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Evolution of Organ-at-Risk Sparing Techniques in Prostate Cancer Radiotherapy: A Narrative Review

Mohamed Saadoune[1*], Samir Barkiche[1], Sana Laatitioui[1], Mouna Khouchani[1]

[1]Mohamed VI University Hospital Center of Marrakech, Morocco, Department of Oncology and Hematology Division of Radiation Oncology

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***Corresponding author:** Mohamed Saadoune
Mohamed VI University Hospital Center of Marrakech, Morocco, Department of Oncology and Hematology Division of Radiation Oncology

Abstract **Review Article**

Background: Prostate cancer is the most commonly diagnosed malignancy among men in developed countries. Radiotherapy is a cornerstone of curative treatment, but proximity to organs at risk (OARs) such as the rectum and bladder remains a major challenge. ***Objective:*** To provide an updated narrative review of the main technological advances that have improved OAR sparing in external beam radiotherapy (EBRT) for prostate cancer. ***Methods:*** A literature review was conducted using PubMed and Scopus (2005–2024), focusing on studies related to conformal radiotherapy, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image-guided radiotherapy (IGRT), rectal spacers, proton therapy, and adaptive radiotherapy. ***Results:*** IMRT and VMAT significantly improve dose conformity and reduce exposure to the rectum and bladder. IGRT and fiducial tracking enhance daily targeting precision, allowing tighter margins. Hydrogel rectal spacers reduce rectal dose by up to 70% and improve patient-reported outcomes. Proton therapy offers theoretical dosimetric advantages, though without clear clinical superiority. Adaptive radiotherapy and AI-based tools represent emerging solutions for further OAR sparing. ***Conclusions:*** Technological progress has led to a substantial reduction in radiation-induced toxicity in prostate cancer radiotherapy. Future directions include personalised treatment through daily plan adaptation and automated planning driven by artificial intelligence.

Keywords: Prostate Cancer, Organs at Risk, Radiotherapy, IMRT, VMAT, Rectal Spacers, IGRT, Proton Therapy, Adaptive Radiotherapy.

1. INTRODUCTION

Prostate cancer remains a major public health concern, accounting for a significant proportion of cancer morbidity in men. External beam radiotherapy (EBRT) is an established curative modality for localised and locally advanced prostate cancer. However, the anatomical proximity of the prostate gland to critical organs at risk (OARs), particularly the rectum, bladder, and neurovascular bundles, presents substantial dosimetric challenges. Reducing the radiation dose to these OARs is crucial to minimising both acute and late toxicities, thereby improving quality of life. This review aims to summarise the evolution of OAR sparing techniques in the context of prostate cancer radiotherapy.

2. METHODS

A narrative review of the literature was conducted in March 2025 using PubMed and Scopus databases. We included peer-reviewed articles published between January 2005 and March 2024 in English, focusing on:

- Technological advances in radiotherapy for prostate cancer
- Studies reporting on OAR dosimetry, toxicity, or treatment outcomes
- Clinical trials, dosimetric studies, and systematic reviews

Search terms included combinations of: “prostate cancer”, “organs at risk”, “IMRT”, “VMAT”, “IGRT”, “spacers”, “proton therapy”, and “adaptive radiotherapy”.

3. RESULTS

3.1 Techniques Evolution

3.1.1 3D Conformal Radiotherapy (3D-CRT)

The introduction of 3D-CRT in the early 2000s marked a turning point in prostate radiotherapy. While it

improved dose distribution compared to 2D techniques, the degree of sparing for OARs remained limited due to the relatively broad margins required.

3.1.2 Intensity-Modulated Radiotherapy (IMRT)

IMRT allows for inverse planning and precise modulation of beam intensity. Multiple prospective and retrospective studies demonstrate significant reductions in grade ≥2 rectal toxicity compared to 3D-CRT. IMRT also facilitates dose escalation without increasing toxicity [1].

3.1.3 Volumetric Modulated Arc Therapy (VMAT)

VMAT delivers radiation via continuous rotation of the gantry, reducing treatment time and enhancing conformity. Comparative studies show improved dose homogeneity and reduced OAR doses compared to fixed-field IMRT.

3.1.4 Image-Guided Radiotherapy (IGRT)

Daily imaging with cone-beam CT (CBCT), fiducial markers, or electromagnetic tracking systems enables tighter planning margins and reduces PTV overlap with OARs. IGRT is now considered standard in modern prostate EBRT.

3.1.5 Prostate SBRT

SBRT has been shown in clinical trials to be as effective in controlling prostate cancer as longer-duration radiation for patients with low- and intermediate-risk disease. Patients receiving SBRT for prostate cancer may initially experience more urinary symptoms, but long-term urinary and bowel function is similar to the function you would have after longer duration radiation treatment.

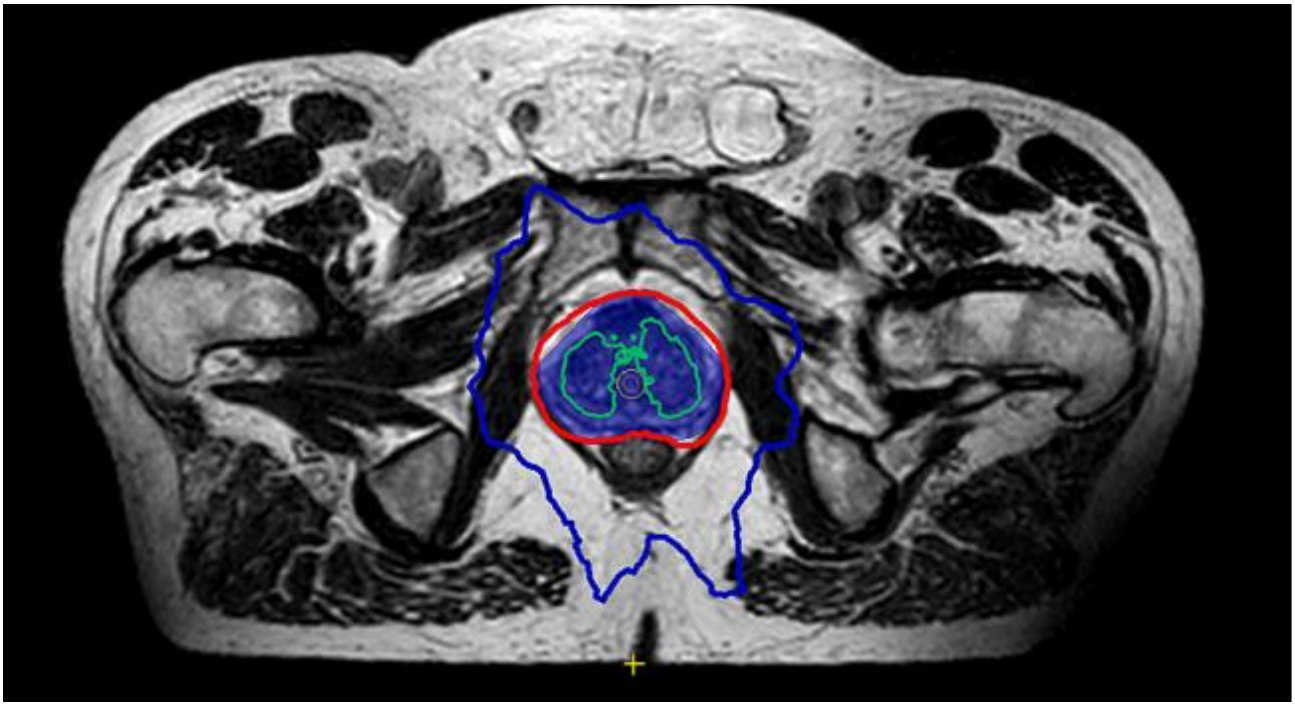

Figure 1: Dose distribution for prostate SBRT using MRI-guided urethra-sparing technique. The stereotactic body radiotherapy plan delivers a total dose of 36.25 Gy in 5 fractions, prescribed to the 80% isodose line, with urethral hotspots constrained to remain below 40 Gy. Target and avoidance structures include: the prostate PTV (blue contour), which encompasses the gland plus a 2 mm margin; the intraprostatic urethra (pink); and the urethral planning risk volume (PRV, yellow), defined as urethra plus a 2 mm margin. Isodose lines shown: 18 Gy (blue), 36.25 Gy (red), and 42 Gy (green).

3.1.6 Rectal Spacers

Hydrogel spacers (e.g., SpaceOAR®) physically displace the rectum from the prostate by ~1 cm. Randomised trials report rectal dose reductions of 50–70% and improved bowel quality of life scores, particularly in hypofractionated or stereotactic protocols [2].

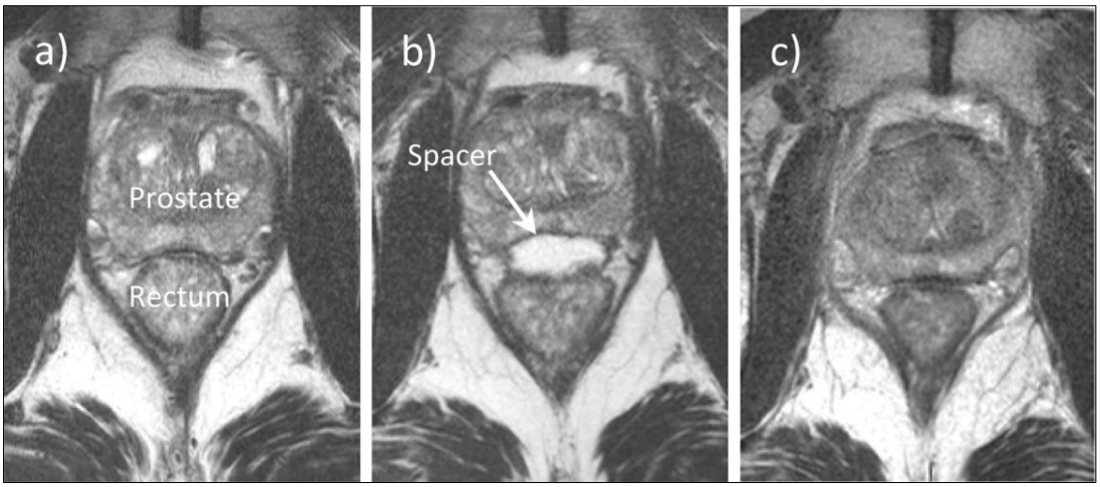

Figure 2 : Images de résonance magnétique pondérées en T2 d'un patient porteur d'un espaceur au départ (a), après l'application (b) et 12 mois après l'application de l'espaceur (c).

3.1.7 Proton Therapy

Proton therapy offers a Bragg peak dose distribution, reducing exit dose to surrounding tissues. Dosimetric studies favour proton therapy for OAR sparing; however, randomised data have yet to demonstrate significant clinical advantages over IMRT or VMAT [3].

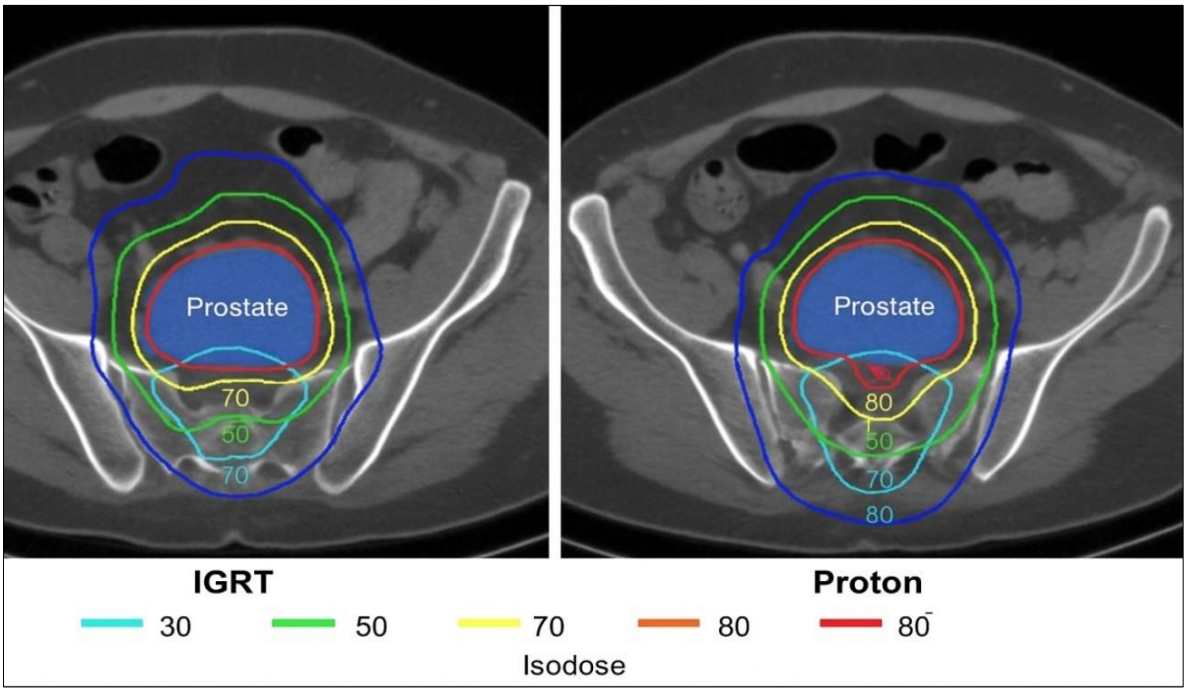

Figure 3: Comparative dose distribution between IGRT (photon-based) and proton therapy for localized prostate cancer

This dosimetric illustration demonstrates the dose coverage of the prostate and surrounding organs at risk (OARs) including the rectum and bladder. The photon-based IGRT plan (left) shows broader low-to-intermediate dose spillage to adjacent tissues, while the proton plan (right) achieves tighter conformality and reduced dose to the rectum and posterior structures due to the Bragg peak effect. These findings support the rationale for organ-at-risk sparing using proton therapy in selected patients.

3.1.8 Adaptive Radiotherapy and Artificial Intelligence

Adaptive radiotherapy platforms allow for daily plan modifications based on anatomical changes. Emerging AI tools now assist in auto-contouring, dose prediction, and treatment planning optimisation, offering potential for further OAR sparing and workflow efficiency [4].

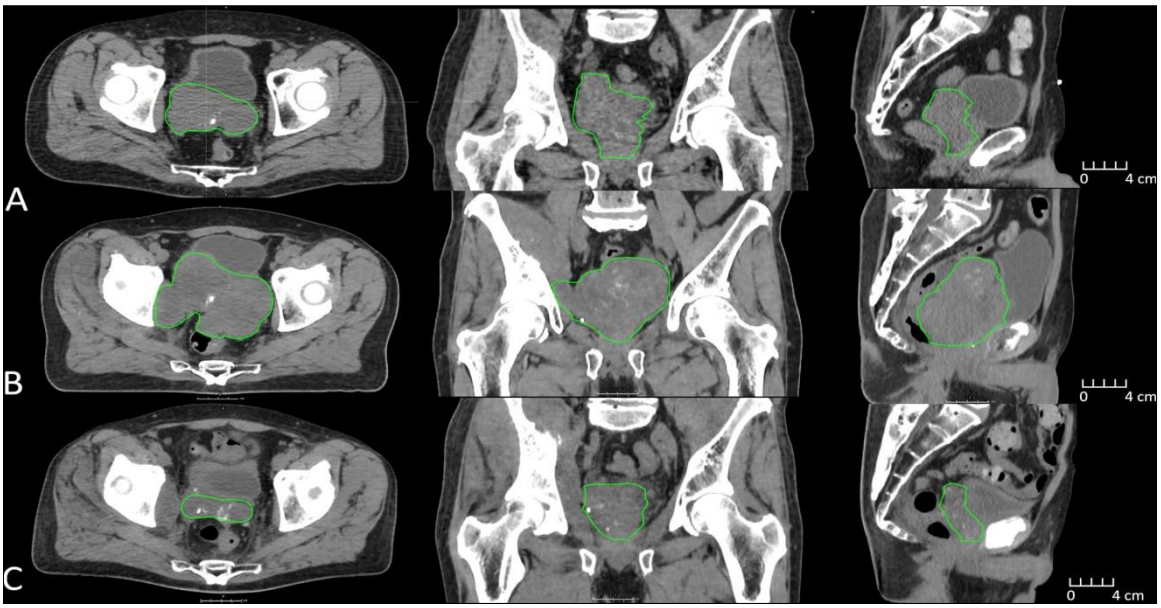

Figure 4 : CT imaging depicting clinical target volume (green) changes approximately 1 year prior to MR-Linac treatment (A), immediately prior to MR-Linac treatment (B), and 6 months post MR-Linac treatment (C)

3.2 Comparative Summary of Techniques and Outcomes (Table 1)

IMRT and VMAT enable highly conformal dose delivery, minimizing exposure to the rectum and bladder. IGRT enhances targeting precision with daily imaging, allowing for reduced planning margins. Two major trials, CHHiP and HYPRO, have evaluated the clinical impact of these techniques:

- CHHiP Trial (Dearnaley *et al*., 2016): A phase III randomized trial with over 3,200 patients compared conventional fractionation (74 Gy in 37 fractions) with moderate hypofractionation (60 Gy in 20 fractions and 57 Gy in 19 fractions) using IMRT and IGRT. The 5-year biochemical relapse-free survival was 88.3% (74 Gy), 90.6% (60 Gy), and 85.9% (57 Gy), respectively. Grade ≥2 GI toxicity at 5 years was lower with 60 Gy (11.9%) compared to 74 Gy (13.7%), supporting the efficacy and improved tolerability of the hypofractionated regimen. [5]
- HYPRO Trial (Aluwini *et al*., 2016): This phase III trial included 820 patients randomized to conventional fractionation (78 Gy in 39 fractions) versus a more intense hypofractionation schedule (64.6 Gy in 19 fractions of 3.4 Gy). While biochemical control at 5 years was similar (80.5% hypo vs 77.1% conventional), grade ≥2 GI toxicity at 3 years was higher in the hypofractionated group (21.9% vs 17.7%). This highlights a potential trade-off between efficacy and toxicity with aggressive hypofractionation [6].
- These trials collectively demonstrate that modern radiotherapy techniques reduce late rectal and urinary toxicity while maintaining oncologic outcomes, particularly when delivered with image guidance and appropriate fractionation.
- Mariados *et al*., (2015): A pivotal multicenter, randomized controlled trial involving 222 patients showed that the spacer increased the prostate-rectum distance from 1.6 mm to 11.2 mm on average, resulting in a 73.5% relative reduction in rectal V70. Acute and late rectal toxicity grade ≥2 were reduced by more than 50% in the spacer group [7].
- Hamstra *et al*., (2017): A follow-up analysis of the same cohort reported long-term toxicity reduction and improved patient-reported bowel quality of life at 3 years. Late grade ≥1 rectal toxicity was 2% in the spacer group vs 9% in controls [8].
- SPACE and SPACER phase IV registries: These multicenter prospective datasets confirm real-world feasibility and safety, with minimal complications from spacer insertion.

Spacer implantation is now widely recommended in dose-escalated or hypofractionated radiotherapy protocols. However, considerations such as cost, patient selection, and procedural expertise remain crucial for implementation.

- Sheets NC, *et al*., determine the comparative morbidity and disease control of IMRT, proton therapy, and conformal radiation therapy for primary prostate cancer treatment. IMRT compared with proton therapy was associated with less gastrointestinal morbidity [3].

Table 1: **summary table of the main clinical studies concerning techniques for sparing organs at risk in radiotherapy for prostate cancer**

Study / Trial	Technique	Population / Setting	Key Findings	Conclusion
CHHiP (Dearnaley *et al*., 2016)	IMRT + IGRT	n=3216, low/intermediate-risk PCa	Non-inferior control with 60 Gy/20 fx; lower GI toxicity vs 74 Gy	Supports moderate hypofractionation
HYPRO (Aluwini *et al*., 2016)	3D-CRT/IMRT	n=820, intermediate/high-risk PCa	Similar control; increased GI toxicity with hypofractionation	Caution with extreme hypofractionation
Mariados *et al*., 2015	Rectal Spacer	RCT, n=222	73.5% reduction in rectal V70; ↓ grade ≥2 GI toxicity	Significant rectal sparing benefit
Hamstra *et al*., 2017	Rectal Spacer	Follow-up of RCT	↓ late rectal toxicity; improved bowel QoL at 3 years	Confirms long-term benefit
Bryant *et al*., 2016	Proton Therapy	Matched cohort	↓ GI toxicity (6% vs 12%) vs IMRT; similar control	Favorable toxicity profile
Mendenhall *et al*., 2014	Proton Therapy	n=1327, prospective	5-yr bNED: 99% (low-risk), 94% (int-risk); low toxicity	High efficacy, low toxicity
Tetar *et al*., 2020	Adaptive MRgRT	Pilot study	↓ rectal mean dose by 15%; maintained target coverage	Effective ART with MRgRT
Hunt *et al*., 2022	Adaptive MRgRT	n=50, prospective	Feasible adaptive workflow; consistent OAR sparing	Validates adaptive feasibility

4. DISCUSSION

The refinement of radiotherapy techniques over the past two decades has led to significant improvements in OAR protection. Modern modalities like IMRT, VMAT, and IGRT have become standard of care, while rectal spacers have gained wide acceptance in certain patient populations.

Most of the models of late radiation toxicity come from three-dimensional conformal radiotherapy dose-escalation studies of early-stage prostate cancer. It is possible that intensity-modulated radiotherapy or proton beam dose distributions require modification of these models because of the inherent differences in low and intermediate dose distributions [9].

Proton therapy is attractive due to the unique physical properties of the heavy charged particles that deliver the majority of dose in sharp Bragg peaks and leave no exit dose. On the other hand, the side by side dosimetric comparison between proton therapy and the best of photon therapy has rarely been performed. In a dosimetric comparison between 3D conformal proton therapy (CPT) and IMRT, Trofimov *et al*., concluded that IMRT resulted in superior bladder sparing and similar rectum sparing compared to 3D CPT, which is superior in reducing the low dose spillage [10]. The same study also pointed out that the lack of dose conformity in 3D CPT would be overcome with the use of scanning pencil beam and intensity modulated proton therapy (IMPT). With the improvement of proton therapy techniques, PBS proton has gradually replaced passive scatter due to its superior dose shaping capability. In our comparison, state of the art PBS based IMPT was used.

The multivariate analysis shows that the magnitude of difference in dosimetric metrics of treatment modalities may depend on the OAR volume but not the relative relationships. For instance, the relative disadvantages and advantages of IMPT for V40 and V80, respectively, widen for larger rectum volumes. This information may be used to steer patient treatment if confirmed with a larger patient cohort. The bladder mean dose decreasing with increasing bladder volumes is intuitive. However, the similar decrease in the bladder maximum dose is less intuitive. It is possibly due to the distance between the bladder and the CTV also increasing with increasing bladder volume.

In the study of Palma *et al*., [11], as well as VMAT and IMRT resulted in a significant reduction of the dose to OAR compared to 3D conformal radiation therapy, these doses were lowest with VMAT. The comparative study of the Memorial Sloan Kettering Cancer Center [12], reported a significant reduction of the dose to the rectum and the rectum-NTCP by 1.5%, the doses to the bladder and the femoral heads were also reduced but not significantly. Similar results were reported by Hardcastle *et al*., [13], with reduced doses to the rectum and therefore a lower rectum-NTCP with VMAT versus IMRT (7F, SS). In a Danish study [14], the VMAT technique has reduced doses to the rectum and bladder compared to IMRT (SW). Ost *et al*., [15], have compared VMAT with three techniques of IMRT (3F, 5F, 7F-SS), for prostate radiotherapy with a simultaneous integrated boost to the intraprostatic lesion defined by MRI spectroscopy, VMAT in this study compared to the three IMRT techniques has reduced the dose to the rectum, this reduction was statistically significant for the volumes receiving doses between 20 and 50 Gy ($p < 0.001$). In Weber *et al*., study [16], comparing VMAT with IMRT (5F, SW) and proton therapy for recurrent prostate cancer after radiation therapy, VMAT and proton therapy allowed a better

sparing of OAR compared to IMRT. In a study of 292 patients, the mean doses to the rectum and bladder were lower with VMAT compared with IMRT (7F, SW), especially in the volumes of high doses [17]. However, the results of many studies have shown that IMRT allow a better OAR sparing compared to VMAT [18-21].

Despite theoretical advantages, the high cost and limited availability of proton therapy limit its widespread adoption. Future efforts should focus on the integration of AI and adaptive planning into routine practice, enabling truly personalised radiotherapy. Further prospective trials are warranted to validate long-term clinical benefits.

5. CONCLUSION

The landscape of prostate cancer radiotherapy has evolved considerably, with major advances in organ-at-risk sparing. These improvements have translated into better patient outcomes, reduced toxicity, and enhanced quality of life. Continuous innovation, particularly in adaptive and AI-guided radiotherapy, holds promise for even safer and more effective treatment in the future.

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