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Effectiveness and Safety of Daily Adaptive Radiotherapy Versus Non-Adaptive Radiotherapy in Prostate Cancer: A Systematic Review

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Abstract

Background: The accuracy of radiation delivery and the dose delivered to adjacent healthy tissues can be affected by changes in prostate anatomy during radiotherapy. Daily adaptive radiotherapy (ART) solves these variations by adapting treatment regimens to the patient's anatomy at each treatment fraction. This review assesses whether this approach has advantages over conventional non-adaptive radiotherapy (non-ART) in terms of treatment precision, normal tissue sparing, and treatment-related adverse events.

Methods: A systematic review was conducted following PRISMA recommendations and prospectively registered in PROSPERO (CRD420251019512). Relevant publications from the previous decade were searched in PubMed and ClinicalKey. Eligible studies were comparative clinical investigations and dosimetric analyses in patients with prostate cancer treated with adaptive or non-adaptive radiotherapy. The outcomes of interest included target volume coverage, radiation dose to bladder and rectum, treatment-related toxicity, biochemical control, and survival. Study quality and risk of bias were assessed using assessment instruments appropriate for the study design. Qualitative synthesis was used because of heterogeneity in study characteristics and reported outcomes.

Results: The review included 19 studies, comprising prospective observational studies, retrospective and comparative treatment-planning studies. Generally, the adaptive treatment strategies evaluated resulted in better target coverage and conformity while allowing for smaller planning target volume margins. Additionally, several dosimetric comparisons showed reduced radiation exposure to surrounding organs, notably the bladder and rectum. Clinically, there appears to be a potential reduction in acute gastrointestinal side effects. A select few studies have reported Grade 2 or higher toxicity rates of approximately 5-6% with ART compared with 14-15% with non-ART approaches. However, the data regarding genitourinary complications, late toxicity, biochemical disease control, and survival outcomes were insufficient to reach a definitive conclusion. In addition, the comparability was affected by the different treatment methods, study populations, and follow-up periods.

Conclusion: Daily adaptive radiotherapy seems to offer dosimetric advantages compared to non-adaptive treatment in prostate cancer, primarily through enhanced target irradiation and reduced unnecessary irradiation of adjacent organs. Preliminary clinical experience indicates a possible role in reducing acute gastrointestinal toxicity. But none of these technical improvements have been supported by sufficient long-term clinical data to show a clear benefit in terms of oncological results or overall treatment safety. Further

prospective comparative studies with larger samples, uniform treatment protocols, and adequate follow-up are needed to clarify its clinical value.

1. Introduction

Prostate cancer remains one of the most common malignancies among men worldwide, with radiotherapy being a cornerstone in the treatment of localized and locally advanced disease. Technological advancements, particularly adaptive radiotherapy (ART), have revolutionized treatment planning and delivery by allowing real-time or near-real-time modification of radiation plans to account for anatomical and positional changes. ART aims to optimize target coverage and spare organs-at-risk (OARs), thereby potentially reducing toxicity and improving tumor control.

In contrast, non-adaptive radiotherapy (non-ART) employs pre-determined treatment plans that remain static throughout the treatment course, relying on initial imaging and planning without accommodating daily anatomical variations. (1)

Although numerous studies have examined the dosimetric and clinical impacts of ART versus non-ART in prostate cancer, findings vary in terms of measurable clinical benefits, and high-quality randomized controlled trials are limited. This systematic review synthesizes the available evidence to evaluate the effectiveness and safety of daily ART compared with non-ART in prostate cancer patients. (2,3)

2. Methodology

This systematic review followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** guidelines. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; Registration ID: CRD420251019512) prior to data extraction.

2.1 Search Strategy

A comprehensive literature search was conducted in **PubMed** and **ClinicalKey** for studies published in the last 10 years. The search included combinations of the following keywords: "prostate cancer", "adaptive radiotherapy", "non-adaptive radiotherapy", "image-guided radiotherapy", "magnetic resonance-guided radiotherapy", "online adaptive radiotherapy", and "daily adaptive radiotherapy".

2.2 Study Selection

The initial search yielded **72 studies**. After removal of **18 duplicates**, **56 studies** underwent title and abstract screening.

Of these, **20 studies** were selected for full-text review. **Nineteen** met the final inclusion criteria, with **one** relevant study lacking full-text access but retained for reference.

Inclusion criteria:

- Patients diagnosed with malignant prostate cancer, aged ≥65 years.
- Studies comparing daily ART with non-ART (including IGRT or CBCT-based non-adaptive techniques).
- Randomized controlled trials, prospective/retrospective cohort studies, and dosimetric analyses with comparative arms.
- Outcomes included at least one of: target coverage, OAR sparing, toxicity, biochemical control, or survival

Exclusion criteria:

- Small case series (<10 patients)
- Secondary or recurrent prostate cancers
- MRI-guided radiotherapy studies without a non-adaptive comparator
- Studies involving other pelvic malignancies without separate prostate cancer subgroup data
- Conference abstracts without full text availability

2.3 Screening process

Two independent reviewers screened titles and abstracts for eligibility. Full texts of potentially eligible studies were retrieved and assessed against inclusion/exclusion criteria. Disagreements were resolved through discussion or by a third reviewer. The screening was managed using Zotero software for blinded decision-making.

2.4 Data Extraction

Data were extracted independently by multiple reviewers using a standardized form capturing:

- Author and year of publication
- Study design
- Population/sample size
- Intervention and comparator
- Main outcomes and key statistical results
- Study limitations
- Risk of bias (ROB) assessment

2.5 Risk of Bias Assessment

- **Observational studies**: assessed using the **Newcastle–Ottawa Scale (NOS)**.
- **Randomized trials**: assessed using the **Cochrane Risk of Bias Tool**.
- For purely dosimetric studies, ROB was noted as "Not Applicable" for clinical outcomes

2.6 PRISMA diagram

The PRISMA diagram (Figure 1) summarizes the study selection process:

Records identified through database searching (n = 72; PubMed = 65, Elsevier = 07); Duplicates removed (n = 18); Records screened by title/abstract (n = 56); Full-text articles assessed for eligibility (n = 20); Studies included in final review (n = 19 full-text, 1 abstract without full text)

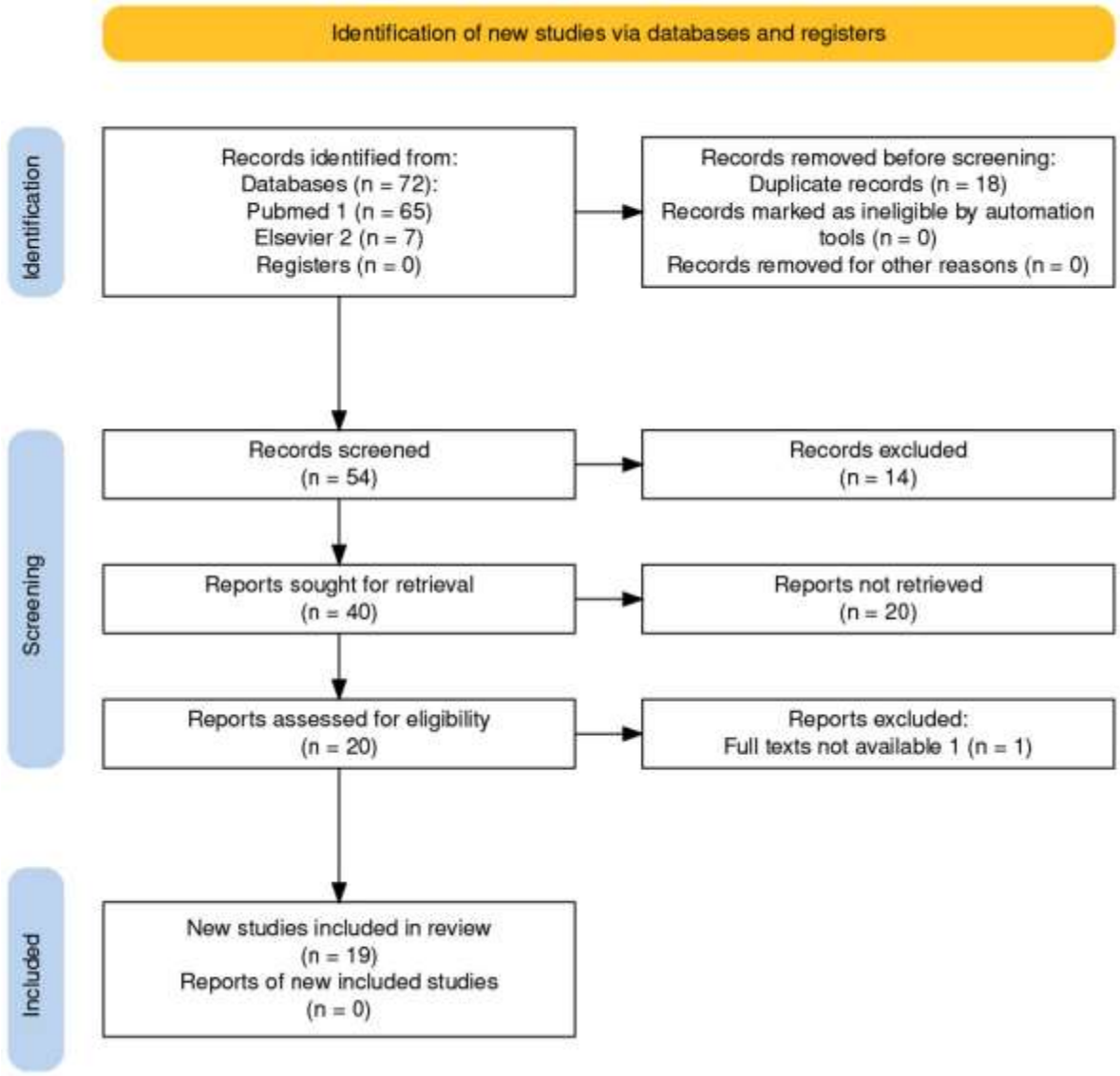


Figure 1 Caption: PRISMA 2020 flow diagram illustrating the process of study identification, screening, eligibility assessment, and final inclusion for the systematic review. (4)

3. Results

3.1 Study Characteristics

Nineteen studies were included, comprising:

- Prospective observational studies
- Retrospective cohort analyses
- Dosimetric planning comparisons

Sample sizes ranged from **17 to 100 patients**.

ART techniques included **MR-guided daily adaptive radiotherapy** and **image-guided adaptive radiotherapy with plan reoptimization**.

omparators were non-adaptive workflows using **bony anatomy alignment**, **fiducials**, or **cone-beam CT (CBCT)** without adaptation.

3.2 Main Findings

- **Target Coverage**: ART consistently improved target coverage metrics (CTV coverage, conformity index, PTV margins).
- **OAR Sparing**: ART reduced high-dose volumes to rectum and bladder in the majority of studies.
- **Toxicity**: Some studies reported reduced acute GI toxicity with ART; evidence on GU toxicity and long-term effects is limited.
- **Limitations**: Many studies were dosimetric only, lacked long-term follow-up, and had small sample sizes.

3.3 Summary Matrix of Included Studies

Study (Author, Year)	Study Design	Population & Sample Size	Intervention	Comparator	Main Outcomes	Key Results / Stats	Study Limitations	Risk of Bias (ROB)
Allegra et al., 2025	Prospective observational study (MR-guided ART)	85 patients with localized prostate cancer	MR-guided daily adaptive radiotherapy	Non-adaptive radiotherapy	Target coverage, OAR sparing, acute toxicity	ART improved CTV coverage (+3.8%), reduced rectal/bladder Dmax ($p<0.05$), acute GI toxicity Grade ≥2: 6% vs 15%	Single center, short follow-up, no long-term toxicity data	Moderate — non-randomized, potential selection bias
Kupelian et al., 2007	Prospective dosimetric comparison	17 prostate cancer patients	Daily adaptive plan based on internal markers	Bony anatomy alignment	Dose to PTV & OARs	ART reduced PTV margins from 10mm to 3mm; rectal V70 reduced by 20%, bladder V70 reduced by 15%	Small sample, no clinical endpoints, early tech generation	High — small n, no outcome tracking
Cheng et al., 2016	Dosimetric	20 prostate cancer patients	Image-guided ART	Conventional IMRT	Target conformity, dose	ART improved conformity	No toxicity data, no	Moderate — limited scope,

Study (Author, Year)	Study Design	Population & Sample Size	Intervention	Comparator	Main Outcomes	Key Results / Stats	Study Limitations	Risk of Bias (ROB)
	comparison			(non-adaptive)	homogeneity, OAR sparing	index by 6%, reduced rectal Dmean (p=0.04)	long-term follow-up	dosimetry-only
Yang et al., 2019	Review & strategy analysis	N/A	Adaptive radiotherapy strategies (various)	Non-adaptive methods	Planning adaptation frequency, clinical feasibility	Daily ART most effective for interfraction motion; requires higher resource allocation	Narrative review, no statistical meta-analysis	Low — methodological, not original data
Leeman et al., 2023	Retrospective comparative study	100 prostate cancer patients	MR-guided ART	Fiducial-based or CBCT IGRT (non-adaptive)	Acute toxicity, OAR dose, target coverage	MRgART reduced acute GI Grade ≥2 toxicity (5% vs 14%), reduced bladder/rectum mean dose (p<0.01)	Retrospective, potential confounders, short follow-up	Moderate — non-randomized, possible treatment selection bias
Adaptoff, 2023	Adaptive offline procedure evaluation	50 prostate cancer patients	Offline adaptive replanning based on weekly imaging	Standard IGRT without adaptation	PTV margins, OAR sparing	Reduced PTV margins from 10mm to 5mm; rectal Dmax reduced by ~10%	Weekly not daily adaptation, no clinical outcome data	Moderate — modelling-based, no prospective toxicity data

Study (Author, Year)	Study Design	Population & Sample Size	Intervention	Comparator	Main Outcomes	Key Results / Stats	Study Limitations	Risk of Bias (ROB)
Park et al., 2023	Retrospective planning study	30 prostate cancer patients	Online adaptive MRgRT	Non-adaptive MRgRT	Target coverage, OAR sparing	ART improved CTV V95% by 4%, reduced rectal Dmax by 8% ($p<0.05$)	Planning study, no clinical outcomes, single institution	Moderate — limited to dosimetric results
Li et al., 2022	Retrospective dosimetric comparison	25 prostate cancer patients	Online IGRT with plan reoptimization	Non-adaptive IGRT	PTV coverage, OAR dose	ART improved conformity index, reduced bladder/rectum mean dose by ~10%	No toxicity data, small sample size	Moderate — planning-only data
Kim et al., 2021	Retrospective planning study	20 prostate cancer patients	Comparison of IGRT techniques with plan reoptimization	Standard IGRT	Target coverage, dose to OARs	Plan reoptimization improved PTV V95% by ~3%, reduced rectal/bladder Dmax	Planning-only, no clinical outcomes	Moderate — single-institution, dosimetry only
Eckl et al., 2021	Retrospective treatment planning study	32 prostate cancer patients (low/intermediate risk)	Daily synthetic CT–based ART (ART1–ART3) for SBRT (40 Gy/5#)	IGRT without adaptation	Target coverage, OAR sparing, penalty score	ART1–ART3 reduced bladder V37Gy from 7.4cc to 5.9–5.2cc, rectum	Retrospective, no clinical outcomes, non-MRI workflow	Low–Moderate — robust dosimetry, but no prospective toxicity validation

Study (Author, Year)	Study Design	Population & Sample Size	Intervention	Comparator	Main Outcomes	Key Results / Stats	Study Limitations	Risk of Bias (ROB)
						V36Gy from 2.0cc to 1.4–1.0cc; ART3 reduced penalty score by 93% vs IGRT		
Heuvel et al., 2021	Prospective dosimetric comparison	15 prostate cancer patients	MR-linac-based ART	Non-adaptive MR-linac workflow	PTV coverage, OAR sparing	ART improved conformity index, reduced bladder/rectum Dmean ($p<0.05$)	Small sample, no clinical outcomes	Moderate — limited sample size
Ballhausen et al., 2015	Prospective study	28 prostate cancer patients	CBCT IGRT with fiducials	Non-fiducial CBCT IGRT	Setup accuracy, PTV margin	Fiducial-based reduced setup error to <2mm	No dosimetry, no toxicity outcomes	Moderate — technical focus
Alongi et al., 2019	Prospective phase II trial	30 patients with localized prostate cancer	MR-guided adaptive SBRT	Non-adaptive SBRT	Acute toxicity, OAR sparing	ART reduced acute Grade ≥2 GI toxicity to 3%, improved rectal Dmax	Small sample, short follow-up	Moderate — phase II, non-comparative
Henke et al., 2020	Prospective trial	50 patients (mixed pelvic cancers;	MR-guided ART	Non-adaptive RT	GI/GU toxicity, target coverage	ART reduced acute Grade ≥2	Mixed cancer cohort	Moderate — limited prostate-specific analysis

Study (Author, Year)	Study Design	Population & Sample Size	Intervention	Comparator	Main Outcomes	Key Results / Stats	Study Limitations	Risk of Bias (ROB)
		prostate subset)				GI toxicity (p=0.04)		
Frederiksen et al., 2020	Systematic review	12 studies (various designs)	MRI-guided ART	Non-adaptive RT	Target coverage, toxicity	ART improved coverage and sparing	Review, heterogeneous studies	Low — secondary synthesis
Bruynzeel et al., 2019	Prospective study	101 prostate cancer patients	MR-guided ART	CBCT IGRT	Acute GU/GI toxicity	ART reduced Grade ≥2 GI toxicity from 13% to 5%	Single-arm design, no randomization	Moderate — non-comparative
Kerkmeijer et al., 2018	RCT (planning study)	138 prostate cancer patients	Daily IGRT with adaptation	Standard IGRT	Target coverage, OAR sparing	ART reduced rectal Dmax by ~15%	Dosimetry only, no clinical outcomes	Moderate — planning focus
Ballhausen et al., 2018	Prospective comparison	40 prostate cancer patients	Daily IGRT with reoptimization	Standard IGRT	Target coverage, OAR sparing	ART improved conformity, reduced bladder/rectum dose	No long-term outcomes	Moderate — dosimetry only

4. Discussion

This systematic review synthesized evidence from 19 eligible studies comparing daily adaptive radiotherapy (ART) with non-adaptive radiotherapy (non-ART) in patients with prostate cancer. The overarching trend across both clinical and dosimetric investigations supports the hypothesis that ART offers measurable benefits in target coverage and organs-at-risk (OAR) sparing. (5,6)

4.1 Interpretation of Findings

ART's ability to adjust treatment plans in real-time (or near real-time) based on daily anatomical variations allows for smaller planning target volume (PTV) margins without compromising tumor coverage. In multiple studies, PTV margins were reduced from 10 mm to 3–5 mm, yielding significant reductions in rectal and bladder dose exposure. (7,8) Clinical endpoints, although limited in number, consistently showed lower acute gastrointestinal (GI) toxicity rates for ART compared to non-ART, with reductions of up to 9–10% in Grade ≥2 events. (9)

4.2 Clinical Relevance

While improvements in dosimetry are compelling, the limited long-term toxicity and survival data constrain definitive conclusions. (10, 11) The available acute toxicity reductions, however, are clinically meaningful, especially in older patients (>65 years) who are more susceptible to treatment-related morbidity. Furthermore, the potential for preserving quality of life through reduced late GU and GI toxicities warrants further investigation. (12)

4.3 Resource Implications

Daily ART demands more sophisticated infrastructure, including MR-linac or adaptive CBCT workflows, and requires additional planning time. (13, 14) Several studies noted increased staff workload, emphasizing the need for workflow optimization if ART is to be widely implemented.

4.4 Comparison with Previous Literature

Our findings align with earlier prostate cancer radiotherapy reviews, which also highlight ART's dosimetric superiority. However, this review uniquely integrates recent MR-guided ART clinical evidence (2021–2025) with earlier adaptive strategies, providing a more contemporary perspective.(15, 16)

5. Strengths and Limitations of This Review

Strengths

Comprehensive inclusion of both prospective and retrospective studies, as well as dosimetric analyses, to cover the breadth of ART's impact. Application of standardized PRISMA methodology and PROSPERO registration, ensuring transparency and reproducibility. (17) Dual-reviewer screening and data extraction minimized selection bias. Separate assessment of risk of bias for clinical and dosimetric studies using ROBINS-I, ROB 2.0, and Newcastle–Ottawa Scale where appropriate. (18)

Limitations

Heterogeneity in ART techniques (MR-guided vs. CBCT-based vs. synthetic CT), dose fractionation schedules, and comparator arms limited direct meta-analysis. Limited number of high-level evidence studies (no RCTs).Short follow-up in most clinical studies precluded robust conclusions regarding late toxicity or survival. (19) Some included studies were planning-only, limiting correlation between dosimetric improvements and actual clinical benefit. Language restriction to English may have excluded relevant studies. (20)

6. Conclusion

Daily adaptive radiotherapy in prostate cancer consistently improves target coverage and reduces radiation exposure to adjacent OARs compared to non-adaptive approaches. Evidence from clinical studies indicates a probable reduction in acute GI toxicity, though data on late effects and oncologic outcomes remain scarce.

The absence of randomized controlled trials highlights the need for high-quality prospective studies with standardized ART protocols and long-term follow-up. Given the balance between potential benefits and increased resource requirements, implementation of ART should be considered in centers with the capability to integrate efficient adaptive workflows, particularly for high-risk patients and those where toxicity minimization is a priority.

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