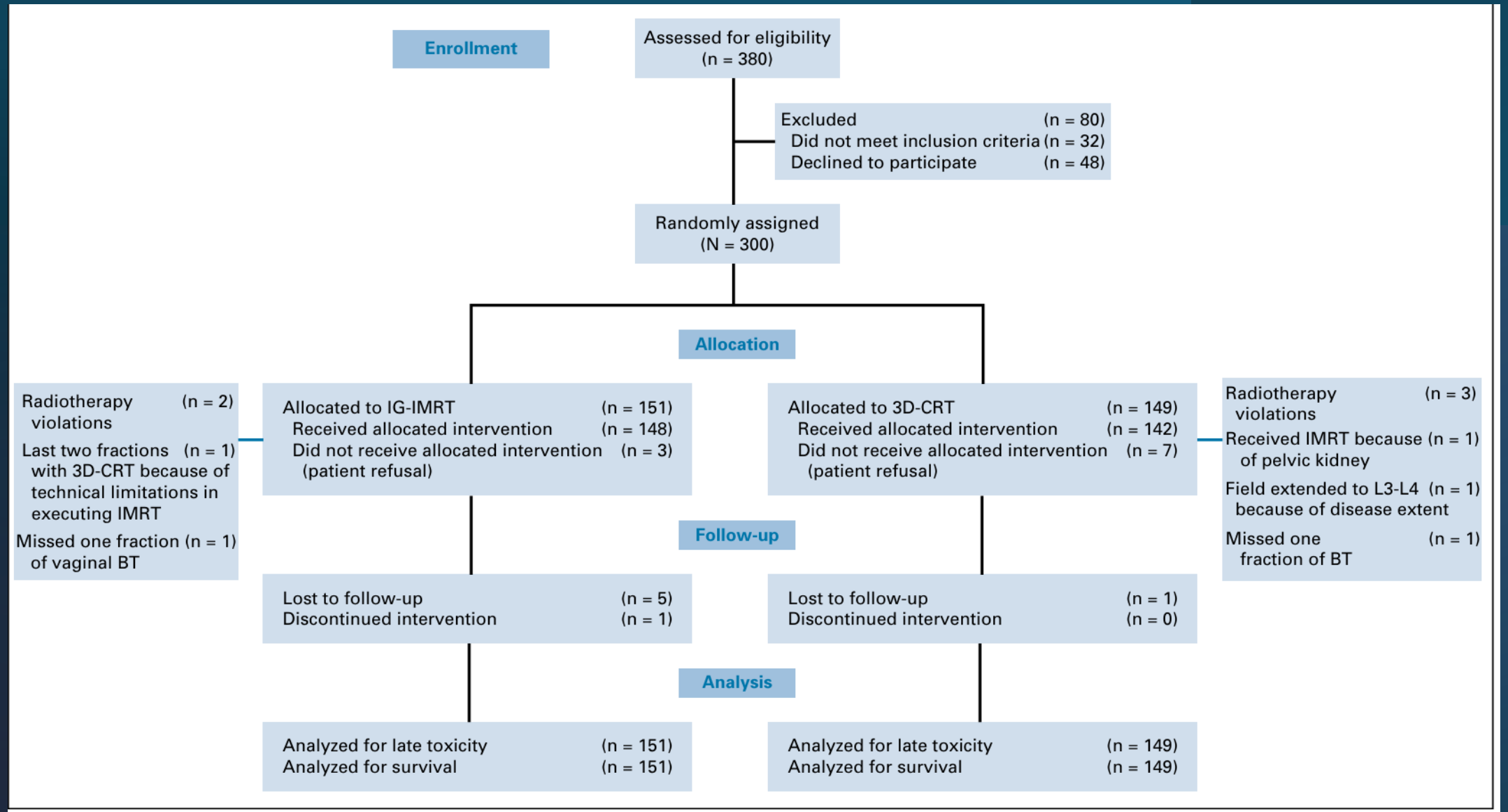


FIG 1. CONSORT diagram. 3D-CRT, three-dimensional conformal radiation therapy; BT, brachytherapy; IG-IMRT, image-guided intensity-modulated radiotherapy.

Trial Schema

Study Type:	Randomization:	Stratification Factors:	Sample Size Calculation:	Statistical Power:	FOLLOW UP
Open-label, parallel-group, phase III randomized controlled trial	Permuted block randomization	Type of hysterectomy (Wertheim's vs simple) Use of concurrent chemotherapy	**Initial Design:** 240 patients (18% to 5% reduction) **Revised After Interim:** 300 patients (24% to 11% reduction)	80% **Alpha:** 0.047 (after accounting for interim analysis)	EVERY 3 MONTHS FOR 3 YEARS THERE AFTER EVERY 6 MONTHS

Treatment Arms

Control Arm (3D-CRT):

- Four-field conformal box technique
- 6-18 MV beams
- Weekly portal imaging
- 95% PTV receives 95% dose

Experimental Arm (IG-IMRT):

- Strict bowel constraints (V15 <190cc, V40 <100cc)
- Daily image verification mandatory
- Individual bowel loop delineation
- Vault marker ITV + 7mm expansion

Quality Control Measures

- Central review of target delineation
- Principal investigator reviewed all plans
- Institutional data safety monitoring board oversight
- **Compliance:** 96% IG-IMRT, 92% 3D-CRT

Treatment details

- **Radiation Dose and Fractionation:**
- External Beam RT: 50 Gy in 25 fractions over 5 weeks
- High-dose-rate vaginal brachytherapy: 12 Gy in 2 fractions over 1 week
- Dose prescribed at 5 mm from cylinder surface
- **Concurrent Chemotherapy:**
- Cisplatin 40 mg/m^2 weekly for up to 5 weeks
- Used in 77% of patients in both arms

Long Term Toxicity

TABLE 2. Late Adverse Events in the IG-IMRT and 3D-CRT Arms

Adverse Event	Grade ≥ 2 Toxicity: IG-IMRT (n = 151), No. (%)	Grade ≥ 2 Toxicity: 3D-CRT (n = 149), No. (%)	Grade ≥ 2 Toxicity: *P*	Grade ≥ 3 Toxicity: IG-IMRT (n = 151), No. (%)	Grade ≥ 3 Toxicity: 3D-CRT (n = 149), No. (%)	Grade ≥ 3 Toxicity: *P*
Diarrhea	6 (3.9)	11 (7.4)	.20	2 (1.3)	4 (2.6)	.44
Anorexia	1 (0.6)	10 (6.7)	.005	0 (0)	1 (0.6)	.50
Nausea	1 (0.6)	3 (2.0)	.37	0 (0)	0 (0)	NA
Vomiting	2 (1.3)	7 (4.7)	.10	0 (0)	0 (0)	NA
Abdominal bloating	20 (13.2)	39 (26.2)	.006	2 (1.3)	1 (0.6)	1.0
Abdominal pain	16 (10.5)	22 (14.8)	.27	0 (0)	4 (2.6)	.06
Malabsorption	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Bowel perforation	1 (0.6)	2 (1.3)	.62	1 (0.6)	2 (1.3)	.62
Bowel obstruction	1 (0.6)	8 (5.3)	.01	1 (0.6)	8 (5.3)	.02
GI stricture	0 (0)	0 (0)	.49	0 (0.0)	1 (0.6)	.50
Rectal bleeding	2 (1.3)	5 (3.4)	.28	1 (0.6)	2 (1.3)	.62
Cystitis	8 (5.3)	9 (6)	.78	2 (1.3)	2 (1.3)	1.0
Urinary frequency	3 (1.9)	6 (4.0)	.33	1 (0.6)	0 (0)	1.0
Urinary incontinence	1 (0.6)	3 (2.0)	.37	0 (0)	1 (0.6)	.50
Bladder spasms	0 (0.0)	2 (1.3)	.25	0 (0)	0 (0)	NA
Urinary fistula	0 (0.0)	0 (0.0)	NA	0 (0)	0 (0)	NA
Induration or fibrosis	0 (0.0)	5 (3.4)	.03	0 (0)	1 (0.6)	.50
Lymphedema	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Vaginal stenosis	2 (1.3)	8 (5.3)	.06	0 (0)	0 (0)	NA
Fatigue	7 (4.6)	20 (13.4)	.008	0 (0)	1 (0.6)	.50
Constitutional symptoms	3 (1.9)	11 (7.4)	.03	0 (0)	2 (1.3)	.24
Any GI toxicity	29 (19.2)	54 (36.2)	.004	5 (3.3)	20 (13.4)	.002
Any GU toxicity	9 (6)	15 (10.1)	.42	2 (1.3)	3 (2)	.68
Any GI toxicity or GU toxicity	34 (22.5)	59 (39.6)	.001	7 (4.6)	22 (14.7)	.003
Any late toxicity	37 (24.5)	61 (40.9)	.002	7 (4.6)	22 (14.7)	.003

Adverse Event	Grade ≥ 2 Toxicity					Grade ≥ 3 Toxicity				
	IG-IMRT (n = 151)		3D-CRT (n = 149)		P	IG-IMRT (n = 151)		3D-CRT (n = 149)		P
	No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Diarrhea	6	(3.9)	11	(7.4)	.20	2	(1.3)	4	(2.6)	.44
Anorexia	1	(0.6)	10	(6.7)	.005	0	(0)	1	(0.6)	.50
Nausea	1	(0.6)	3	(2.0)	.37	0	(0)	0	(0)	NA
Vomiting	2	(1.3)	7	(4.7)	.10	0	(0)	0	(0)	NA
Abdominal bloating	20	(13.2)	39	(26.2)	.006	2	(1.3)	1	(0.6)	1.0
Abdominal pain	16	(10.5)	22	(14.8)	.27	0	(0)	4	(2.6)	.06
Malabsorption	2	(1.3)	2	(1.3)	1.0	0	(0)	0	(0)	NA
Bowel perforation	1	(0.6)	2	(1.3)	.62	1	(0.6)	2	(1.3)	.62
Bowel obstruction	1	(0.6)	8	(5.3)	.01	1	(0.6)	8	(5.3)	.02
GI stricture	0	(0)	0	(0)	.49	0	(0.0)	1	(0.6)	.50
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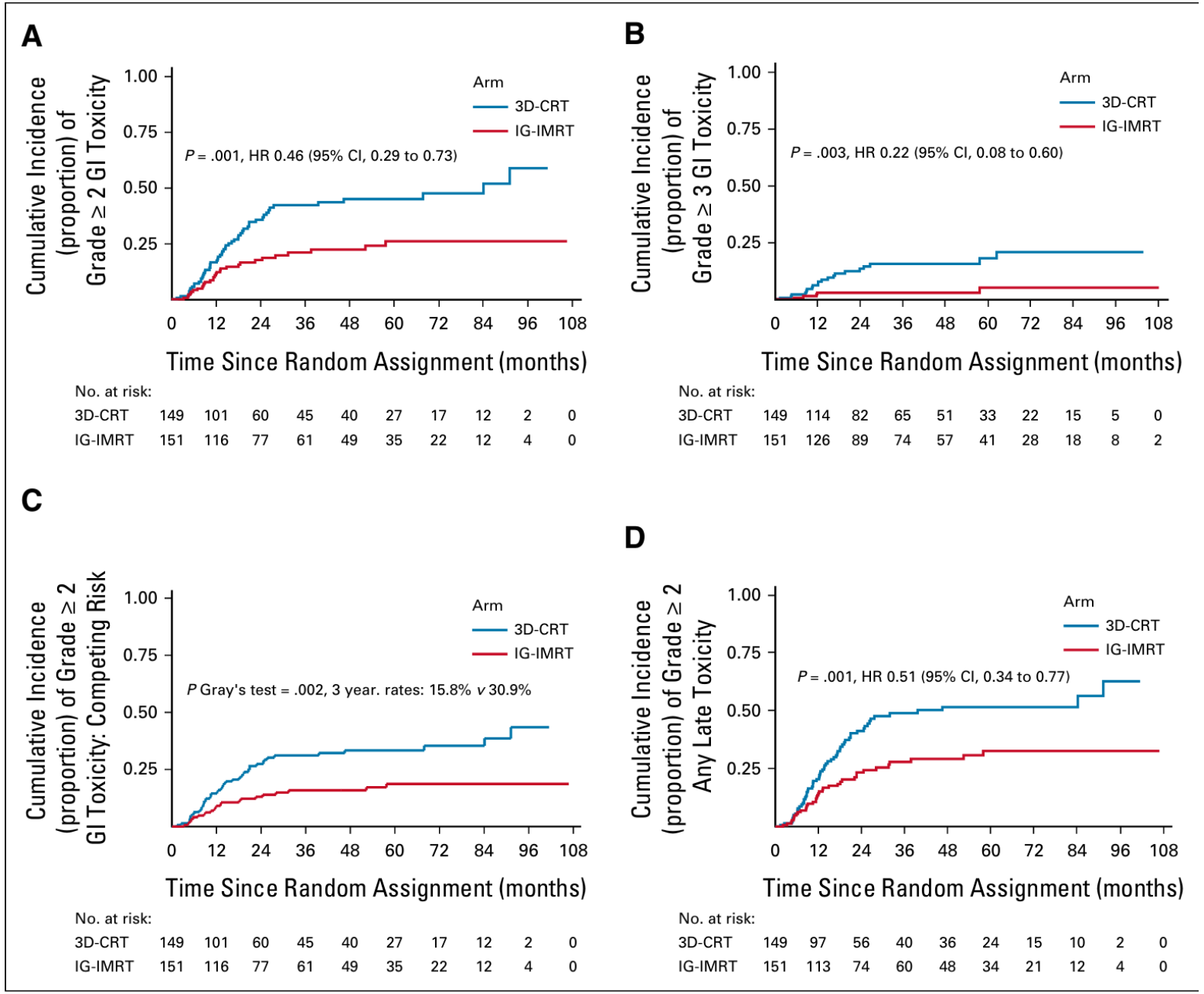
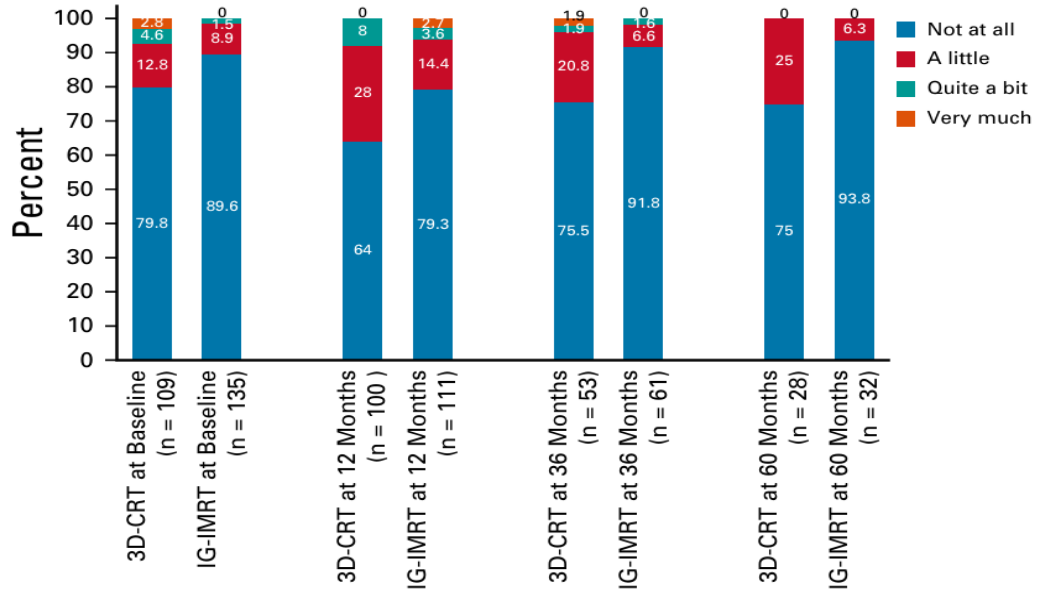
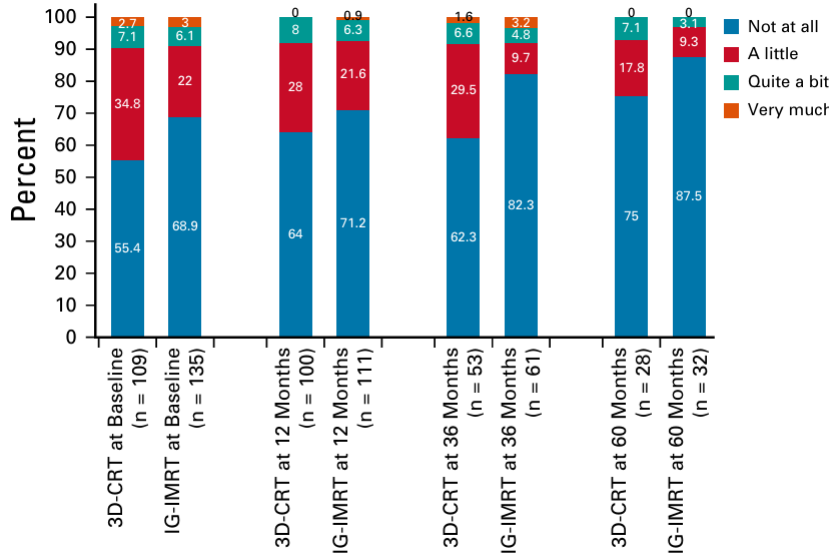
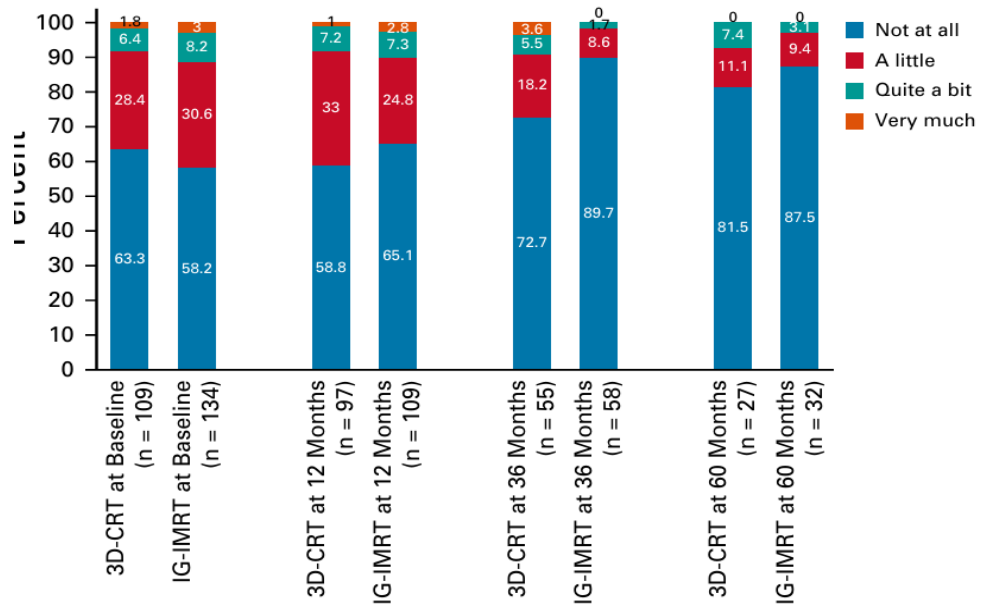
Urinary incontinence	1	(0.6)	3	(2.0)	.37	0	(0)	1	(0.6)	.50
Bladder spasms	0	(0.0)	2	(1.3)	.25	0	(0)	0	(0)	NA
Urinary fistula	0	(0.0)	0	(0.0)	NA	0	(0)	0	(0)	NA
Induration or fibrosis	0	(0.0)	5	(3.4)	.03	0	(0)	1	(0.6)	.50
Lymphedema	2	(1.3)	2	(1.3)	1.0	0	(0)	0	(0)	NA
Vaginal stenosis	2	(1.3)	8	(5.3)	.06	0	(0)	0	(0)	NA
Fatigue	7	(4.6)	20	(13.4)	.008	0	(0)	1	(0.6)	.50
Constitutional symptoms	3	(1.9)	11	(7.4)	.03	0	(0)	2	(1.3)	.24
Any GI toxicity	29	(19.2)	54	(36.2)	.004	5	(3.3)	20	(13.4)	.002
Any GU toxicity	9	(6)	15	(10.1)	.42	2	(1.3)	3	(2)	.68
Any GI toxicity or GU toxicity	34	(22.5)	59	(39.6)	.001	7	(4.6)	22	(14.7)	.003
Any late toxicity	37	(24.5)	61	(40.9)	.002	7	(4.6)	22	(14.7)	.003

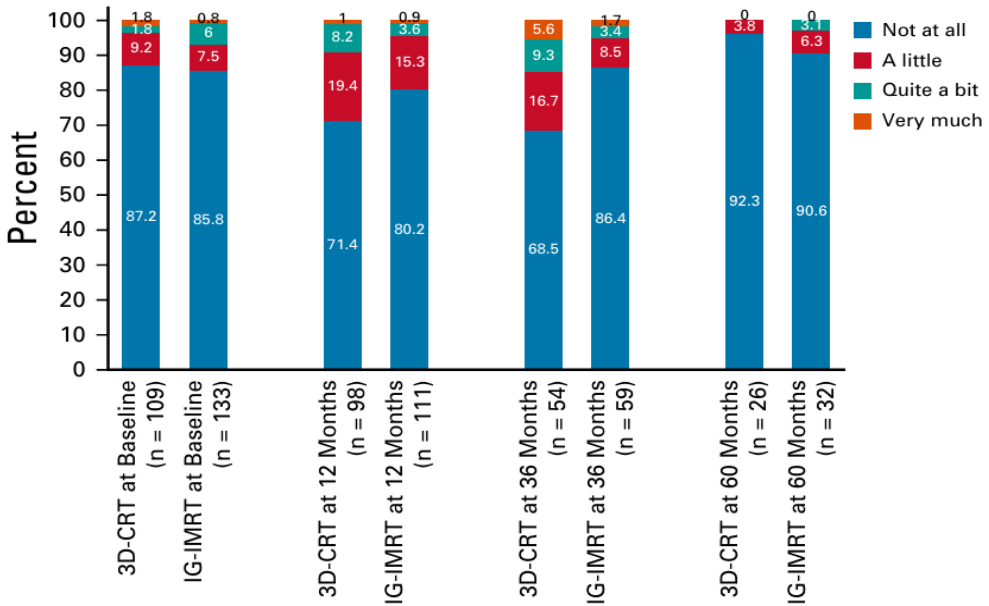

A
Cumulative Incidence (proportion) of Grade ≥ 2 GI Toxicity
1.00
0.75
0.50
0.25
Arm
3D-CRT
IG-IMRT
P = .001, HR 0.46 (95% CI, 0.29 to 0.73)
0 12 24 36 48 60 72 84 96 108
Time Since Random Assignment (months)
No. at risk:
3D-CRT 149 101 60 45 40 27 17 12 2 0
IG-IMRT 151 116 77 61 49 35 22 12 4 0
B
Cumulative Incidence (proportion) of Grade ≥ 3 GI Toxicity
1.00
0.75
0.50
0.25
Arm
3D-CRT
IG-IMRT
P = .003, HR 0.22 (95% CI, 0.08 to 0.60)
0 12 24 36 48 60 72 84 96 108
Time Since Random Assignment (months)
No. at risk:
3D-CRT 149 114 82 65 51 33 22 15 5 0
IG-IMRT 151 126 89 74 57 41 28 18 8 2
C
Cumulative Incidence (proportion) of Grade ≥ 2 GI Toxicity: Competing Risk
1.00
0.75
0.50
0.25
Arm
3D-CRT
IG-IMRT
P Gray's test = .002, 3 year. rates: 15.8% v 30.9%
0 12 24 36 48 60 72 84 96 108
Time Since Random Assignment (months)
No. at risk:
3D-CRT 149 101 60 45 40 27 17 12 2 0
IG-IMRT 151 116 77 61 49 35 22 12 4 0
D
Cumulative Incidence (proportion) of Grade ≥ 2 Any Late Toxicity
1.00
0.75
0.50
0.25
Arm
3D-CRT
IG-IMRT
P = .001, HR 0.51 (95% CI, 0.34 to 0.77)
0 12 24 36 48 60 72 84 96 108
Time Since Random Assignment (months)
No. at risk:
3D-CRT 149 97 56 40 36 24 15 10 2 0
IG-IMRT 151 113 74 60 48 34 21 12 4 0

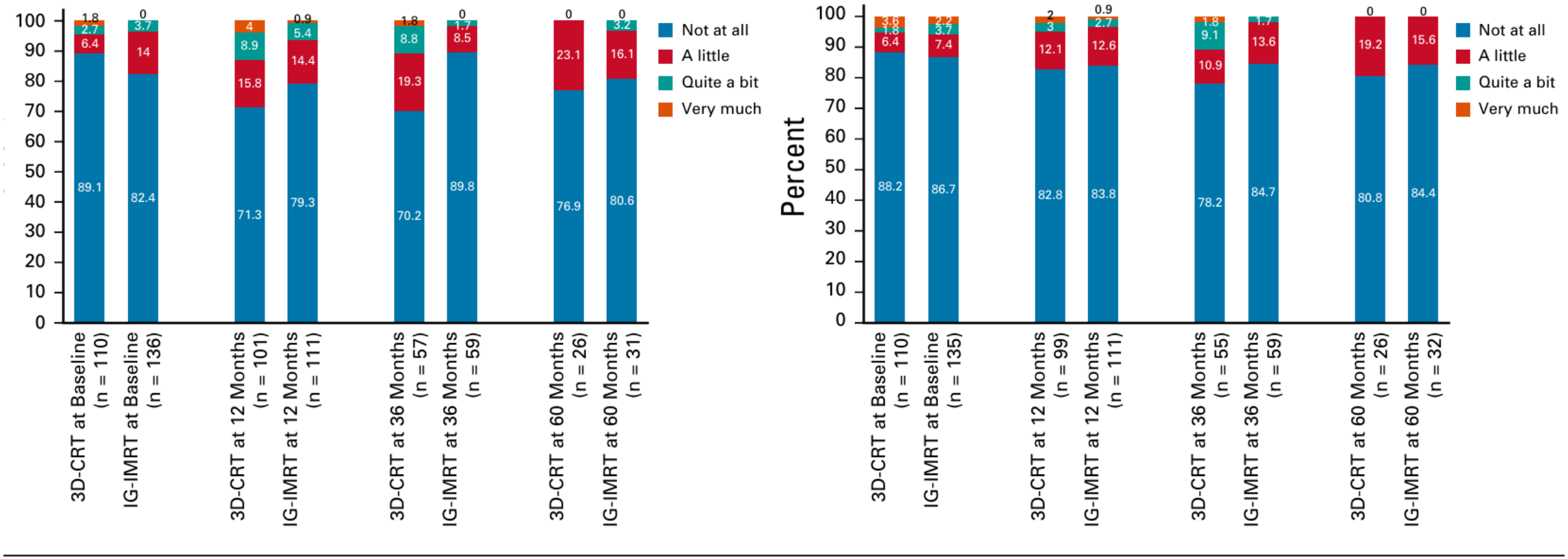
QOL Outcomes


Percent
Not at all
A little
Quite a bit
Very much
3D-CRT at Baseline (n = 109)
IG-IMRT at Baseline (n = 135)
3D-CRT at 12 Months (n = 100)
IG-IMRT at 12 Months (n = 111)
3D-CRT at 36 Months (n = 53)
IG-IMRT at 36 Months (n = 61)
3D-CRT at 60 Months (n = 28)
IG-IMRT at 60 Months (n = 32)

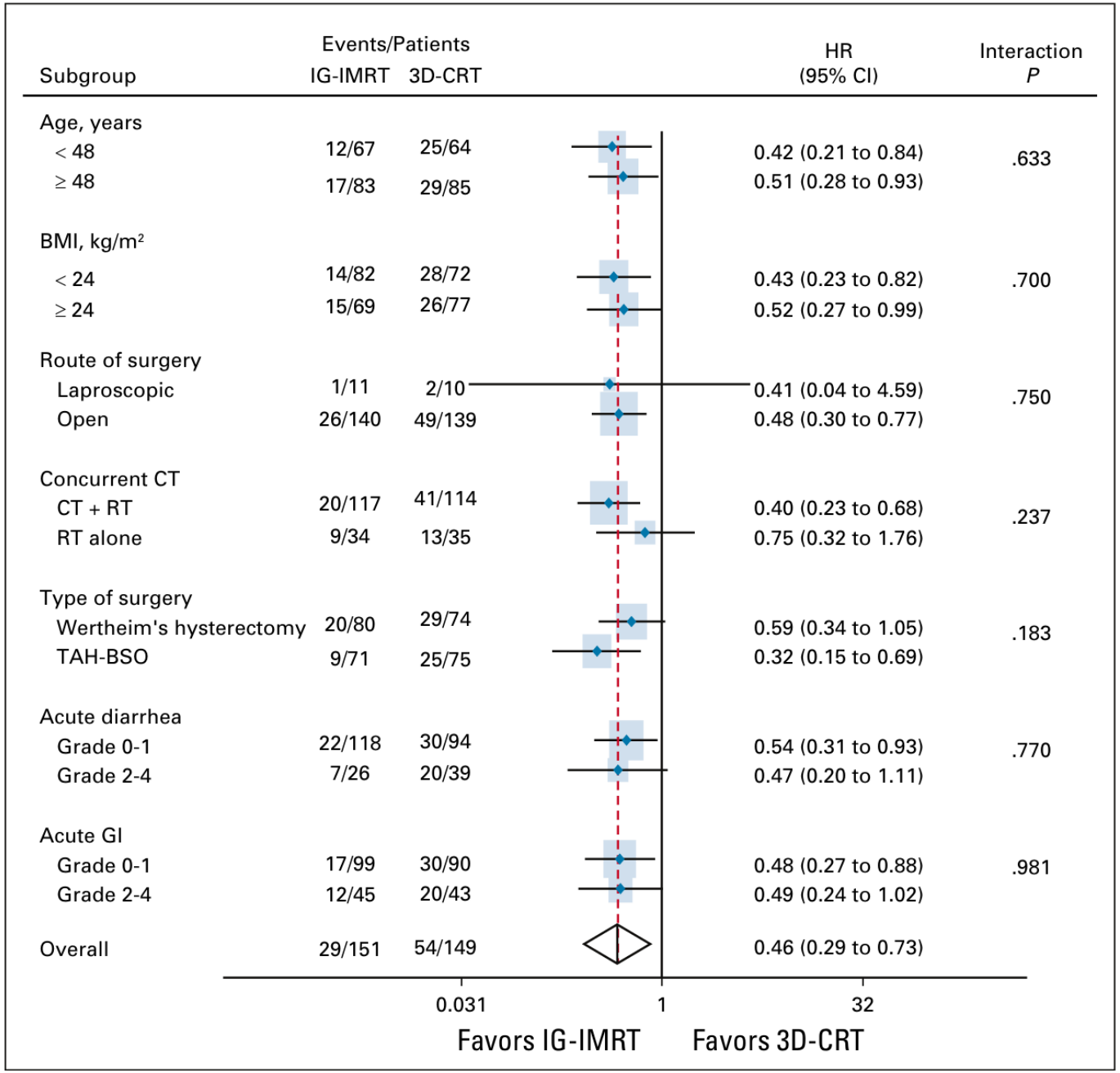

Percent
Not at all
A little
Quite a bit
Very much
3D-CRT at Baseline (n = 109)
IG-IMRT at Baseline (n = 135)
3D-CRT at 12 Months (n = 100)
IG-IMRT at 12 Months (n = 111)
3D-CRT at 36 Months (n = 53)
IG-IMRT at 36 Months (n = 61)
3D-CRT at 60 Months (n = 28)
IG-IMRT at 60 Months (n = 32)


Not at all
A little
Quite a bit
Very much
3D-CRT at Baseline (n = 109)
IG-IMRT at Baseline (n = 134)
3D-CRT at 12 Months (n = 97)
IG-IMRT at 12 Months (n = 109)
3D-CRT at 36 Months (n = 55)
IG-IMRT at 36 Months (n = 58)
3D-CRT at 60 Months (n = 27)
IG-IMRT at 60 Months (n = 32)

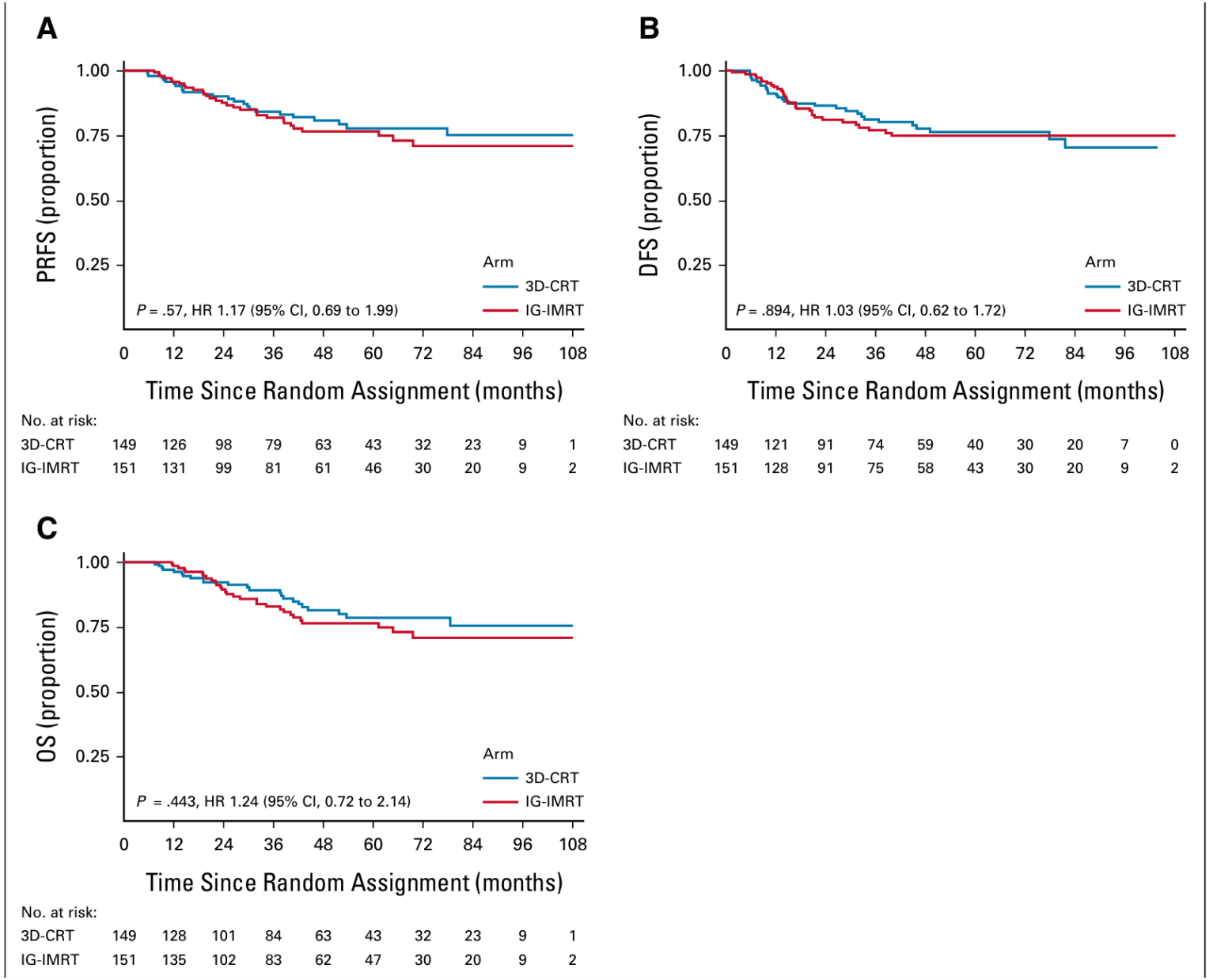

Percent
Not at all
A little
Quite a bit
Very much
3D-CRT at Baseline (n = 109)
IG-IMRT at Baseline (n = 133)
3D-CRT at 12 Months (n = 98)
IG-IMRT at 12 Months (n = 111)
3D-CRT at 36 Months (n = 54)
IG-IMRT at 36 Months (n = 59)
3D-CRT at 60 Months (n = 26)
IG-IMRT at 60 Months (n = 32)


Percent
100
90
80
70
60
50
40
30
20
10
0
Not at all
A little
Quite a bit
Very much
3D-CRT at Baseline (n = 110)
IG-IMRT at Baseline (n = 136)
3D-CRT at 12 Months (n = 101)
IG-IMRT at 12 Months (n = 111)
3D-CRT at 36 Months (n = 57)
IG-IMRT at 36 Months (n = 59)
3D-CRT at 60 Months (n = 26)
IG-IMRT at 60 Months (n = 31)
89.1
6.4
2.7
1.8
82.4
14
3.7
0
71.3
15.8
8.9
4
79.3
14.4
5.4
0.9
70.2
19.3
8.8
1.8
89.8
8.5
1.7
0
76.9
23.1
0
80.6
16.1
3.2
0
3D-CRT at Baseline (n = 110)
IG-IMRT at Baseline (n = 135)
3D-CRT at 12 Months (n = 99)
IG-IMRT at 12 Months (n = 111)
3D-CRT at 36 Months (n = 55)
IG-IMRT at 36 Months (n = 59)
3D-CRT at 60 Months (n = 26)
IG-IMRT at 60 Months (n = 32)
88.2
6.4
1.8
3.6
86.7
7.4
3.7
2.2
82.8
12.1
3
2
83.8
12.6
2.7
0.9
78.2
10.9
9.1
1.8
84.7
13.6
1.7
80.8
19.2
0
84.4
15.6
0

Outcome Impact On Various Factors



Survival Outcomes



Late Toxicity Outcome

TABLE A7. 3- and 5-Year Disease and Toxicity Outcomes for Intention-to-Treat Population in the IG-IMRT and 3D-CRT Arms

	3-Year Rates (%)		5-Year Rates (%)	
Outcome	**IG-IMRT**	**3D-CRT**	**IG-IMRT**	**3D-CRT**
Grade ≥ 2 late GI toxicity	21.1 (14.7 to 29.7)	42.4 (33.7 to 52.3)	26 (18.3 to 36.2)	45 (36.1 to 55.1)
Grade ≥ 3 late GI toxicity	2.9 (1.1 to 7.6)	15.5 (9.9 to 23.6)	5.1 (1.8 to 13.4)	17.9 (11.3 to 27.6)
Grade ≥ 2 late GI and GU toxicities	25.5 (18.5 to 34.6)	46.7 (37.8 to 56.5)	30.1 (22 to 40.2)	49.4 (40.2 to 59.4)
Grade ≥ 3 late GI and GU toxicities	4.0 (1.6 to 9.4)	15.5 (9.9 to 23.6)	6.1 (2.5 to 14.4)	20.1 (13.1 to 30.1)
Grade ≥ 2 any late toxicity	28.1 (20.7 to 37.4)	48.9 (40 to 58.7)	32.7 (24.4 to 43)	51.5 (42.3 to 61.4)
Grade ≥ 3 any late toxicity	4.0 (1.6 to 9.4)	15.5 (9.9 to 23.6)	6.1 (2.5 to 14.4)	20.1 (13.1 to 30.1)
PRFS	81.8 (73.5 to 87.7)	84 (76 to 89.5)	76.5 (67.4 to 83.3)	77.6 (68.1 to 84.7)
DFS	76.9 (68.4 to 83.4)	81.2 (72.9 to 87.2)	74.8 (65.9 to 81.7)	76.2 (66.9 to 88.3)
OS	82.9 (74.6 to 88.6)	89.2 (82.1 to 93.6)	76.5 (67.3 to 83.4)	78.5 (68.8 to 85.5)

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; DFS, disease-free survival; GU, genitourinary; IG-IMRT, image-guided intensity-modulated radiotherapy; OS, overall survival; PRFS, pelvic relapse-free survival.

Points to be Cautious On

- Resource-intensive.
- Requires technical expertise.
- Limited access in LMICs.
  - Diagnostic
  - Therapeutic
  - Manpower

Limitations of the Study

1. Unblinded Design:

- Open-label trial with potential for ascertainment bias
- Both investigators and patients knew treatment allocation
- Could influence toxicity reporting

2. Long Recruitment Period:

- 8-year recruitment period (2011-2019)
- Potential for evolving standards of care
- Technology improvements during study period

3. Bowel vs Bone Marrow Sparing:

- Study focused on bowel sparing constraints
- Did not prospectively study bone marrow sparing
- Simultaneous bowel and marrow sparing techniques need development

4. Dose-Volume Relationships:

- Clear dose-volume relationship for late GI toxicity not established
- Published constraints used may not be optimal
- Multivariable analysis did not confirm dose-volume correlation

Beyond PARCER

- Development of a new toxicity assessment scale
- MOSES: Time-weighted toxicity scoring.
- Better correlation with QOL.
- Confirms IG-IMRT advantage in long-term toxicity burden
- Understanding the economic impact of the upfront IGIMRT and long term toxicity management

MOSES (Time-Weighted Toxicity Assessment)

Limitations of Classical CTCAE Reporting:

- Relies on **worst grade** in organ system
- **Cumulative effect** of toxicity evolution not considered
- **Multiplicity of events** within organ system ignored
- **Modest to low correlation** between physician and patient reported outcomes

MOSES Hypothesis

"Time-weighted CTCAE scores provide a better description of symptom burden and may better correlate with quality of life."

Steps in MOSES Calculation:

- **Symptom Selection:** 6 most common symptoms with corresponding QOL items
- **Score Calculation:** MOSES = ΣP × S (Proportion × Severity)
- **ROC Analysis:** Against substantial symptom on QOL (50% threshold)
- **Cut-off Determination:** 0.20 (range 0.14-0.22) for individual symptoms
- **Composite Score:** C-MOSES with cut-off 0.70 for multiple symptoms

- **Result:** 10-fold difference in MOSES scores despite both patients having maximum grade 3 toxicity

QOL Symptom	CTCAE Method			MOSES Method			
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy	AUC
Diarrhea	50%	73%	69%	43%	94%	85%	0.67
Anorexia	25%	63%	51%	9%	85%	61%	0.45
Abdominal Pain	88%	24%	57%	58%	85%	71%	0.76
Urinary Incontinence	65%	59%	61%	30%	91%	72%	0.65
Fatigue	90%	24%	76%	63%	70%	64%	0.71

MOSES Score Example

Patient A (24 months total follow-up):

- Grade 3 diarrhea for 15/24 months
- Grade 2 diarrhea for 3/24 months
- Grade 0 for 3/24 months
- **MOSES Score:** (15/24 × 3) + (3/24 × 2) + (3/24 × 0) = 1.88 + 0.25 + 0 = **2.13**

Patient B (84 months total follow-up):

- Grade 3 diarrhea for 4.5/84 months
- Grade 1 diarrhea for 6/84 months
- Grade 0 for 73.5/84 months
- **MOSES Score:** (4.5/84 × 3) + (6/84 × 1) + (73.5/84 × 0) = 0.16 + 0.07 + 0 = **0.23**

Healthcare Cost Considerations:

- **Reduced Long-term Complications:**
  - 50% reduction in Grade ≥2 any late toxicity
  - Fewer interventions for bowel obstruction (0.7% vs 7.3%)
  - Reduced management of chronic GI symptoms
- **Quality-Adjusted Life Years (QALYs):**
  - Improved functional scores in IG-IMRT arm
  - Better role functioning and emotional functioning
  - Reduced symptom burden scores
- **Technology Investment Analysis:**
  - Higher upfront costs for IG-IMRT implementation
  - Long-term savings from reduced complication management
  - Improved patient productivity and quality of life

- **Conclusion**
- IG-IMRT reduces late GI toxicity without compromising survival.
- Should be new standard for post-op adjuvant RT in cervical cancer where resources allow.

Summary and Conclusions

- **Key Findings from PARCER Trial**
- **Efficacy:** IG-IMRT significantly reduces late GI toxicity compared to 3D-CRT
  - 21.1% vs 42.4% Grade ≥2 late GI toxicity (HR 0.46, $p<0.001$)
  - 50% reduction in any late toxicity burden
- **Safety:** Equivalent oncologic outcomes maintained
  - No difference in pelvic relapse-free survival, disease-free survival, or overall survival
  - Toxicity reduction achieved without compromising cure rates
- **Quality of Life:** Meaningful improvements in patient-reported outcomes
  - Better functional scores and lower symptom scores
  - Sustained benefits at long-term follow-up

Clinical Practice Impact

- IG-IMRT should represent the new standard of care for postoperative pelvic RT in cervical cancer patients
- **Implementation Considerations:**
- Requires appropriate technology and expertise
- Quality assurance programs essential
- Cost-effectiveness favorable over long term
- Patient selection remains important

- **Advancement in Toxicity Assessment:**
- Time-weighted scoring provides more accurate symptom burden assessment
- Better correlation with patient-reported quality of life
- Complementary to traditional CTCAE reporting
- Potential for broader application across cancer types

Thank you