

Role of Palliative Surgery and Whole Pelvic Radiotherapy on Symptom Palliation and Quality of Life in Advanced Rectal Cancer: A Prospective Observational Study

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ABSTRACT

Introduction: Patients with metastatic / advanced inoperable rectal cancer usually complain of symptoms like per rectal bleeding, local pain and irregular bowel habits. The main objective of care in these patients is to improve overall survival (OS) while palliating the symptoms and maintaining the Health Related Quality of Life (HRQoL). This may be achieved by either palliative surgery or radiotherapy along with systemic chemotherapy and we aimed to investigate these two modalities for symptom palliation, HRQoL and OS.

Material and methods: The advanced rectal cancer (AJCC Stage group IV) patients with pelvic symptoms (rectal bleeding, pain or obstructive features) aged 18-75 years with ECOG PS 0-3 were included in this prospective non randomized observational study. Choice of palliative surgery or radiotherapy was done by MDT discussion. Symptoms and HRQoL (using FACT-G) were assessed at baseline, after intervention and every three months thereafter till one year.

Results: Between February 2017 to June 2020, 102 patients of advanced rectal cancer were accrued. Eighty six patients were ultimately evaluated. Change in bowel habit (76%), pain (62%) rectal bleeding (37%) were the most common symptoms. Sixty seven patients received pelvic radiotherapy and nineteen underwent palliative surgery. Overall response rate at 3rd month after completion of treatment was 59%. Symptom control rates and time to symptom progression were comparable. The mean score of HRQoL were higher in the

Radiotherapy arm. There were no grade III-IV toxicity. Median OS was eight and ten months in the surgery and radiotherapy arms, respectively.

Conclusion: Morbid surgical procedure renders no advantage over palliative radiotherapy in metastatic rectal cancer with respect to palliation of pelvic symptoms and maintenance of HRQoL.

Keywords: Rectal cancer, advanced, symptom, palliation, HRQoL.

INTRODUCTION

There is a rising incidence of rectal cancer in India. Approximately 25 % - 30 % rectal cancer patients present with metastatic disease at the time of diagnosis and needs palliative treatment^{1,2}. The annual disease specific death rate for colorectal cancer is approximately 35% and the liver is the most common site of metastasis^{1,2}. Patients with metastatic rectal cancer are at risk for depression, anxiety and impaired quality of life even after treatment³.

The treatment goal of this advanced stage disease is to improve OS without compromising HRQoL. Chemotherapy for metastatic disease is the current recommendation for asymptomatic disease or symptom from the distant metastasis⁴. Metastatic rectal cancer frequently presents with pelvic symptoms includes intestinal obstruction, per rectal bleeding, pain or combination of more than one symptom.

Patients with pelvic symptoms are particularly difficult challenges and can be treated with chemotherapy in conjunction with individualized local palliative treatment - surgical procedure or radiotherapy to relieve their symptoms. The surgical intervention includes extirpative resection, diversion colostomy, endoscopic stent or laser photocoagulation. Palliative hypofractionated pelvic radiotherapy is another modality of treatment used for symptom relief⁵⁻⁷. HRQoL depends upon demographic, socio-economic as well as clinical variable of disease⁸.

The choice of treatment depends upon the patient's symptom, age, comorbidity and extent of disease. Careful multidisciplinary team (MDT) approach including surgical, radiation and medical oncologists is warranted, to ensure the most appropriate treatment strategy for each patient. In addition to the improvement in overall survival, palliation of symptoms and HRQoL are important parameters for assessing the efficacy of treatment in advanced cancer. With this aim, we prospectively evaluated the role of palliative surgery vis a vis radiotherapy in symptom control and maintenance of HRQoL in patients with advanced rectal cancer.

MATERIAL AND METHODS

Between February 2017 to June 2020, we prospectively evaluated 102 patients with metastatic / advanced inoperable rectal cancer (AJCC stage group IV) who had pelvic symptoms at initial presentation in the Department of Radiotherapy in a Tertiary Medical College and Hospital in Eastern India. Patients were considered if they were 18 – 75 years of age, has ECOG PS 0 – 3, no uncontrolled major comorbidities and baseline hemoglobin > 8 gm/dl. The optimum treatment was decided in the MDT setting and patients were not randomized. The patients were treated with either up-front palliative surgery (diversion colostomy/ extirpative resection) or palliative pelvic radiotherapy followed by chemotherapy.

Sixteen patients were excluded from the study (poor ECOG PS or general condition, refusal of treatment, treated elsewhere, lack of informed consent) and the remaining eighty-six patients were evaluated. Informed consent was obtained from all patients and the study was approved by the Institutional Ethical Committee.

Table I: Baseline characteristic of all eligible patients according to assigned treatment

Characteristic	Group A (Palliative Surgery)	Group B (Palliative Pelvic RT)
Number of patients	19	67
Sex		
Male	11	44
Female	8	23
Median age years (range)	59 (42 – 67)	62 (27 – 74)
Marital status		
Married	14	54
Unmarried/widow/divorced/single	5	13
Educational		
Illiterate	5	18
Under graduate	9	34
Post graduate	5	15
Body mass index		
Under weight	5	10
Normal	4	28
Over weight	7	15
Obese	3	14
Smoking status		
Smoker	8	34
Non / never smoker	11	33
ECOG Performance Status		
0 - 1	9	27
2 - 3	10	40
Pelvic symptoms		
Pelvic pain	6	33
Per-rectal bleeding	1	15
Intestinal obstruction	6	4
Pain and per-rectal bleeding	2	12
Pain and intestinal obstruction	3	2
Per-rectal bleeding and obstruction	1	1

Nineteen patients were treated with palliative surgery and sixty-seven patients with palliative pelvic radiotherapy to control the pelvic symptoms. All the patients received palliative chemotherapy according to their PS after the loco-regional therapy. The common metastatic sites were liver, lung and para-aortic lymph nodes. The most common clinical symptom was pain followed by rectal bleeding and obstructive symptoms. The baseline patient characteristics by palliative strategy treatment have shown in the Table I.

Palliative radiotherapy to the pelvis was delivered using conventional AP/PA portal with a Theratron 780C Tele-cobalt machine. Radiation dose was delivered according to the patient's age, compliance, performance status and extra-pelvic tumor burden. Thirty-nine patients received 30 Gy in 10 fractions over 2 weeks and twenty-eight patients were treated with 20 Gy in 5 fractions in one week schedule.

All these patients were independently included in the statistical analysis (intention to treat) and analyzed with respect to palliation of pelvic symptom after palliative surgery or radiotherapy, HRQoL and overall survival.

Pelvic symptoms: The palliation of pelvic symptom was assessed at three months after the palliative local treatment. The effective pain palliation was defined as decreased or resolved pain or decreased uses of analgesia. For patients with bleeding, the effective palliation was defined as stable hemoglobin or resolved hemochezia. For patients with obstruction, the effective palliation was defined as improvement or resolution of constipation or decreased laxative use and no need for surgical intervention. Time to progression of pelvic symptoms was defined as time from initiation of palliative locoregional treatment to first worsening of the index symptom (in case of multiple symptoms, the symptom which was most agonizing to the patient was considered).

Health related quality of life: Quality of life was assessed with the FACT-G questionnaire⁹ (FACT-G, Bengali translated and validated version) at baseline, 12th weeks (3 months), 6 months and 12 months after completion of palliative loco-regional therapy.

FACT-G, a health related quality of life general module, is grouped into the domains of physical, functional, social and emotional well-being. Each domain has seven questions except emotional well-being, which has six items – all arranged in

Likert like scales¹⁰. The other ten items, corresponding to the domains of additional concern for rectal cancer were also assessed.

Overall survival: OS was defined as the time from the start of palliative loco-regional therapy until death due to any cause or loss to follow up.

Toxicities: Radiation induced acute toxicity assessed according to the Common Terminology Criteria v 3.0¹¹

Statistical analysis: Statistical analysis performed using the SPSS software (SPSS for windows, version 20, IBM, USA). The overall survival and time to progression of pelvic symptoms were estimated using the Kaplan–Meier survival method and the comparisons between the two groups were determined using Log-rank test. Multivariate analysis was performed to assess the relationship between the outcomes and the possible prognostic variables using the Cox proportional hazard model. Categorical data were analysed using the Chi-square statistics among treatment groups (palliative surgery vs. palliative pelvic radiotherapy).

RESULTS

The median age of the entire cohort was 60 years (range 27 years to 74 years). The median follow-up for the entire cohort was 20 months.

Symptom control: Overall, palliation of pelvic symptoms achieved in 74.4 % of patients with palliative surgery or radiotherapy. Fifty-three patients had the symptom of pelvic pain at initial presentation and 73% and 72% achieved palliation of pain with palliative surgery and radiotherapy respectively (p=0.76). Thirty-two cases had per-rectal bleeding at presentation and 100% and 75% patients achieved control of bleeding with palliative surgery and radiotherapy, respectively (p=0.55). Patients with intestinal obstruction were mostly treated with

diversion procedures and few patients with sub-acute obstruction were treated with palliative chemotherapy and radiotherapy (p=0.25). Diversion colostomy alleviated

intestinal obstruction in 90% of cases where as radiotherapy-relieved symptom in only 57 % patients. (Table II)

Table II: Palliation of pelvic symptoms after palliative surgery or radiotherapy

	Palliative surgery	Palliative radiotherapy	P value
Pain	66.6 % (4/6)	72.72 % (24/33)	0.76
Bleeding	100 % (1/1)	73.33 % (11/15)	0.55
Intestinal obstruction	100 % (6/6)	50 % (2/4)	0.25
Pain and bleeding	100% (2/2)	75 % (9/12)	0.42
Pain and obstruction	66.6 % (2/3)	50 % (1/2)	0.70
Per rectal bleeding and intestinal obstruction	100 % (1/1)	100 % (1/1)	-
Overall symptom palliation	84.2% (16/19)	71.6 % (48/67)	0.41

The median time to progression of pelvic symptoms was six months (range 2-9 months) in the entire cohort and there was a

statistically significant difference between the two treatment groups (HR 0.88, 95% CI 0.66 – 1.17, Log rank p=0.373). (Figure I)

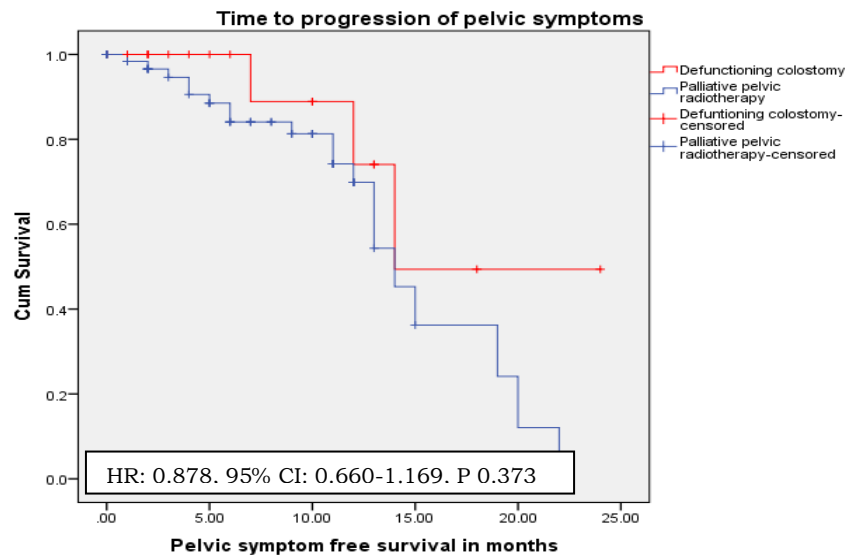


Figure I : Time to progression of pelvic symptoms according to palliation treatment modalities

HRQoL Analysis: Mean scores for all the domains of FACT-G questionnaires at baseline and during follow up are listed in the Table III. At three months follow up, mean HRQoL scores reduced compared to baseline mean scores irrespective of treatment group. Patients who received

palliative radiotherapy had declining trends in mean HRQoL scores up to six months follow up and then increase to reach almost baseline levels. In patients treated with palliative surgery, mean HRQoL scores decreasing throughout the follow up period from baseline.

Table III: Mean scores of FACT-G items module at 12th week, 6th month and 12th month after of palliative surgery or pelvic radiotherapy in metastatic rectal cancer

	Baseline mean score		3 rd month mean score		6 th month mean score		12 th month mean score	
	Pall. surgery	Pall. RT	Pall. surgery	Pall. RT	Pall. surgery	Pall. RT	Pall. surgery	Pall. RT
FACT-G Physical	17	16.7	12.6	14.5	11.8	12.5	12.2	16.7
FACT-G Functional	16.6	15.9	11.4	12.6	11.3	12	11.7	15.1
FACT-G Social	15.4	14.7	9.7	13.5	9.5	12.2	9.3	13.3
FACT-G Emotional	13.8	13.7	11	11.6	10.3	10.9	9.8	12.6

Patient's in palliative surgery group reported significantly reduced social well being mean scores compared to palliative

pelvic RT patients in the follow up period. (Figure II)

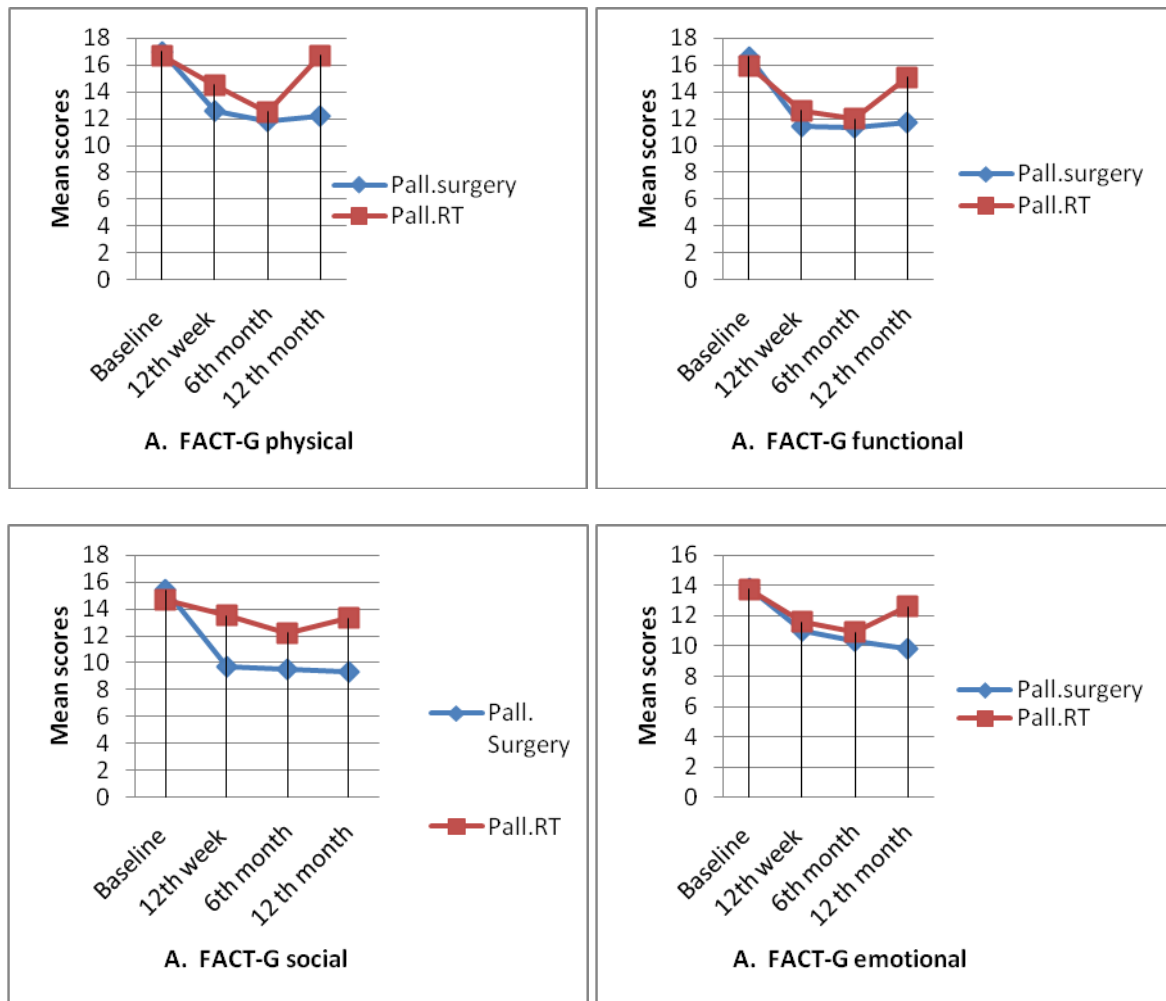


Figure II : Health Related Quality of Life scores (baseline to 12 months) for FACT – G physical (A), functional (B), social (C), emotional (D).

Overall survival: The median overall survival was nine months for the entire cohort. Thirty four percent patients survived at one-year. Upfront palliative loco regional treatments (diversion procedure/ extirpative resection or palliative radiotherapy) did not per se contribute to any significant difference in median overall survival. (Figure III) The median overall survival was eight months and nine months in group A and B (HR 1.002, 95% CI 0.76-1.31, Log rank $p=0.95$), respectively. There was significant association ($p=0.015$) between the performance status and the median overall survival of the patients, with the

median OS being 11 months in patients with good PS (ECOG0-1) as compared to 8 months with those poor PS (ECOG 2-3). (Figure IV)

On univariate analysis factor like gender, histo-pathological type, radiation dose and fractionation, treatment portal size had no significant effect on overall survival. However, factors like patients performance status had significant difference in OS. On multivariate analysis of the same using Cox regression model, only the PS found to be significant factor influencing overall survival.

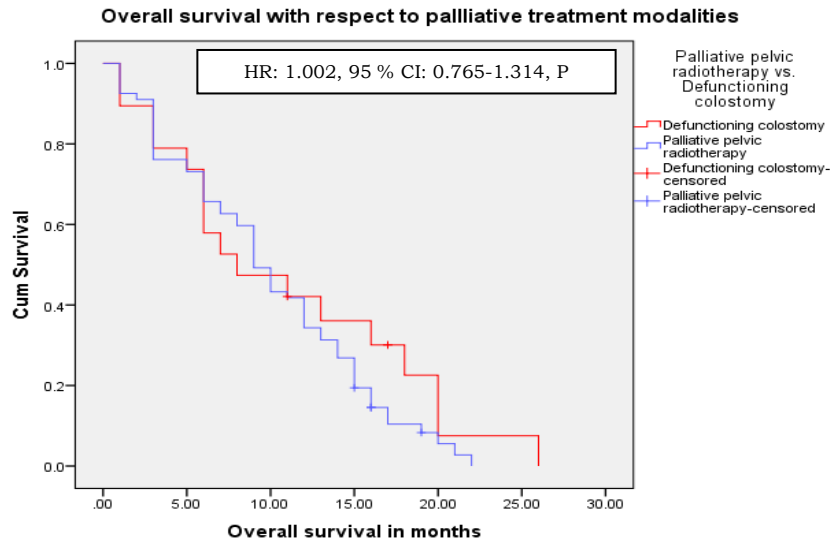


Figure III : Overall Survival according to palliative treatment modalities

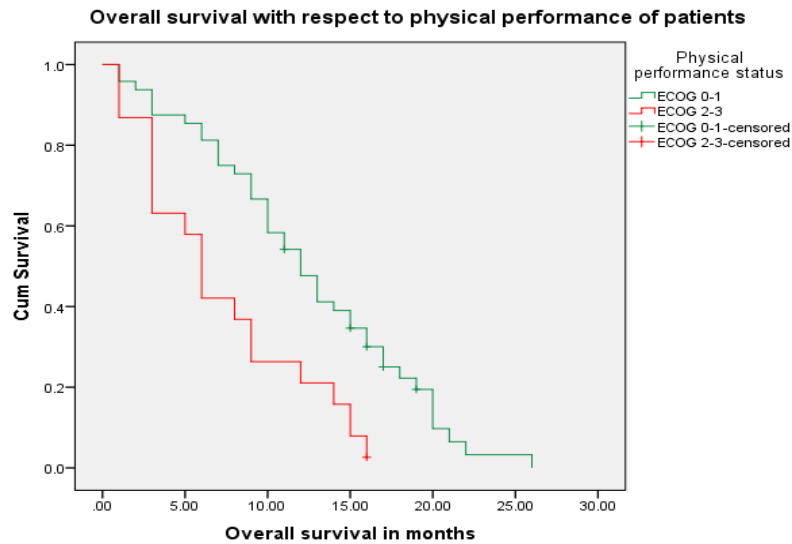


Figure IV

Toxicity: The acute radiation induced GI toxicities of palliative pelvic radiotherapy for rectal cancer, are self-limiting and usually resolved within 4-6 weeks of completion of treatment. All the patients tolerated pelvic RT well and there was no grade III toxicity. (Table IV)

Table IV: Acute radiation toxicities after palliative pelvic radiotherapy (grade II, CTC V.3)

Toxicity	Number	Percentage
Hematological	9	13.4
Genitourinary	4	5.9
Gastro-intestinal	31	46.3
Dermatological	19	28.3

DISCUSSION

Metastatic colorectal cancer is a major cause of morbidity and mortality throughout the world.¹² Although there has been a paradigm shift in the approach to treatment, out-comes in advanced disease remain modest. Customized treatment based on the symptoms, performance status and genetic profile has become the standard of care¹³. Systemic chemotherapy with the 5FU based doublets is the standard of care in metastatic rectal cancer¹⁴. This leads to modest survival advantage and improves Quality of Life. Diversion colostomy / extirpative resection or palliative pelvic RT remains important treatment modality for

patients with symptom from local pelvic mass⁴. There is no consensus which treatment modality is to be used for palliation of pelvic pain, per rectal bleeding or GI obstruction.

This prospective observational study evaluated the symptom palliation (pain, per rectal bleeding, sub acute intestinal obstruction) and analyzed whether the loco-regional modality of palliative treatment have an effect on HRQoL and OS. Considering the poor prognosis for these patients, the primary objective of the study was the relief from pelvic symptoms and secondarily the overall survival.

This is consistent with the result of Kleespies et al¹⁵. There was significant difference in trends HRQoL data between the treatment arms. There was reduction of physical, functional, social and emotional mean score of FACT-G in both the groups. There was improvement of HRQoL in those patients treated with palliative radiotherapy after six months of radiation completion which almost reached baseline values at twelve months. There was slow but clear deterioration of the patients HRQoL over time in the surgery arm.

Mean quality-of-life scores in most domains after surgery and during the first year after surgery were lower than those patients were treated with palliative radiotherapy and were most significant in social functioning domain. The psychosomatic care of patients after surgical treatment must comprise the analysis of HRQoL with colostomy¹⁶. Forty percent were seriously worried about the reaction of their social environment and significant decreased social reaction could be observed.

Performance status is the most important prognostic factor for overall survival according to the study of Daniel et al¹⁷. In our study, as well, we observed longer survival times in patients with good PS, as expected. However, there was no significant difference detected in OS among the two treatment groups.

External beam radiotherapy is an effective modality of palliative treatment to

pelvis in patients with metastatic rectal cancer. The palliation of pain and rectal bleeding supposed to be achieved in approximately 75% of patients with palliative pelvic low dose radiotherapy¹⁸⁻²². These studies have shown that, the median duration of pain relief was 6-9 months. In our study, 72.7 % of patients achieved pain relief with palliative radiotherapy where as 73.3 % and 50 % relief from per rectal bleeding and obstructive feature with palliative pelvic radiotherapy. The rate and duration of symptom palliation in our study were similar to those of above studies.

Study Limitations

Our study has some limitations. Firstly, it had a heterogeneous patient population. Secondly, there was also some heterogeneity in interventions in term of palliative surgery and radiation dose. Thirdly, it was not a randomized study, because individualized best treatment choices were taken by the MDT. The results could therefore be affected by the selection bias. Fourthly, this study was single institutional had a small sample size and relatively short follow up.

To conclusively define the effectiveness of palliative surgery and palliative pelvic radiotherapy, over one another, in terms of symptom control in metastatic rectal cancer, a prospective randomized study would ideally needed. However, traditionally, such studies are difficult to design and conduct and suffer from skewed patient accrual and one has to revert to indirect cross trail comparisons.

Patients with metastatic rectal cancer have a relatively short duration of survival and especially those with pelvic symptoms. When evaluating the patients with metastatic rectal cancer, the patient's age, co-morbidities, disease burden, tumor characteristic, functional status, social support and symptoms must be taken in to account to determine the best treatment approach.

CONCLUSIONS

Symptomatic patients with advanced /metastatic rectal cancer require individually tailored multidisciplinary approach to determine the most efficacious palliative intervention for palliation of symptoms – surgery or radiotherapy. Both palliative surgical interventions and palliative pelvic radiotherapy are equally effective without compromising overall survival. However, the symptom control rate and maintenance of HRQoL appears to be better with pelvic RT in our cohort of patients.

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Conflicts of Interest: None

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