Title: Efficacy and safety of IMRT after surgery in patients with endometrial cancer: RTOG 0418 phase II study

Short/Running Title: RTOG 0418 Endometrial arm

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Conflict of Interest Statement (If available)

(Insert conflict-of-interest statement here)

Funding Statement

"This project was supported by RTOG U10 CA21661, CCOP U10 CA37422, and ATC U24 CA 81647 grants from the National Cancer Institute (NCI)."

Data Availability Statement

All data will be made available per the NCTN Data Archive rules. The link for the archive is:

https://nctn-data-archive.nci.nih.gov/.

Presentation Information: (if available)

Keywords: Endometrial carcinoma, radiotherapy, Intensity modulated radiation therapy (IMRT)

Acknowledgements (if available)

www.ClinicalTrials.gov

RTOG 0418 NCT00331760

Citation

Jhingran A, Witner K, Portelance L, Miller BE, Salehpour MR, Gaur R, Souhami L, Small W, Gaffney D. Efficacy and Safety of IMRT After Surgery in Patients with Endometrial Cancer: RTOG 0418 Phase II Study. NRG Oncology Unpublished Research Series. 2016 May 2

NRG Oncology Unpublished Research Series. Uploaded 2023 Feb 20

https://www.nrgoncology.org/Portals/0/Publications/Unpublished%20Research%20Series/Unpublished%20Manuscript%20(Jhingran)%20eq.pdf?ver=lgpP0NXamlp9HuHPrSJHPA%3d%3d

ABSTRACT

Purpose: To estimate the rates of local-regional recurrence, distant recurrence, disease-free survival (DFS), and overall survival (OS) in patients treated with intensity-modulated radiation therapy (IMRT) for endometrial cancer in a multi-institutional setting and to assess adverse events (AEs) from this treatment.

Methods: From March 2006 through June 2007, 58 patients with stage FIGO stage I-IIIC adenocarcinoma of the endometrium from 25 institutions were enrolled in a phase II study that evaluated the use of IMRT for treatment of the pelvis after surgery.

OS and DFS were estimated univariately with the Kaplan-Meier method. Adverse events (AEs) were scored using the Common Terminology Criteria for Adverse Events version 3.0.

Results: Forty-three patients were eligible for analysis. With a median follow-up of 5.03 years, the 4-year estimates of OS and DFS were 90% and 88%, respectively. There were 4 deaths; 2 patients died of disease, 1 patient died of an intracranial hemorrhage, and 1 patient died of an unknown cause. Five patients had recurrence. The first site of recurrence was regional/para-aortic in 1 patient, local (suburethral) in 1, para-aortic in 1, and distant in 2.

Treatment-related gastrointestinal (GI) AEs were the most common AEs $\leq$ 90 days after the start of IMRT.; 18 patients (42%) had grade 1, 11 (26%) had grade 2, and 3 (7%) had grade 3. Eleven patients (26%) had grade 2 or 3 non-hematologic AEs > 90 days after the start of IMRT reported

as treatment-related. Again, GI AEs were the most common; 11 patients (26%) had grade 1, 3 (7%) had grade 2, and 1 (2%) had grade 3.

Conclusion: Pelvic IMRT after surgery for patients with endometrial carcinoma delivered in a multi-institutional trial with centralized quality assurance is a safe and effective treatment.

Introduction

Randomized trials have demonstrated that whole-pelvic radiation therapy (WPRT) after hysterectomy for selected patients with endometrial carcinoma reduces the rate of pelvic disease recurrence (1-2). The highly conformal technique of intensity-modulated radiation therapy (IMRT) has been shown to improve dose distribution to the postoperative bed and other areas at risk for disease recurrence while sparing adjacent normal tissues in patients with endometrial and cervical cancers. Early studies of IMRT for gynecologic malignancies showed that, compared to WPRT, IMRT reduced the volume of small bowel receiving prescription dose by 30-60% (3, 4). Retrospective studies of IMRT for gynecologic malignancies showed that this reduction in dose resulted in a reduction in both acute (5) and chronic gastrointestinal (6) side effects compared to historic controls.

RTOG 0418 was a Phase 2 trial designed with the primary objectives to evaluate the feasibility and transportability of delivering post-operative IMRT in a multicenter setting for patients with endometrial cancer under a centralized quality assurance review and to assess the rate of acute toxicity. Initial results of the study **(7)** confirmed that IMRT could be apppropiately delivered across multiple institutions with strict adherence to protocol guidelines with a potential reduction in the rate of grade ≥ 2 bowel toxicity.

The secondary endpoints of this trial were to estimate the rates of local-regional recurrence (LRF); distant recurrence (DF); disease-free survival (DFS); overall survival (OS); and to assess adverse events (AEs). These findings will be addressed in this report.

Patients and Methods

Eligibility criteria were as follows: hysterectomy and bilateral salpingo-oophorectomy for endometrioid carcinoma of the endometrium within 8 weeks prior to study entry and indications for postoperative WPRT; full surgical staging (complete lymph node dissection) and International Federation of Gynecology and Obstetrics (FIGO) (1988) (8) stage IB, grade 3; stage IC, grade 1-3; or stage IIA, IIB, or IIIC (positive pelvic nodes only) disease or no surgical staging (no lymph node dissection); and FIGO stage IB, grade 2, disease; Zubrod performance status of 0-2; and no previous pelvic radiation therapy. Concurrent chemotherapy was not allowed. Patients with papillary serous or clear cell carcinoma were excluded from the study. The protocol was reviewed and approved by Institutional Review Boards (IRBs) in all institutions participating and informed consent was obtained from all patients.

Simulation and contouring

The simulation, contouring and treatment details have been reported previously (7). Briefly, patients were properly immobilized in a supine position. Two separate treatment-planning CT scans (full and empty bladder) were required. Patients were to be treated with a full bladder. No specific recommendation was given about rectal filling.

The full-bladder and empty-bladder CT scans were fused, and a vaginal-parametrial internal target volume (vaginal ITV) was defined that included the positions of the vagina and paravaginal tissues on both scans. In addition, a nodal CTV was defined that included the regional nodes (common iliac, internal and external iliac, and obturator lymph nodes) and paravaginal tissues. The sacral lymph nodes were included only if there was cervical stromal involvement. An online atlas detailing the nodal CTV and the vaginal CTV was posted at the RTOG web site to help standardize delineation of these two target volumes (http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx).

Critical normal structures, including the entire bladder, entire rectum (from anus to sigmoid junction), bowel (entire peritoneal cavity), and femoral heads, were contoured on every slice of the full-bladder scan. The peritoneal space was contoured through the pelvis and superiorly until 2 cm above the uppermost nodal planning target volume (PTV).

The PTVs were 7 mm around the vaginal and nodal CTVs. The definition of volumes was in accordance with the 1993 International Commission on Radiation Units and Measurements Report #50 (8).

Planning

For all patients, treatment planning was done using the full-bladder scan. The prescribed dose was 50.4 Gy to the vaginal and nodal PTVs in 28 fractions. The prescription dose was defined as the isodose that encompassed at least 97% of the vaginal and nodal PTVs. The protocol strongly encouraged the following dose constraints for critical normal structures: small bowel, < 30% of the volume to receive ≥ 40 Gy; rectum, < 60% of the volume to receive ≥ 45 Gy; bladder, < 35% of the volume to receive ≥ 45 Gy; and femoral heads, ≤15% of the volume to receive ≥ 30 Gy. More details can be found in the primary endpoint paper (7)

Quality assurance

Each participating institution had to be preapproved to deliver IMRT by the Radiological Physics Center (RPC), the Image-Guided Therapy Center (ITC) at Washington University, and the RTOG radiation therapy quality assurance group.

All institutions were required to submit their first case to the ITC for a rapid review, and the treatment plan and contours had to be approved by one of the study chairs before the patient could be treated on protocol. If the study chair did not approve the plan or contours, it was sent

back to the institution for correction and resubmission for approval. Study chairs did not review cases from their own institutions, and the number of cases entered by the study chairs' institutions was limited. At the end of the study, both study chairs working together reviewed all cases.

For the vaginal and nodal PTVs, the dose was classified as per protocol if at least 97% of the PTV received 50.4 Gy and < 20% of the PTV received >110% of 50.4 Gy; as an acceptable variation if 90% of the PTV received 95% to 98% of 50.4 Gy and < 5% of the PTV received > 115% of 50.4 Gy; and as an unacceptable variation if 90% of the PTV received <95% of 50.4 or > 5% of the PTV received > 115% of 50.4 Gy.

Statistical methods

The protocol-defined secondary efficacy endpoints were overall survival (OS), disease-free survival (DFS), local-regional failure (LRF), para-aortic nodal failure (PAF), and distant failure (DF). These endpoints form the basis of this report. The trial was designed to report the results of these endpoints and was not powered to statistically compare these endpoints to historical controls.

For the purpose of calculating OS, failure was defined as death due to any cause. For the purpose of calculating DFS, the first appearance of disease was defined as LRF, PAF, DF, or death. LRF was defined as any failure in the treatment field, which will be the pelvis only. PAF was defined as para-aortic nodal failure. DF defined as the appearance of distant metastases (para-aortic nodal disease is not considered a distant failure). All efficacy endpoints were measured from study entry to date of first failure or last follow-up for censored patients.

OS and DFS were estimated univariately with the Kaplan-Meier method (9) and LRF, PAF, and DF rates were estimated by the cumulative incidence method (10).

Another secondary endpoint was the evaluation of adverse events (AEs) as graded by the Common Terminology Criteria for AEs version 3.0. Acute AEs were defined as occurring within 90 days of treatment start and late AEs were defined as > 90 days from treatment start.

RESULTS

Fifty-eight patients, from 25 institutions, were enrolled in the study from March 2006 through June 2007. A total of 15 patients were excluded from all analyses. Of these, 12 were ineligible due to abnormal creatinine clearance (4 patients, 27%), registration time from surgery being > 8 weeks (3 patients, 20%), ineligible stage (1 patient, 7%), and 4 patients did not follow protocol specifications for labs and/or scans (27%). Three patients (20%) were excluded because they did not receive any protocol treatment, leaving 43 patients for analysis. The median age of the 43 evaluable patients was 57 years (min-max, 36–73 years). The median follow-up time for all patients was 5.03 years (min-max, 0.98-6.29). For surviving patients the median follow-up was 5.07 years (min-max, 0.98-6.29).

Patient characteristics are shown in Table 1. All the staging in this report is reported using 1988 FIGO staging for endometrium. (8). Radiation treatment delivery was previously reported (7). There were no cases with a deviation unacceptable score for the PTV Vagina dose score and only one patient with a deviation unacceptable score for the PTV Nodal dose score.

Treatment results

The 3-year OS, DFS, and LRF rates were 92.8%, 90.6%, and 4.7%, respectively; the corresponding 4-year rates were 90.3%, 88.1%, and 4.7% (table 2, and figures 1&2). Two

patients failed in the para-aortic nodes (5%) and 4 patients had distant metastatic disease (9%). A total of 5 patients (12%) had any kind of disease recurrence and 4 of these failures occurred within the 1st two years of study registration. The sites of 1st failure are shown in Table 3. The patient with a regional failure had an acceptable contour by review of the primary investigators.

Only 4 patients had died at the time of this analysis and of these 4 patients 2 died of cancer (50%).

Side effects

For acute AEs, 32 patients (74%) had some type of gastrointestinal (GI) toxicity definitely, probably or possibly related to treatment with 3 (7%) patients having grade 3 GI AEs. All three patients had grade 3 diarrhea, and there were no grade 4 or higher GI AEs. Eighteen patients (42%) had grade 1 GI AEs, majority of these being diarrhea and nausea and 11 (26%) had grade 2 with majority being diarrhea and enteritis. Because, no chemotherapy was allowed for the protocol, bone marrow toxicity was low with 16 (37%) patients having grade 1-3 hematologic AEs, of which 7 (16%) were grade 3 (all lymphopenia). Acute genitourinary (GU) AEs were low, with only 11 (26%) patients having grade 1-2 AEs.

GI AEs were the most common late AEs with 15 (35%) patients having grade 1-3 AEs definitely, probably or possibly related to treatment. The one patient with grade 3 GI AEs (2%) had a colonic obstruction and the three grade 2 toxicities (7%) included anal stenosis, colitis, and diarrhea. Late GU AEs were low with only 10 patients (23%) having grade 1-3 AEs. Grade 2 AEs included pollakiuria, urinary incontinence, and vaginal stricture; and the one grade 3 AEs was urinary incontinence. Late grade 1-2 sexual dysfunction including vaginal atresia, mucositis, and dryness was reported for 13 (30%) patients.

DISCUSSION

The results of the first multi-institutional study of IMRT in the treatment of endometrial cancer were recently published (7). The study protocol included strict criteria for target definition and delineation, dose prescription, and dose constraints for the targets and critical structures; the protocol also included centralized QA review of the physical and dosimetric aspects of IMRT delivery. These findings indicate that IMRT for endometrial cancer is feasible in a multi-institutional setting when there is a carefully designed protocol guidelines and centralized QA. They also showed that IMRT was associated with a nonsignificant 12% reduction in the rate of grade ≥ 2 short-term bowel AEs when compared to historic controls.

In this paper, the secondary endpoints of OS, DFS and LRF as well as late toxicity are reported. The 4-year rates for OS, DFS and LRF were 90.3%, 88.1% and 4.7%, respectively. These results compare favorable to other reports from single institutional retrospective studies (Table 4). Beriwal et al. (9) reported a 3-year OS and DFS of 90% and 84%, respectively, in 47 patients with endometrial carcinoma (stage I-III) treated with post-operative IMRT. Another study by Shih et al.(10) reported 5-year OS and DFS of 97% and 88%, respectively, in patients with endometrial carcinoma (Stage I-III) treated with IMRT. In the Shih at al. study, 78% of the patients had stage IIIC and they had a 9% relapse rate at 5-years.

The primary aim of IMRT in the post-operative setting is to reduce both acute and late toxicities, especially to the bowel. In this study, 32 patients had acute treatment-related GI toxicities, including 42% with grade 1, 26% with grade 2, and 7% with grade 3. Late treatment-related GI toxicity was seen in 35% of the patients with 1 patient (2%) having a grade 3 and 3 patients (7%) having grade 2 toxicities. Mundt et al.(5) reported 50% chronic GI toxicity in patients treated with conventional treatments, 30% with grade 1, 16% with grade 2, and 3.3%

with grade 3. In this same report, IMRT resulted in 11% overall chronic GI toxicity, 8.3 % grade 1, 2.8% grade 2, and no grade 3 (5). RTOG 0418 reports similar reduction in chronic GI toxicity, as compared to historical controls, with the use of IMRT. Other single institutional retrospective studies have also shown similar results. Shih et al. (10) reported that 45/46 patients had some form of acute GI toxicity, but only 2% grade 3 and 39% grade 2 toxicity. They had 13% late GI toxicity but only one grade 3 toxicity. Beriwal et al. (9) reported a rate of 2% grade 3 late GI toxicity and Shih et al. also reported a 2% grade 3 late GI toxicity. Another retrospective study by Bouchard et al (11) reported 3/15 patients with late grade 2 GI toxicity and no grade 3 toxicity. Both acute and chronic GU toxicity was rare and again compared favorable to other studies (9-11).

RTOG 0418 is the first multi-institutional prospective study evaluating IMRT in the post-operative setting for patients with endometrial carcinoma. The results highlight excellent OS, DFS, LRF and low toxicity rates with the use of IMRT in a multi-institutional trial with centralized QA review.

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Figure 1. Disease-free survival

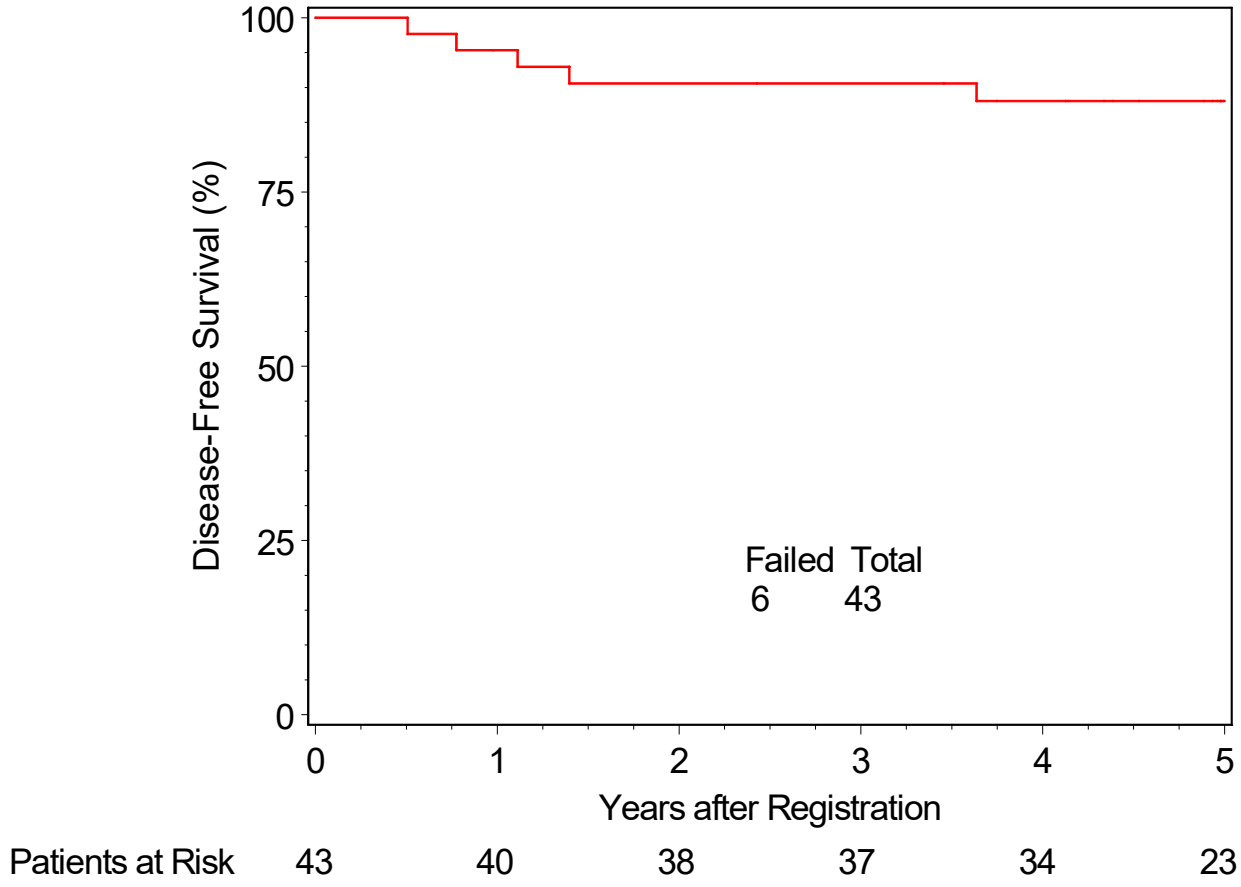
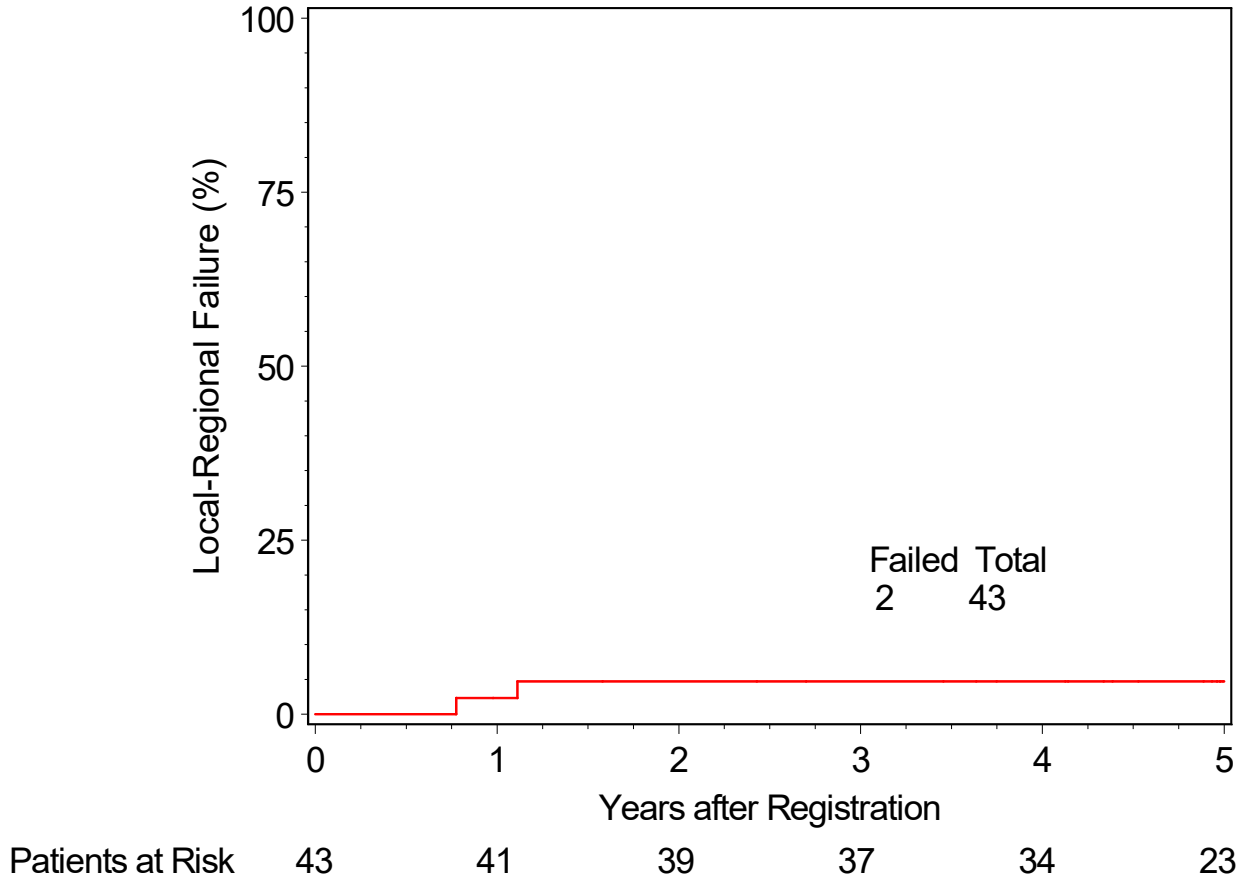


Figure 2. Local-regional failure



Insert Supplemental Materials (If applicable)

Table 1

Patient characteristics.

Characteristic	n	%
Surgical Procedure		
TAH	32	74
Radical hysterectomy	5	12
Laparoscopic assisted vaginal hysterectomy	6	14
Disease stage (FIGO 1988)		
IB Grade 3	1	2
IC Grade 1-3	19	44
IIA	5	12
IIB	14	33
IB Grade 2 (no lymph nodes sample)	1	2
IIIC (+pelvic nodes, neg PA nodes)	3	7
Zubrod		
0	38	88
1	5	12
Age		
Median	57	
Range	36-73	

Table 2

Outcomes at 3 and 4 years

Endpoint	**Number of Events**	**Estimated 3-Year Rate (%) (95% CI)**	**Estimated 4-Year Rate (%) (95% CI)**
Overall survival	4	92.8 (79.3, 97.6)	90.3 (76.1, 96.2)
Disease-Free Survival	6	90.6 (76.8, 96.4)	88.1 (73.6, 94.9)
Local-Regional Failure	2	4.7 (0, 11.2)	4.7 (0, 11.2)
Para-aortic nodes	2	4.8 (0, 11.3)	4.8 (0, 11.3)
Distant (excluding Para-aortic nodes)	4	7.1 (0, 14.9)	7.1 (0, 14.9)

Table 3. Patterns of Failure

Site	Tumor Stage	n	%
Local (sub-urethral) → DF: lung {7 months later}	IC grade1-3	1	2.3
Para-aortic	IIB	1‡	2.3
Regional, para-aortic → DF: brain {1 month later}	IC grade1-3	1*	2.3
DF: paratracheal/lung	IIIC	1*	2.3
DF: lung	IC grade1-3	1	2.3
Death only (intracranial hemorrhage)	IIB	1	2.3
No Failures	--	37	86.0

DF: distant failure

*Patients subsequently died of endometrial cancer

‡Patient subsequently died of an unknown cause

Table 4. Studies using IMRT in patients with endometrial cancer.

	# Patients	Time Interval	OS (%)	DFS (%)	LRF (%)	Acute GI toxicity (≥3) (%)	Late GI Toxicity (≥3) (%)
Shih et. al.	46	5 yrs.	97	88	9	13	2
Beriwal et al.	47	3 yrs.	90	84	0	0	2
Present study	43	4 yrs.	90	88	4.7	7	2