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The Role of Various Radiotherapy Techniques in Prostate Cancer Treatment (Review Article)

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ABSTRACT

Prostate cancer is a prevalent disease among older men, with treatment strategies ranging from active surveillance to radical interventions depending on disease stage and risk stratification. This review explores the evolution and application of various radiotherapy techniques in managing prostate cancer, emphasizing recent advancements aimed at improving accuracy and minimizing harm to healthy tissues. Techniques discussed include 3D conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), and stereotactic body radiation therapy (SBRT). The review highlights the benefits of IMRT and IGRT in enhancing tumor control, reducing toxicity, and improving biochemical failure-free survival. Studies comparing these modalities demonstrate that IGRT, in particular, is associated with reduced acute genitourinary and gastrointestinal toxicity, and improved biochemical tumor control in high-risk patients. This review underscores the importance of tailored radiotherapy approaches in optimizing outcomes and preserving the quality of life for prostate cancer patients.

Keywords: Radiotherapy, IGRT, 3DCRT, VMAT, IMRT, Brachytherapy

Introduction

Prostate cancer is the most common cancer affecting North American men older than age 60 years. Patients with palpable cancer involving both sides of the prostate, or extension into the seminal vesicles or periprostatic tissue have locally advanced prostate cancer. Recently, several investigators have combined palpable T stage, pretreatment prostate-specific antigen (PSA), and biopsy Gleason score to stratify patients into low-, intermediate-, and high-risk groups [1].

These risk groups are better predictors of prognosis and treatment-related outcomes than palpable T stage alone. Patients with intermediate- and high-risk disease are considered to have locally advanced prostate cancer with poor prognosis. External-beam radiation therapy (EBRT) with or without hormonal therapy has been the mainstay of treatment for this condition.

Prostate cancer is a common disease among men, but it is not always serious. Some cases are slow-growing and do not require treatment, while others are serious and require medical intervention.

Methods of dealing with the disease:

1. Monitoring: If the cancer is not serious, it is monitored without treatment.
2. Surgery: Removal of the prostate if the disease is in an advanced stage.
3. Radiotherapy: Uses radiation to kill cancer cells.
4. Hormone therapy: Stops the growth of cancer by controlling hormones.

Research says surgery is beneficial for young men and advanced cases of the disease.

Radiation with hormone therapy is best for widespread cases.

Monitoring is sufficient for simple cases [2].

Radiation may lead to the development of new cancers in healthy tissue, especially in children and women. The risk depends on the dose, and increases with time, Cardiac effects, its effect on implanted devices, Risks to fetuses, Cataracts and Skin effects so that recent developments by Improving radiation

techniques to make treatment more accurate and less harmful and using advanced imaging (such as magnetic resonance imaging) to accurately locate the cancer is crucial [3].

In radiotherapy, we want to deliver an accurate dose of radiation to the tumor without harming healthy tissue. To calculate this dose accurately, we use computer programs that take images of the patient and simulate how the radiation spreads inside the body.

So we have Dose calculation methods including:

1. Simple (corrective) method: It relies on previous measurements but is not accurate for the human body due to the difference in tissues.
2. Advanced (model) method: It uses physical equations to estimate the radiation distribution, but it requires some simplification.

3. Exact method (based on basic physics): Such as the Monte Carlo method, which simulates the movement of radiation accurately but slowly. Therefore, the Acuros XB algorithm emerged, which provides high accuracy more quickly.

The most accurate is: Monte Carlo > Acuros XB > other methods. The future is moving towards developing calculations that take into account the biological effect of radiation, not just the dose, to improve treatment [4].

External Beam Radiation Therapy (EBRT)

External beam radiation therapy (EBRT) is an advanced cancer treatment technique that targets cancer cells with high-energy radiation to destroy them while minimizing damage to normal cells. Its techniques include: 3DCRT: Uses computed tomography to improve tumor targeting accuracy. IMRT: Adjusts radiation intensity to minimize damage to surrounding tissue. VMAT: Delivers a radiation dose over a full rotation, reducing treatment time and improving protection of nearby organs IGRT: Uses imaging during treatment to adjust positioning and minimize errors. SBRT: Delivers high doses with extreme precision to treat small or metastatic tumors. Each technique has its advantages and challenges, and is used according to the type and location of the tumor to achieve the best treatment results [5].

A study was conducted on 601 patients with prostate cancer (stages A2 to C) who were treated with radiation without hormone therapy before relapse. The proportion of patients with stage C (disease that had spread outside the prostate) was 80%. Patients were followed for a median of 7.7 years. The results showed that patients who did not experience local relapse had significantly lower rates of metastases and higher survival rates than those who experienced local relapse, suggesting the role of local control in reducing cancer spread and improving survival [6].

Another study investigated the effect of external beam radiation therapy on patients with stage C prostate cancer. It found that the treatment provided good local control of the disease, with only 7% of patients requiring subsequent surgery due to prostate obstruction. The 5-year survival rate was 59%, with no treatment-related deaths [7].

Another study compared biochemical relapse-free survival (bRFS) rates for localized prostate cancer after five treatment modalities. It included 2991 patients with a median follow-up of 56 months. The results showed that radical resection (RP), high-dose radiation therapy (EBRT >72), radioactive implant (PI), and combination therapy (COMB) were superior in similar bRFS rates, while low-dose radiation therapy (EBRT <72) was the least effective [8].

After prostatectomy, a small amount of cancer may remain that cannot be seen. So, radiation is used to kill the remaining cells and prevent the cancer from coming back. Radiation is given

1. Before there are any signs of the cancer coming back → if tests after surgery show that there is a high chance of the cancer coming back.
2. After there are signs of it coming back → if the disease is discovered years after surgery [9].

Radiation is effective when used before the disease comes back, it has a high success rate (94%) in preventing local recurrence.

If it is given after the disease has come back, the success rate is lower, but it is still useful in some cases.

Most patients experience mild symptoms such as burning during urination.

In some cases, complications such as minor bleeding or narrowing of the urethra may occur, but severe cases are rare [10].

Intensity Modulated Radiation Therapy (IMRT)

Intensity-Modulated Radiation Therapy (IMRT) is an advanced form of radiotherapy that uses computer-controlled linear accelerators to deliver precise radiation doses to tumors while minimizing exposure to surrounding healthy tissues. By modulating the intensity of radiation beams and shaping them to conform to the three-dimensional structure of the tumor, IMRT allows for higher radiation doses to be directed at the cancerous area with reduced risk to adjacent organs. This precision is particularly beneficial for treating tumors located near critical structures, such as the prostate gland, which is surrounded by sensitive tissues like the bladder and rectum. IMRT involves a meticulous planning process that uses imaging techniques like CT or MRI scans to map the tumor's exact location and size, followed by computerized calculations to optimize dose delivery [11]. In prostate cancer treatment, IMRT has demonstrated significant advantages over conventional radiotherapy techniques. Long-term studies have shown excellent tumor control outcomes, with

8-year prostate-specific antigen (PSA) relapse-free survival rates reaching 85% for favorable-risk patients and 72% for unfavorable-risk patients. Additionally, IMRT reduces the likelihood of severe side effects; for example, only 1.6% of patients experienced grade 2 rectal bleeding after high-dose IMRT, and no grade 4 complications were reported. However, some late toxicities, such as erectile dysfunction (affecting 49% of initially potent patients), remain a concern. Compared to older methods like three-dimensional conformal radiotherapy (3D-CRT), IMRT offers improved targeting capabilities that enhance cancer control while limiting damage to surrounding tissues. Despite its higher cost, these benefits make IMRT a valuable tool in managing prostate cancer, particularly in cases where precision is critical for preserving quality of life [12].

Image-Guided Radiation Therapy (IGRT)

Image guided radiation therapy (IGRT) is a term that has been applied to the use of various imaging technologies in both the planning and the execution of radiation treatment, and it is becoming central to the management of cancer patients being treated with radiation therapy. Use for IGRT help in applying to pretreatment, in-room imaging for increased treatment delivery accuracy. In addition to precise delivery, the benefits of precise pretreatment alignment also include reducing setup margins, which may further limit irradiation of normal tissue [13].

The IGRT paradigm attempts to optimize the therapeutic ratio by imaging and localizing the targeted anatomy during treatment. The accuracy of IGRT is entirely dependent on the accuracy with which the imaging modality is able to direct the radiation beam. Nonuse of IGRT may result in inaccuracies in the localization process. This in turn may mean that the target is missed and that the surrounding healthy tissues receive an unintended dose of radiation, which may have short-term or long-term [13].

The evolution of radiotherapy has been ontogenetically linked to medical imaging. Over the years, major technological innovations have resulted in substantial improvements in radiotherapy planning, delivery, and verification. The increasing use of computed tomography imaging for target volume delineation coupled with availability of computer-controlled treatment planning and delivery systems have progressively led to conformation of radiation dose to the target tissues while sparing surrounding normal tissues. Recent advances in imaging technology coupled with improved treatment delivery allow near-simultaneous soft-tissue localization of tumor and repositioning of patient. The integration of various imaging modalities within the treatment room for guiding radiation delivery has vastly improved the management of geometric uncertainties in contemporary radiotherapy practice ushering in the paradigm of image-guided radiation therapy (IGRT). Image-guidance should be considered a necessary and natural corollary to high-precision radiotherapy that was long overdue. Image-guided radiation therapy not only provides accurate information on patient and tumor position on a quantitative scale, it also gives an opportunity to verify consistency of planned and actual treatment geometry including adaptation to daily variations resulting in improved dose delivery. The two main concerns with IGRT are resource-intensive nature of delivery and increasing dose from additional imaging. However, increasing the precision and accuracy of radiation delivery through IGRT is likely to reduce toxicity with potential for dose escalation and improved tumor control resulting in favorable therapeutic index. The radiation oncology community needs to leverage this technology to generate high-quality evidence to support widespread adoption of IGRT in contemporary radiotherapy practice [14].

Intensity-modulated radiotherapy (IMRT) has become the standard radiotherapy technology utilized for the treatment of prostate cancer, as it permits the delivery of highly conformal radiation dose distributions. Image-guided radiotherapy (IGRT) is an essential companion to IMRT that allows the treatment team to account for daily changes in target anatomy and positioning.

The definitive treatment of prostate cancer with external beam RT has drastically improved in the past score with modern techniques such as IMRT or SBRT. The implementation of daily image guidance techniques has helped reduce the impact of prostate motion associated with the positional variability of the prostate. In addition, image guidance has also allowed for a reduction in PTV margin and thus an improved toxicity profile which translates to an improved patient-reported QOL [15].

In a review included 18 studies (3 randomized clinical trial and 15 cohort studies) involving 6521 men, with a median duration of patient follow-up of 46.2 months in the IGRT group vs 52.7 months in the control group. The *meta*-analysis demonstrated that IGRT significantly reduced acute genitourinary GU (risk ratio [RR], 0.78; 95 % confidence interval [CI], 0.69–0.88; $P < 0.001$ [9 studies]) and GI toxicity (RR, 0.49; 95 % CI, 0.35–0.68; $P < 0.001$ [4 studies]) and late GI toxicity (HR, 0.25; 95 % CI, 0.07–0.87; $P = 0.03$ [3 studies]) compared with non-IGRT. Meanwhile, compared with prospective studies, retrospective studies showed that IGRT had a more significant effect in reducing the late GI toxicity. Compared with non-daily IGRT, daily IGRT significantly improved 3-year prostate specific antigen relapse free survival PRFS (HR, 0.45; 95 % CI, 0.28–0.72; $P = 0.001$ [2 studies]) and biochemical failure-free survival BFFS (HR, 0.57; 95 % CI, 0.39–0.83; $P = 0.003$ [3 studies]). Furthermore, high-frequency daily IGRT could lead to greater 3-year BFFS benefit in prostate cancer patients than weekly IGRT. However, no significant effects of IGRT on acute rectal toxicity, late GU toxicity, 5-year overall survival (OS) and second cancer mortality (SCM) were found, For men receiving prostate radiotherapy, IGRT was associated with an improvement in biochemical tumor control and a reduction in GI and acute GU toxicity, but did not significantly improve 5-year OS or increase 5-year SCM [16].

It has been demonstrated in most body sites that IGRT reduces the set-up error and the volume of healthy tissue adjacent to the target that is required to be irradiated. Orthogonal MV imaging and kV imaging, using implanted radio-opaque markers or soft tissue surrogates for tumor, can reduce set-up error. Real-time tumor tracking significantly reduces the volume of lung and liver irradiated because of breathing motion. Ultrasound guidance of vascular structures as surrogates for upper abdominal tumors and for prostate cancer significantly improves the residual set-up error. Finally, volumetric image guidance (eg, with kV or MV cone-beam CT or MV tomotherapy) can reduce the volume of irradiated healthy tissue in prostate, lung, liver, bladder, and head and neck cancers [17].

To compare toxicity profiles and biochemical tumor control outcomes between patients treated with high–dose image-guided radiotherapy (IGRT) and high–dose intensity-modulated radiotherapy (IMRT) for clinically localized prostate cancer, a prestigious study reported that a significant reduction in late urinary toxicity was observed for IGRT patients compared with the non-IGRT patients. The 3-year likelihood of grade 2 and higher urinary toxicity for the IGRT and non-IGRT cohorts were 10.4% and 20.0%, respectively (p = 0.02). Multivariate analysis identifying predictors for grade 2 or higher late urinary toxicity demonstrated that, in addition to the baseline International Prostate Symptom Score, IGRT was associated with significantly less late urinary toxicity compared with non-IGRT. The incidence of grade 2 and higher rectal toxicity was low for both treatment groups (1.0% and 1.6%, respectively; p = 0.81). No differences in prostate-specific antigen relapse-free survival outcomes were observed for low- and intermediate-risk patients when treated with IGRT and non-IGRT. For high-risk patients, a significant improvement was observed at 3 years for patients treated with IGRT compared with non-IGRT. IGRT is associated with an improvement in biochemical tumor control among high-risk patients and a lower rate of late urinary toxicity compared with high–dose IMRT. These data suggest that, for definitive radiotherapy, the placement of fiducial markers and daily tracking of target positioning may represent the preferred mode of external-beam radiotherapy delivery for the treatment of prostate cancer [18].

Volumetric Modulated Arc Therapy (VMAT)

Volumetric Modulated Arc Therapy (VMAT) is an advanced radiotherapy technique that delivers intensity-modulated radiation dynamically as the treatment machine's gantry rotates around the patient. This approach optimizes radiation dose distribution by continuously adjusting the multileaf collimator aperture, dose rate, and gantry speed, enabling precise targeting of tumors while sparing surrounding healthy tissues. Compared to traditional intensity-modulated radiation therapy (IMRT), VMAT achieves similar or superior dosimetric outcomes with significantly shorter treatment times, making it particularly advantageous for prostate cancer, where minimizing exposure to the rectum and bladder is critical [19]. In prostate cancer treatment, VMAT has demonstrated several key benefits:

- **Improved Efficiency:** VMAT reduces beam-on time by up to 55% compared to IMRT, with monitor unit (MU) counts dropping from 642 MU for IMRT to 290 MU for VMAT. Delivery times can decrease by up to 69%, enhancing patient comfort and clinic workflow [20].
- **Enhanced Rectal Sparing:** Studies report a 1.5% reduction in normal tissue complication probability (NTCP) for the rectal wall with VMAT compared to IMRT, alongside an 8.2% average reduction in rectal V25Gy (volume receiving 25 Gy). These improvements correlate with lower rates of acute grade ≥2 gastrointestinal toxicity (6–12%) and genitourinary toxicity (13%) [21].
- **Comparable Tumor Control:** VMAT maintains tumor control probabilities (0.920 vs. 0.929 for IMRT) and planning target volume (PTV) coverage (V95: 96% vs. 97%). For high-risk prostate cancer, 4-year biochemical relapse-free survival rates reach 85.2%, with 96.8% metastasis-free survival [20].
- **Long-Term Safety:** Late grade ≥2 toxicity rates for VMAT are low (15.8% genitourinary, 11.0% gastrointestinal), with no grade 4 complicationsreported.

  VMAT's precision is further enhanced when combined with whole-pelvic radiotherapy (WPRT) for high-risk cases, achieving 52 Gy to the prostate and 46.8 Gy to pelvic nodes without increasing toxicity. Advanced imaging techniques like PSMA PET-CT further optimize outcomes by improving staging accuracy and guiding simultaneous integrated boosts to involved nodes. While VMAT's dosimetric advantages over 3D conformal radiotherapy (3D-CRT) include reduced rectal and bladder doses, its clinical impact on late toxicity remains under investigation. Overall, VMAT represents a robust, efficient option for prostate cancer radiotherapy, balancing efficacy with minimized side effects [20].

Brachytherapy (Internal Radiation)

Brachytherapy is a highly targeted form of internal radiation therapy used to treat prostate cancer by implanting radioactive sources directly into the prostate gland. This minimally invasive procedure is performed under anesthesia, typically on an outpatient basis, and involves two main types: low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy [22]. LDR brachytherapy uses permanent radioactive seeds that emit radiation over several months, while HDR brachytherapy delivers temporary, concentrated bursts of radiation through catheters in one or two short sessions. Both methods allow precise targeting of the tumor, minimizing damage to surrounding healthy tissues such as the bladder and rectum. Brachytherapy has demonstrated excellent outcomes for localized prostate cancer, with five-year survival rates exceeding 95% for low-risk patients and long-term prostate cancer-specific survival rates reaching 95% at 15 years. Studies have shown that LDR brachytherapy provides durable disease control, with a 15-year overall survival rate of 81%, and is particularly effective when combined with other therapies for intermediate- or high-risk cases. The procedure also offers advantages such as shorter recovery times, fewer treatment sessions compared to external beam radiation therapy (EBRT), and a lower risk of severe side effects like urinary incontinence and erectile dysfunction. While side effects such as temporary urinary discomfort or bowel irritation may occur, most patients experience significant improvement within 6–12 months [22]. Moreover, modern imaging techniques like real-time CT and MRI guidance have enhanced the precision of seed placement, further improving outcomes. Despite its benefits, brachytherapy carries a small long-term risk of secondary malignancies (6.4% at 15 years), though this risk is comparable to other treatments. Overall, brachytherapy remains a highly effective and well-tolerated option for treating localized prostate cancer across various risk categories [23].

Side effects of radiation therapy in prostate cancer

Radiation therapy (RT) for prostate cancer often causes side effects such as fatigue and sleep problems, which can negatively affect patients' daily lives, including their work, social interactions, and emotions [24].

Exercise has been shown to be a safe and effective way to support prostate cancer patients undergoing radiation therapy. Studies have found that it helps improve physical function and reduce urinary symptoms without making other side effects, like digestive issues, depression, or sleep problems, worse. Because of these benefits, patients should be encouraged to stay active during treatment as part of their overall care. However, more research is needed to fully understand how exercise can help in the long term and what types or intensities work best. Ongoing studies, like the EXERT trial, are already looking into how exercise might benefit men receiving palliative radiation therapy for metastatic prostate cancer. Future research should also explore whether exercising during or after treatment makes a bigger difference and how different exercise programs affect side effects [25].

Furthermore, research on prostate-only or pelvic stereotactic radiation therapy (SRT) in prostate cancer has explored its potential side effects, which can be both short-term and long-term. Short-term effects, occurring during or shortly after treatment, often include urinary symptoms such as increased frequency, urgency, or discomfort, as well as bowel disturbances like diarrhea or cramping. Fatigue is also frequently reported. Long-term effects, which may appear months or years later, can involve persistent urinary dysfunction, bowel complications like rectal bleeding, and sexual dysfunction due to nerve or vascular damage. Radiation therapy is a common cancer treatment, but it can cause side effects that need proper management. Skin irritation (radiation dermatitis) is treated with creams and steroids, while lung inflammation (radiation pneumonitis) is managed with prednisone. Swallowing problems (radiation esophagitis) can be eased with dietary changes and medications, and nausea is treated with anti-nausea drugs and steroids. Bladder issues (radiation cystitis) may require medication [26].

Androgen-deprivation therapy (ADT) for prostate cancer is linked to an increased risk of bone fractures, diabetes, heart disease, and dementia, though the severity of these effects varies. Additionally, surgery and radiation appear to have a greater negative impact on sexual function than ADT. These findings highlight the need for further research to better understand how ADT affects cognitive function. Resistance training has been shown to improve muscle strength, functional performance, and balance in older men undergoing androgen deprivation therapy (ADT) for prostate cancer. A 20-week training program led to significant gains in strength, endurance, walking speed, stair climbing, and balance, while preserving lean body mass without affecting fat mass or hormone levels. These results suggest that resistance exercise can help counteract the negative effects of ADT, reducing musculoskeletal side effects and maintaining physical function [27].

With the increasing use of extreme hypofractionation and combination therapy for high-risk cases, there is a shift in side effects from GI toxicity to GU toxicity. Protecting critical GU structures, such as the bladder neck and urethra, is essential to reduce complications. There are also overlooked side effects of prostate cancer treatment that can affect patients' quality of life, such as urinary leakage during orgasm or arousal, ejaculation issues, and changes in penile shape [28].

The short-term side effects of prostate cancer treatment differ between robot-assisted radical prostatectomy (RARP) and radiotherapy (RT). RARP carries a higher risk of urinary incontinence and erectile dysfunction, while RT is more associated with urinary irritation and bowel issues. However, overall qualify life (QoL) remains similar for both treatments. RARP offers several advantages, including greater surgical precision, less bleeding and pain, faster recovery, and a lower risk of infection, making it a preferred option for some patients. These findings highlight the differences between treatments, helping guide informed decision-making during medical consultations [29].

Conclusion

Modern radiotherapy techniques, including 3DCRT, IMRT, VMAT, IGRT, and SBRT, have significantly advanced prostate cancer treatment by improving precision and minimizing damage to surrounding healthy tissues. Studies indicate that IGRT, particularly with daily application, enhances biochemical tumor control and reduces acute genitourinary and gastrointestinal toxicities. Advanced imaging and dose calculation algorithms, such as Acuros XB, further optimize radiation delivery. While IMRT has become a standard for delivering conformal radiation doses, IGRT is crucial for managing daily anatomical changes and positional variations. Meta-analysis confirms that IGRT reduces acute genitourinary and gastrointestinal toxicity and improves biochemical failure-free survival, especially with high-frequency daily use. These advancements collectively aim to refine treatment planning by incorporating the biological effects of radiation, improving outcomes, and maintaining the quality of life for prostate cancer patients.

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