

3. Radiotherapy

Intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) with image-guided RT (IGRT) is currently widely recognised as the standard treatment approach for external beam radiation therapy (EBRT).

External beam radiation therapy

Technical aspects

IMRT and VMAT use dynamic multi-leaf collimators to adapt to the target volume's contours, offering reduced genito-urinary (GU) and gastro-intestinal (GI) toxicity compared to three-dimensional conformal RT (3D-CRT). IMRT combined with IGRT remains the standard of care for prostate cancer, with VMAT providing shorter treatment times. While MR-guided RT shows promise in reducing organ-at-risk doses, its implementation is still investigational due to longer treatment times and workflow challenges. The MIRAGE trial suggests reduced toxicity with MRI-guided SBRT and margin reduction.

Dose escalation

Local control is crucial for the outcome of radiotherapy, with inadequate dosing linked to increased mortality due to a second wave of metastases years later. Dose escalation (74–80 Gy) significantly improves long-term outcomes, including biochemical relapse, metastases, and disease-specific mortality, especially in intermediate- and high-risk PCa patients. IMRT/VMAT with IGRT offers dose escalation with manageable severe late side effects (2–6%). Focal boosting of the dominant intraprostatic lesion (DIL) improves biochemical progression-free survival without significantly increasing late GU or GI toxicity, though longer follow-up is needed to fully assess late toxicity risks.

Hypofractionation

Fractionated RT exploits differences in DNA repair capacity between normal and tumour tissue, with hypofractionated RT potentially more effective for PCa due to its slow proliferation rate. Moderate hypofractionation (2.5–3.4 Gy/fx) shows comparable efficacy and safety to conventional fractions, though long-term data are still needed. Ultra-hypofractionation (>3.4 Gy/fx) achieves similar short-term biochemical control but raises concerns regarding high-grade GU and rectal toxicity and lacks extensive long-term side effect data. Systematic reviews suggest SBRT may be a viable standard treatment for localized PCa, yet longer follow-up is required to confirm these findings fully.

Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of radiotherapy with luteinising hormone-releasing hormone (LHRH) agonist-based androgen deprivation therapy (ADT) shows superiority over RT alone followed by deferred ADT in reducing relapse in prostate cancer, as demonstrated by phase III RCTs. For intermediate-risk disease, a short duration of ADT (four to six months) is optimal, while high-risk patients benefit from a longer duration (2-3 years). Although a large RCT in intermediate-risk patients did not show an overall survival (OS) advantage with six months of ADT, it did reduce PSA failure, distant metastases, and prostate cancer-specific mortality. The added value of combining RT with ADT has been confirmed by three RCTs, all showing clear OS benefits from adding RT to long-term ADT in high-risk patients.

Combined dose-escalated radiotherapy and androgen-deprivation therapy

The combination of ADT with RT is well-supported by evidence, with a meta-analysis from the MARCAP consortium showing significant improvements in BCR, metastatic recurrence, MFS, and OS across various risk groups, independent of RT dose. Extending neoadjuvant ADT duration offers no added benefit. Three RCTs confirmed that ADT's benefits do not depend on RT dose escalation, and both neoadjuvant/concomitant and adjuvant ADT with dose-escalated RT are effective standards for intermediate- and high-risk prostate cancer.

Proton beam therapy:

Protontherapy, is possible but it a randomised trial showed no advantage in terms of QoL or PFS.

Spacer during external beam radiation therapy:

Biodegradable spacers, like hydrogel, are used to increase the distance between the prostate and rectum, reducing rectal radiation exposure. A meta-analysis showed a 5-8% reduction in rectal high-dose radiation volume, but study heterogeneity exists. Long-term data suggest spacers prevent bowel function deterioration, though rare but severe complications have been reported, such as prostatic abscess and sepsis. Spacer insertion requires experienced teams due to a learning curve, and its role in hypofractionated RT remains uncertain.

Brachytherapy

Low-dose rate brachytherapy (LDR BT):

LDR BT involves permanently implanting radioactive seeds into the prostate. Patients with favourable intermediate-risk disease and good urinary function may be suitable. Studies show a significant correlation between the implanted dose and biochemical control. However, neoadjuvant or adjuvant ADT does not improve OS when combined with LDR BT. LDR BT can be combined with EBRT for higher-risk patients. Adding LDR BT to EBRT improves progression-free survival at 10 years but is associated with increased urinary increases toxicity.

High-dose rate brachytherapy (HDR BT):

HDR BT delivers radiation via a temporary radioactive source and is often combined with EBRT. It can be delivered in single or multiple fractions and is associated with better distant metastasis-free survival when used as a boost. Combining HDR BT with EBRT improves biochemical disease-free rates, though it may increase urinary symptoms. HDR BT as monotherapy can be effective for intermediate-risk patients, with high PSA control rates and low toxicity. However, single-fraction HDR monotherapy is less effective than fractionated HDR.

Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFx) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Offer focal therapy with HIFU or cryotherapy within a clinical trial or prospective registry.	Strong

\*All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	<ul style="list-style-type: none"> <li>Permanent seeds implanted</li> <li>Uses Iodine-125 (I-125) (most common), Palladium-103 (<sup>103</sup>Pd-) or Cesium-131 isotopes</li> <li>Radiation dose delivered over weeks and months</li> <li>Acute side effects resolve over months</li> <li>Radiation protection issues for patient and carers</li> </ul>
High dose rate (HDR)	<ul style="list-style-type: none"> <li>Temporary implantation</li> <li>Iridium-192 (Ir-192) isotope introduced through implanted needles or catheters</li> <li>Radiation dose delivered in minutes</li> <li>Acute side effects resolve over weeks</li> <li>No radiation protection issues for patient or carers</li> </ul>